ResearchGate

See discussions, stats, and author profiles for this publication at: https://www.researchgate.net/publication/51637265

ChemInform Abstract: Divergent Regioselective Synthesis of 2,5,6,7-Tetrahydro-1H-1,4-diazepin-2-ones and 5H-1,4-Benzodiazepines.

ARTICLE *in* THE JOURNAL OF ORGANIC CHEMISTRY · SEPTEMBER 2011

Impact Factor: 4.72 · DOI: 10.1021/jo201497r · Source: PubMed

CITATIONS
9

READS
56

5 AUTHORS, INCLUDING:

Gianfranco Favi
Università degli Studi di Urbino "Carlo Bo"
88 PUBLICATIONS **936** CITATIONS
SEE PROFILE

Fabio Mantellini
Università degli Studi di Urbino "Carlo Bo"
112 PUBLICATIONS **1,156** CITATIONS
SEE PROFILE

Simona Nicolini
Università degli Studi di Urbino "Carlo Bo"
14 PUBLICATIONS **96** CITATIONS
SEE PROFILE

Available from: Gianfranco Favi
Retrieved on: 02 February 2016

JOC The Journal of Organic Chemistry

ARTICLE

pubs.acs.org/joc

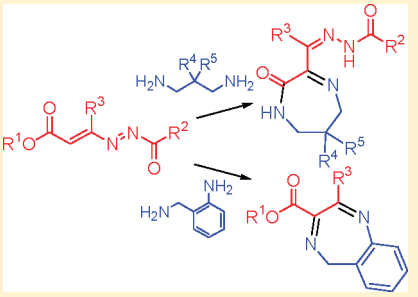
Divergent Regioselective Synthesis of 2,5,6,7-Tetrahydro-1*H*-1,4-diazepin-2-ones and 5*H*-1,4-Benzodiazepines

Orazio A. Attanasi, Lucia De Crescentini,* Gianfranco Favi, Fabio Mantellini, and Simona Nicolini

Istituto di Chimica Organica, Università degli Studi di Urbino "Carlo Bo", Via I Maggetti 24, 61029 Urbino, Italy

Supporting Information

ABSTRACT: A novel and simple one-pot synthesis of 3-substituted 2,5,6,7-tetrahydro-1*H*-1,4-diazepin-2-ones from 1,2-diaza-1,3-dienes (DDs) and N-unsubstituted aliphatic 1,3-diamines is described. Here we also report a procedure to selectively obtain alkyl 5*H*-1,4-benzodiazepine-3-carboxylates from the DDs and 2-aminobenzylamine. Both processes occur by means of sequential 1,4-conjugated addition followed by regioselective 7-exo cyclization. The behavior of *N*-methyl- and *N*,*N*′-dimethyl-1,3-diaminopropanes toward the DDs furnished pyrazol-3-ones and bis-α-aminohydrazones, respectively.



INTRODUCTION

The exploration of privileged structures in drug discovery has gained increasing interest and relevance.[1] Among the small molecules employed in this field, molecular scaffolds that mimic peptide secondary structures are particularly useful for the identification and development of therapeutic agents.[1,2] For example, 1,4-benzodiazepine is a privileged scaffold or fragment that has been studied extensively and frequently appeared in the biologically active molecules and drugs.[3] In particular, a large number of 1,4-benzodiazepines act as anxiolytic, antidepressant, anticonvulsant, and antihypnotic agents[4] and some of them exhibit antitumor activity.[5]

The seven-membered 1,4-diazepin-2-one ring mimics β- and γ-turn secondary structures[6−8] and exhibits anticonvulsant activity,[9] antibacterial activity against multidrug-resistant *Mycobacterium tubercolosis* strains,[10] antitumor properties,[11] and lymphocyte function-associated antigen-1 (LFA-1) antagonists.[12] For these reasons, the development of new strategies for the synthesis of 1,4-diazepin-2-ones is ever evolving.

The most reported synthetic approaches to 1,4-benzodiazepine skeletons include reaction of 2-aminobenzoic acids and their derivatives or 2-aminobenzophenones with α-amino acids,[13] cyclocondensation of 2-halobenzoic acid derivatives or 2-halobenzophenones with diamines,[14] and Pictet−Spengler reaction of *N*,*N*′-dimethyl-*N*-phenyl-1,2-ethanediamine with aldehydes.[15]

The diazepinone ring is reported in the literature to be prepared from linear precursors by intramolecular reductive amination,[8,16−18] lactam formation,[19−21] and transamidation.[22] Also, the preparation of 1,4-diazepin-2-ones involves iminophosphorane intermediates by means of intramolecular aza-Wittig reaction or hydrolysis of the iminophosphoranes to the corresponding amino derivatives followed by intramolecular cyclocondensation.[23] The limit of these procedures is that they involve some preparative difficulties and require several steps.

1,2-Diaza-1,3-dienes[24] (DDs) are versatile intermediates and react with a wide range of nucleophiles at its highly electrophilic center (at C-4),[25] leading to a wide variety of heterocyclic rings.[24,26]In particular, we went back to our previous investigations on the reaction of DDs **1** with 1,2-diamines to obtain 1,2,5,6-tetrahydro-2-pyrazinones **I**[27] or pyrazines **II**,[27] depending from the conditions used, and with 1,3-diamines (in the molar ratio 2:1) that furnished the corresponding bis-α-aminohydrazones **III**,[28] respectively (Scheme 1).

On the basis of these experiences, and in continuation of our ongoing interest in the discovery of reactions for the synthesis of new heterocycles from azo-ene systems, we have designed a novel method for the preparation of 1,4-diazepin-2-ones **A** and/or 1,4-diazepines **B** from DDs **1** and 1,3-diamines **2** in the molar ratio 1:1 (Scheme 2). Our analysis of the seven-membered heterocyclic core emphasizes strategic disconnections along the C(2)−N(1) and C(3)−N(4) bonds. This reveals two subunits that trace the lower-half to the pertinent diamines **2**, and the upper half to the α,β-dications **C** and **D**, that further can be correlated to the 4-alkoxycarbonyl azoene system of the DDs **1**. The high electrophilicity at the carbon terminus of the heterodiene system[25] permits the formation of C(3)−N(4) junction in **A** and in **B**, by means of a 1,4-Michael-type addition with one of the nitrogens in diamine **2**.

At this point, two different C(2)−N(1) junctions can be obtained by means of a subsequent intramolecular 7-exo cyclization of the second nitrogen of the diamine that can occur on the carboxylic function of **C**, giving 1,4-diazepin-2-ones **A**, or on the hydrazonic function of **E**, furnishing 1,2-diazepines **B**, respectively.

To the best of our knowledge, only one example[29] for the synthesis of 1,4-diazepin-2-ones was reported in literature, using

Received: July 19, 2011
Published: September 09, 2011

ACS Publications © 2011 American Chemical Society

dx.doi.org/10.1021/jo201497r | *J. Org. Chem.* 2011, 76, 8320–8328

this disconnection approach. In 1969, in fact, McDougal and Malik attempted to prepare simple 1,4-diazepine starting from glyoxal sodium hydrogen sulfite and 2,4-diaminopentane; instead they obtained *cis*-dimethylhexahydro-1,4-diazepin-2-one.[29] The authors tried unsuccessfully to enlarge the scope of this methodology by using both 1,3-diamines and 1,2-dicarbonyl or α-halogen carbonyl derivatives. The same method was then used by Knapp et al.[30] starting from the same glyoxal derivative with *N*,*N*-dimethylpropane-1,3-diamine, obtaining the expected 1,4-dimethyl-1,4-diazepan-2-one but in very poor yield while employing harsh reaction conditions. Thus, the reaction had limited scope. On the other hand, only relatively few methods are reported for the synthesis of 1,4-diazepines, starting from diamine derivatives and bis-electrophiles, and often they are unsatisfactory.[29,31]

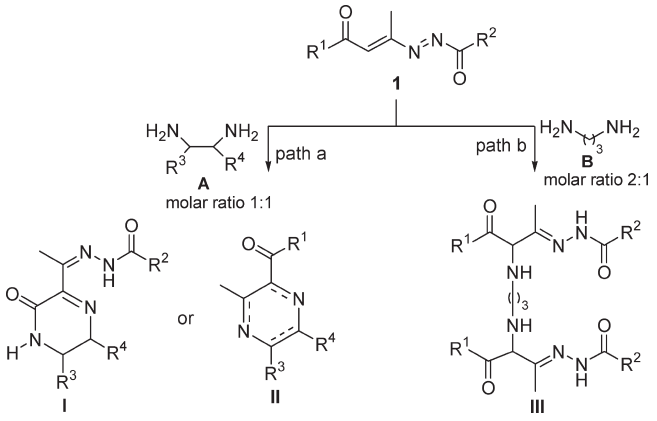
RESULTS AND DISCUSSION

Therefore, with the aim to synthesize 1,4-diazepin-2-ones or 1,4-diazepines, initially we explored the reaction of DDs **1a**−**c**[32] with aliphatic 1,3-diamines **2a**−**c** at room temperature in diethyl ether (Scheme 3). To avoid the formation of bis-α-aminohydrazones,[31] we carried out the reaction in equimolar ratio and by adding reagents **1** to **2**.

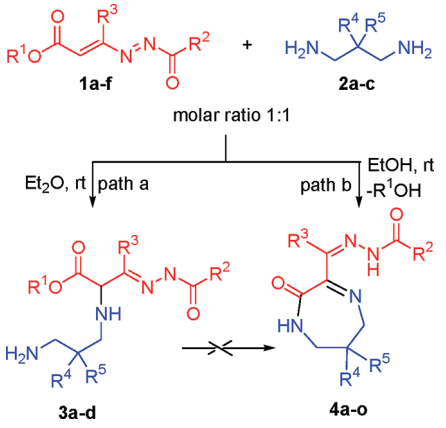
Under these conditions, the disappearance of the typical red color of the starting DDs indicated the completion of the reaction rapidly (1 min), and TLC revealed one as major spot. The products were isolated as solids, simply by partial evaporation of the reaction solvent, and identified to be the α-aminohydrazones **3a**−**d** (Scheme 3, path a, Table 1). As compounds **3** are not very stable in solution, their spectroscopic NMR analyses must be done promptly. Their formation takes place by means of an aza-Michael addition by one of the two nitrogens in **2a**−**c** to the terminus carbon of the azo-ene system of the DDs **1**.

When DDs **1a**−**f** were allowed to react with the same aliphatic 1,3-diamines **2a**−**c** in 1:1 molar ratio, in ethanol rather than in diethyl ether, we directly obtained the expected 3-substituted 2,5,6,7-tetrahydro-1*H*-1,4-diazepin-2-ones **4a**−**o**, which precipitated out from the reaction medium with satisfactory yields (48−67%) (Scheme 3, path b, Table 2).

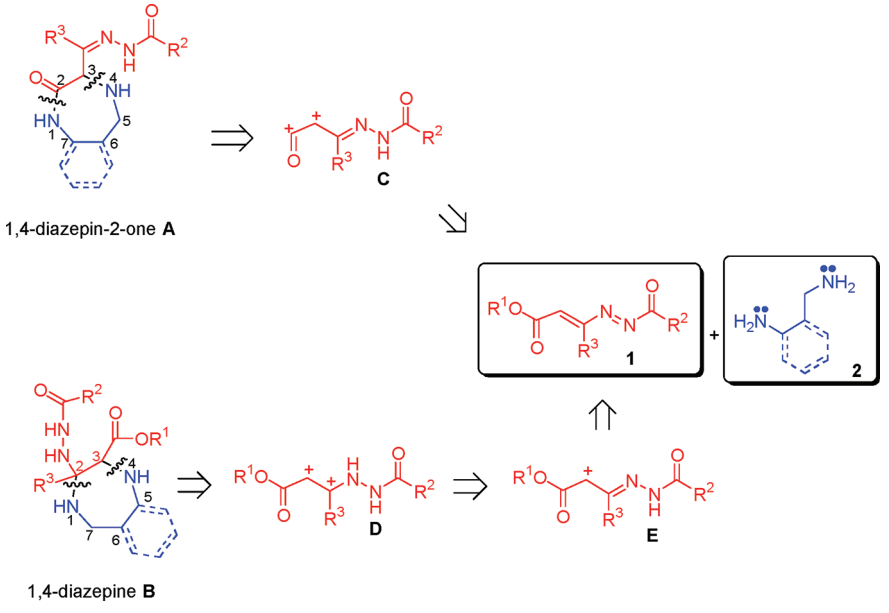
Scheme 1. Reactivity of 1,2-Diaza-1,3-dienes 1 with 1,2-Diamines A and with 1,3-Diamines B (in the molar ratio 1:2)



Scheme 3. Synthesis of α-Aminohydrazones 3a−d and of 3-Substituted 2,5,6,7-Tetrahydro-1*H*-1,4-diazepin-2-ones 4a−o



Scheme 2. Retrosynthetic Strategy for the Preparation of 1,4-Diazepin-2-ones A or 1,4-Diazepines B



dx.doi.org/10.1021/jo201497r |*J. Org. Chem.* 2011, 76, 8320–8328

Table 1. Synthesis of α-Aminohydrazones 3a−d

	1,2-diaza-1,3-dienes 1				1,3-diamines 2			products 3	
entry	1	R^1	R^2	R^3	2	R^4	R^5	3	yield (%)[a]
1	**1a**	Et	O*t*-Bu	Me	**2a**	H	H	**3a**	90
2	**1b**	Me	NHPh	Me	**2a**	H	H	**3b**	100
3	**1c**	Me	O*t*-Bu	Me	**2b**	H	Me	**3c**	98
4	**1c**	Me	O*t*-Bu	Me	**2c**	Me	Me	**3d**	90

[a] Yield of pure isolated products **3** based on DDs **1**.

Table 2. One-Pot Synthesis of 3-Substituted 2,5,6,7-Tetrahydro-1*H*-1,4-diazepin-2-ones 4a−o

	1,2-diaza-1,3-dienes 1				1,3-diamines 2			products 4		
entry	1	R^1	R^2	R^3	2	R^4	R^5	4	time (h)	yield (%)[a]
1	**1a**	Et	O*t*-Bu	Me	**2a**	H	H	**4a**	3.0	58
2	**1b**	Me	NHPh	Me	**2a**	H	H	**4b**	2.5	48
3	**1d**	Me	OBn	Me	**2a**	H	H	**4c**	2.0	44
4	**1e**	Me	NH_2	Me	**2a**	H	H	**4d**	2.0	57
5	**1f**	Me	NH_2	Et	**2a**	H	H	**4e**	2.5	48
6	**1b**	Me	NHPh	Me	**2b**	H	Me	**4f**	4.0	63
7	**1c**	Me	O*t*-Bu	Me	**2b**	H	Me	**4g**	4.0	62
8	**1d**	Me	OBn	Me	**2b**	H	Me	**4h**	4.0	40
9	**1e**	Me	NH_2	Me	**2b**	H	Me	**4i**	6.0	57
10	**1f**	Me	NH_2	Et	**2b**	H	Me	**4j**	2.0	61
11	**1b**	Me	NHPh	Me	**2c**	Me	Me	**4k**	3.0	63
12	**1c**	Me	O*t*-Bu	Me	**2c**	Me	Me	**4l**	2.5	62
13	**1d**	Me	OBn	Me	**2c**	Me	Me	**4m**	8.0	42
14	**1e**	Me	NH_2	Me	**2c**	Me	Me	**4n**	1.0	54
15	**1f**	Me	NH_2	Et	**2c**	Me	Me	**4o**	4.0	65

[a] Yield of isolated pure product **4** based on DD **1**.

In this case, the initial 1,4-addition of the amino group in 1,3-diamines **2a−c** takes place at the terminus carbon of the heterodiene DDs **1a−f** to form hydrazones **3**, followed by regioselective nucleophilic attack of the second amino group at the ester function, with the loss of an alcohol molecule. Then spontaneous oxidation of the C−N bond furnishes 2,5,6,7-tetrahydro-1*H*-1,4-diazepin-2-ones **4a−o**. The role of the air in this process was confirmed, performing the same reaction under inert atmosphere: in fact, under these conditions, no products **4** were detected, but we obtained complicated reaction mixtures. Probably, the presence of three conjugated double bonds confers stability to these compounds **4**. It should be noted that synthesis of these interesting molecules are limited in the literature.[33] All attempts to convert α-aminohydrazones **3a−d** into the corresponding **4** failed, giving complicated reaction mixtures, and this is ascribed to the poor stability of compounds **3** in solution.

The 7-exo cyclization has been confirmed by comparing the ^{1}H chemical shifts of the hydrogens bound to the nitrogens involved in this process. In particular, the amine NH_2 in the 1,4-adducts **3** show a chemical shift at ∼2.20 ppm; on the contrary, the amide NH in the diazepinone derivatives **4** is at 8.19−8.65 ppm. Also, the multiplicity of this diagnostic signal in the latter that appears as a triplet confirms unequivocally that the nitrogen responsible for the ring closure process derives from the starting reagents **2**. With respect to the analogous six-membered compounds obtained from DDs and 1,2-diamines,[27] there is a good agreement in the diagnostic signals both at ^{1}H and ^{13}C NMR.

Scheme 4. Synthesis of α-Aminohydrazones 3e−h and of Alkyl 5*H*-1,4-Benzodiazepine-3-carboxylates 5a−d

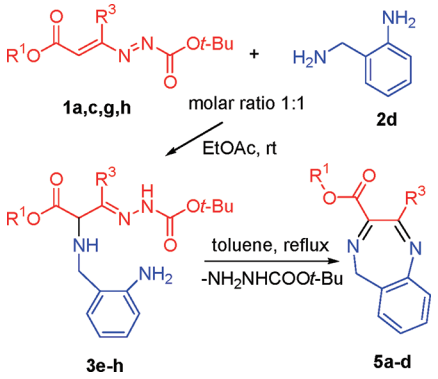


Table 3. Synthesis of α-Aminohydrazones 3e−h and Alkyl 5*H*-1,4-Benzodiazepine-3-carboxylates 5a−d

	1,2-diaza-1,3-dienes 1			products 3		products 5		
entry	1	R^1	R^3	3	yields (%)[a]	5	time (h)	yields (%)[b]
1	**1a**	Et	Me	**3e**	72	**5a**	4.0	47
2	**1c**	Me	Me	**3f**	96	**5b**	5.0	53
3	**1g**	Me	Et	**3g**	95	**5c**	4.0	62
4	**1h**	*i*-Pr	Me	**3h**	66	**5d**	3.0	71

[a] Yield of pure isolated products **3** based on DDs **1**. [b] Yield of pure isolated products **5** based on α-aminohydrazones **3**.

In order to obtain the 1,4-benzodiazepine core, we examined the reaction of DDs **1a,c,g,h** and 2-aminobenzylamine **2d**, in 1:1 molar ratio. The best conditions we found involved the use of 1-*tert*-butoxycarbonyl-DDs in ethyl acetate at room temperature, obtaining the corresponding α-aminohydrazones **3e−h** in good to excellent yields (66−96%) simply by precipitation from the reaction medium (Scheme 4, Table 3).

Compounds **3** are formed by means of an aza-Michael addition of the more nucleophilic benzylic nitrogen of the diamine **2d** at the terminus carbon of the azo-ene system of DDs **1**. Compounds **3e−h** in toluene under reflux were converted into the corresponding alkyl 5*H*-1,4-benzodiazepine-3-carboxylates **5a−d** in satisfactory yields (47−71%) (Scheme 4, Table 3). Their formation involves a regioselective ring closure by the anilinic nitrogen on the hydrazonic function and the subsequent spontaneous loss of *tert*-butyl carbazate moiety.

The peculiar regioselectivity observed in the ring closure process of these reactions depends on the differential nucleophilicity of the involved nitrogen atoms in aliphatic (**2a−c**) or aromatic (**2d**) 1,3-diamines, respectively, together with the diverse nucleophilic affinity of ester and hydrazone groups. Also the different strain of monocyclic 1,4-diazepin-2-ones **4** compared with that of bicyclic 1,4-benzodiazepines **5** could play an important role.

Then, we studied the behavior of N-monosubstituted 1,3-diamine toward DDs. When the reactions between DDs **1a,b,g,i** and *N*-methyl-1,3-diaminopropane **2e** were carried out in dichloromethane at room temperature, in a 1:1 molar ratio,

dx.doi.org/10.1021/jo201497r |*J. Org. Chem.* 2011, 76, 8320–8328

Scheme 5. Synthesis of 4-[(3-Aminopropyl)-(methyl)amino]-1*H*-pyrazol-3-ones 6a−d and Bis-α-amino-hydrazones 7a,b

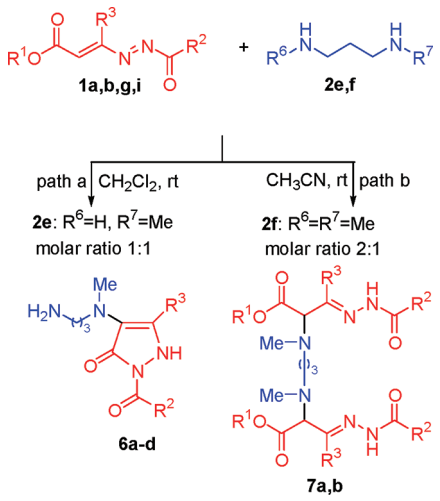


Table 4. Synthesis of 4-[(3-Aminopropyl)(methyl)amino]-1*H*-pyrazol-3-ones 6a−d and Bis-α-aminohydrazones 7a,b

	1,2-diaza-1,3-dienes 1				1,3-diamines 2			products 6			products 7	
									time	yield		yield
entry	1	R^1	R^2	R^3	2	R^6	R^7	6	(h)	(%)[a]	7	(%)[b]
1	**1a**	Et	O*t*-Bu	Me	**2e**	H	Me	**6a**	0.1	54		
2	**1b**	Me	NHPh	Me	**2e**	H	Me	**6b**	0.2	50		
3	**1g**	Me	O*t*-Bu	Et	**2e**	H	Me	**6c**	0.1	91		
4	**1i**	Et	OMe	Me	**2e**	H	Me	**6d**	0.1	60		
5	**1a**	Et	O*t*-Bu	Me	**2f**	Me	Me				**7a**	98
6	**1b**	Me	NHPh	Me	**2f**	Me	Me				**7b**	98

[a] Yield of pure isolated products **6** based on DDs **1**. [b] Yield of pure isolated products **7** based on DDs **1**.

pyrazol-3-ones **6a−d** were obtained as sole products in good to excellent yields (Scheme 5, Table 4).

The mechanism for the formation of pyrazol-3-one ring provides the preliminary formation of nonisolable α-aminohydrazones that can occur by the 1,4-addition of the more nucleophilic secondary nitrogen or of the less nucleophilic NH_2 of diamine **2e**. The subsequent intramolecular nucleophilic attack of the hydrazonic nitrogen atom on the ester group with loss of an alcohol molecule and tautomerism can furnish structures I or II of pyrazolone ring, respectively (Figure 1).[24]

The exact structure of pyrazol-3-ones **6** was determined by NOE experiments on compound **6a**, chosen as example, that showed considerable NOE enhancement of N−CH_3 at 2.52 ppm by irradiation of CH_3 at 2.16 ppm and *vice versa*: this evidence suggests the proximity of these two groups, in agreement with 4-[(3-aminopropyl)(methyl)amino]-1*H*-pyrazol-3-ones of structure I (Figure 1) obtained by the initial nucleophilic attack of the secondary nitrogen. Hence, in this case, the lack of the hydrogen bound to the tertiary nitrogen derived from the diamine **2e** probably drives the different regioselectivity of the ring closure to pyrazol-3-ones, preventing the formation of the C=N bond. Pyrazoles are molecules of interest because they often recur in organic, biological and medicinal chemistry and they have been applied also in the analytical and agricultural fields.[34]

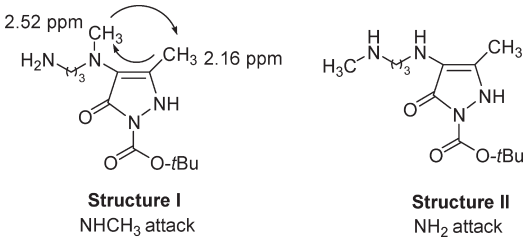


Figure 1. NOE experiments on compound **6a**.

Then we extended this study to the reactions of *N*,*N*′-dimethyl-1,3-diaminopropane **2f** with DDs **1a,b**. We explored several conditions without much success, except when carried out in acetonitrile at room temperature, in a 2:1 molar ratio: bis-α-aminohydrazones **7a,b** were obtained in 5 min, in very good yields (Scheme 5, Table 4).[31]

Under conditions employed for the formation of 2,5,6,7-tetrahydro-1*H*-1,4-diazepin-2-ones **4**, the reactions of DDs with diamines **2e,f** furnished complicated reaction mixtures.

CONCLUSION

In summary, we have reported novel regioselective syntheses of 2,5,6,7-tetrahydro-1*H*-1,4-diazepin-2-ones and alkyl 5*H*-1,4-benzodiazepine-3-carboxylates, starting from DDs and aliphatic as well as aromatic 1,3-diamines, respectively. Also, the reactivity of N-unsubstituted, N-mono-, or N,N′-disubstituted 1,3-diamines were compared in the transformation process, that gave 2,5,6,7-tetrahydro-1*H*-1,4-diazepin-2-ones and 5*H*-1,4-benzodiazepines, 4-[(3-aminopropyl)(methyl)amino]-1*H*-pyrazol-3-ones, and bis-α-aminohydrazones, respectively.

Therefore, the utility of the described syntheses to obtain interesting heterocyclic scaffolds, together with mild and simple reaction conditions (no dry solvents or inert atmosphere) makes them well suitable for the generation of combinatorial libraries that might be useful in the chemical biology research.

EXPERIMENTAL SECTION

General Remarks. All the commercially available reagents and solvents were used without further purification. 1,2-Diaza-1,3-dienes **1a−i** were synthesized as a mixture of *E*/*Z* isomers as previously reported.[32] Chromatographic purification of compounds was carried out on silica gel (60−200 μm). TLC analysis was performed on preloaded (0.25 mm) glass-supported silica gel plates (Kieselgel 60); compounds were visualized by exposure to UV light and by dipping the plates in 1% $Ce(SO_4)\cdot 4H_2O$, 2.5% $(NH_4)_6Mo_7O_{24}\cdot 4H_2O$ in 10% sulfuric acid followed by heating on a hot plate. All ^1H NMR and ^{13}C NMR spectra were recorded at 400 and 100.56 MHz, respectively. Proton and carbon spectra were referenced internally to solvent signals, using values of δ = 2.50 ppm for proton (middle peak) and δ = 39.50 ppm for carbon (middle peak) in DMSO-d_6 and δ = 7.27 ppm for proton and δ = 77.00 ppm for carbon (middle peak) in $CDCl_3$. The following abbreviations are used to describe peak patterns where appropriate: s = singlet, d = doublet, t = triplet, dd = double doublet, dt = double triplet, q = quartet, qi = quintet, sex = sextet, sept = septet, m = multiplet, and br = broad signal. All coupling constants (*J*) are given in hertz. FT-IR spectra were obtained as Nujol mulls. Mass spectra were

dx.doi.org/10.1021/jo201497r |*J. Org. Chem.* 2011, 76, 8320–8328

recorded in the EI (70 eV) or ESI mode. Melting points were determined in open capillary tubes and are uncorrected.

General Procedure for the Synthesis of α-Aminohydrazones ***3a*****—*****h***. To a solution of aliphatic 1,3-diamines **2a**—**c** (1.0 mmol) in diethyl ether (2 mL) or 2-aminobenzylamine **2d** (1.0 mmol) in ethyl acetate (2 mL) magnetically stirred at room temperature, a solution of 1,2-diaza-1,3-dienes **1a**—**c**,**g**,**h** (1.0 mmol) in diethyl ether (3 mL) in the case of aliphatic 1,3-diamines **2a**—**c** or ethyl acetate (3 mL) in the case of 2-aminobenzylamine **2d** was added. At the disappearance of the red color of **1a**—**c**,**g**,**h** that occurred within 1 min, products **3a**—**d** were crystallized by partial evaporation of the solvent under reduced pressure, while products **3e**—**h** directly crystallized from the reaction solvent. Compounds **3** are not very stable in solution, and in some cases, it is difficult to record ^{13}C NMR spectra. Spectroscopic data for α-aminohydrazones **3a**—**d** are given below.

*tert-Butyl 2-{2-[(3-Aminopropyl)amino]-3-ethoxy-1-methyl-3-oxopropylidene}hydrazinecarboxylate (**3a**).* White powder from diethyl ether; mp 140—2 °C. ^{1}H NMR (DMSO-d_6): δ = 1.15 (t, *J* = 7.2 Hz, 3H), 1.41 (s, 9H), 1.47—1.50 (m, 2H), 1.73 (s, 3H), 2.25 (br s, 2H), 2.31—2.48 (m, 4H), 3.30 (s, 1H), 3.81 (s, 1H), 4.09 (dq, *J* = 7.2 Hz, *J* = 2.4 Hz, 2H), 9.56 (s, 1H). ^{13}C NMR (DMSO-d_6): δ = 12.8 (q), 14.0 (q), 28.1 (q), 29.6 (t), 45.3 (t), 45.4 (t), 60.5 (t), 67.5 (d), 79.2 (s), 149.7 (s), 152.9 (s), 170.9 (s). IR: ν_{max} = 3229, 1744, 1732, 1712, 1678 cm^{-1}. MS: *m*/*z* (%) = 316 [M$^+$] (12), 298 (12), 286 (6), 272 (16), 260 (49), 236 (45), 216 (100), 204 (84), 185 (54), 172 (60), 155 (76), 143 (52), 130 (70), 111 (52). Anal. calcd for $C_{14}H_{28}N_4O_4$: C, 53.15; H, 8.92; N, 17.71. Found: C, 53.28; H, 8.79; N, 17.91.

*Methyl 2-[(3-Aminopropyl)amino]-3-[(anilinocarbonyl)hydrazono]-butanoate (**3b**).* White powder from diethyl ether; mp 110—2 °C. ^{1}H NMR (DMSO-d_6): δ = 1.54—1.59 (m, 2H), 1.83 (s, 3H), 2.46—2.57 (m, 4H), 2.65—2.70 (m, 2H), 3.66 (s, 3H), 3.67 (s, 1H), 4.05 (s, 1H), 6.99 (t, *J* = 7.2 Hz, 1H), 7.28 (t, *J* = 7.6 Hz, 2H), 7.55 (d, *J* = 8.0 Hz, 2H), 8.73 (s, 1H), 9.68 (br s, 1H). ^{13}C NMR (DMSO-d_6): δ = 13.1 (q), 29.5 (t), 45.3 (t), 45.4 (t), 51.9 (q), 67.1 (d), 119.2 (d), 122.3 (d), 128.5 (d), 138.9 (s), 146.8 (s), 153.2 (s), 171.5 (s). IR: ν_{max} = 3372, 3194, 1745, 1693 cm^{-1}. MS: *m*/*z* (%) = 321 [M$^+$] (1), 264 (7), 185 (7), 176 (63), 165 (11), 149 (18), 136 (24), 119 (100), 111 (40). Anal. calcd for $C_{15}H_{23}N_5O_3$: C, 56.06; H, 7.21; N, 21.79. Found: C, 56.28; H, 7.19; N, 21.91.

*tert-Butyl 2-{2-[(3-Amino-2-methylpropyl)amino]-3-methoxy-1-methyl-3-oxopropylidene}hydrazinecarboxylate (**3c**).* White powder from diethyl ether; mp 111—3 °C. ^{1}H NMR (DMSO-d_6): δ = 0.80—0.83 (m, 3H), 1.38—1.40 (m, 1H), 1.44 (s, 9H), 1.76 (s, 3H), 2.18—2.47 (m, 6H), 3.63 (s, 3H), 3.85 (br s, 1H), 3.86 (s, 1H), 9.62 (br s, 1H). ^{13}C NMR (DMSO-d_6): δ = 12.9 (q), 15.1 (q), 28.1 (q), 35.7 (d), 45.2 (t), 51.8 (9), 64.9 (t), 67.6 (d), 79.2 (s), 149.5 (s), 152.9 (s), 171.4 (s). IR: ν_{max} = 3370, 3198, 1743, 1698 cm^{-1}. MS: *m*/*z* (%) = 316 [M$^+$] (8), 286 (11), 263 (15), 251 (51), 216 (100), 184 (44), 171 (51), 158 (86), 130 (60), 110 (40). Anal. calcd for $C_{14}H_{28}N_4O_4$: C, 53.15; H, 8.92; N, 17.71. Found: C, 53.18; H, 8.81; N, 18.01.

*tert-Butyl 2-{2-[(3-Amino-2,2-dimethylpropyl)amino]-3-methoxy-1-methyl-3-oxopropylidene}hydrazinecarboxylate (**3d**).* White powder from diethyl ether; mp 116—8 °C. ^{1}H NMR (DMSO-d_6): δ = 0.88 (s, 6H), 1.51 (s, 9H), 1.81 (s, 3H), 2.20—2.27 (m, 4H), 2.47—2.49 (m, 2H), 2.63 (s, 1H), 3.73 (s, 3H), 4.01 (s, 1H), 7.57 (s, 1H). (It is impossible to obtain a good ^{13}C NMR spectrum, because of the poor stability of the compound in solution.) IR: ν_{max} = 3224, 1738, 1718, 1702, 1662 cm^{-1}. MS: *m*/*z* (%) = 330 [M$^+$] (7), 312 (10), 295 (8), 269 (13), 258 (33), 238 (34), 202 (100), 185 (32), 167 (60), 142 (64), 130 (70), 111 (75). Anal. calcd for $C_{15}H_{30}N_4O_4$: C, 55.52; H, 9.15; N, 16.96. Found: C, 55.47; H, 9.21; N, 17.01.

*tert-Butyl 2-{2-[(2-Aminobenzyl)amino]-3-ethoxy-1-methyl-3-oxopropylidene}hydrazinecarboxylate (**3e**).* White powder from ethyl acetate; mp 122—4 °C. ^{1}H NMR ($CDCl_3$): δ = 1.27 (t, *J* = 7.2 Hz, 3H), 1.52 (s, 9H), 1.78 (s, 3H), 2.27 (br s, 1H), 3.71 and 3.79 (AB-system, *J* = 12.0 Hz, 2H), 4.12 (s, 1H), 4.18—4.25 (m, 2H), 4.52 (br s, 2H), 6.64—6.69 (m, 2H), 7.01 (d, *J* = 7.2 Hz, 1H), 7.08 (t, *J* = 7.2 Hz, 1H), 7.51 (s, 1H). ^{13}C NMR ($CDCl_3$): δ = 12.3 (q), 14.1 (q), 20.2 (q), 50.4 (t), 61.4 (t), 67.0 (d), 81.2 (s), 115.6 (d), 117.7 (d), 123.0 (s), 128.5 (d), 130.3 (d), 146.5 (s), 147.2 (s), 152.3 (s), 170.7 (s). IR: ν_{max} = 3475, 3378, 3138, 1749, 1726, 1618 cm^{-1}. MS: *m*/*z* (%) = 364 [M$^+$] (1), 258 (3), 232 (19), 202 (12), 188 (8), 159 (40), 143 (17), 130 (50), 121 (65), 106 (100). Anal. calcd for $C_{18}H_{28}N_4O_4$: C, 59.32; H, 7.74; N, 15.37. Found: C, 59.28; H, 7.79; N, 15.19.

*tert-Butyl 2-{2-[(2-Aminobenzyl)amino]-3-methoxy-1-methyl-3-oxopropylidene}hydrazinecarboxylate (**3f**).* White powder from ethyl acetate; mp 120—2 °C. ^{1}H NMR (DMSO-d_6): δ = 1.44 (s, 9H), 1.78 (s, 3H), 2.59 (br s, 1H), 3.49 and 3.55 (AB-system, *J* = 12.4 Hz, 2H), 3.65 (s, 3H), 5.13 (s, 1H), 4.50 (br s, 2H), 6.48 (t, *J* = 7.6 Hz, 1H), 6.62 (d, *J* = 7.6 Hz, 1H), 6.92—6.98 (m, 2H), 9.65 (s, 1H). ^{13}C NMR (DMSO-d_6): δ = 13.4 (q), 28.1 (q), 48.8 (t), 52.0 (q), 66.3 (d), 79.3 (s), 114.7 (d), 115.8. (d), 122.3 (s), 127.9 (d), 129.7 (d), 147.3 (s), 147.4 (s), 152.9 (s), 171.4 (s). IR: ν_{max} = 3496, 3372, 3149, 1749, 1738, 1624 cm^{-1}. MS: *m*/*z* (%) = 350 [M$^+$] (3), 322 (4), 256 (6), 218 (25), 188 (18), 174 (14), 159 (31), 144 (19), 130 (63), 121 (93), 106 (100). Anal. calcd for $C_{17}H_{26}N_4O_4$: C, 58.27; H, 7.48; N, 15.99. Found: C, 58.33; H, 7.65; N, 15.73.

*Methyl N-(2-Aminobenzyl)-3-[(tert-butoxycarbonyl)hydrazono]norvalinate (**3g**).* White powder from ethyl acetate; mp 84—6 °C. ^{1}H NMR ($CDCl_3$): δ = 1.02 (t, *J* = 7.6 Hz, 3H), 1.50 (s, 9H), 1.74 (br s, 1H), 2.18—2.24 (m, 2H), 3.64—3.78 (m 2H), 3.72 (s, 3H), 4.05 (s, 1H), 4.53 (br s, 2H), 6.60—6.66 (m, 2H), 6.97—7.06 (m, 2H), 7.90 (s, 1H). ^{13}C NMR ($CDCl_3$): δ = 9.3 (q), 20.1 (t), 28.1 (q), 50.3 (t), 52.1 (q), 65.2 (d), 81.2 (s), 115.6 (d), 117.6 (d), 122.7 (s), 128.5 (d), 130.1 (d), 146.4 (s), 151.4 (s), 152.5 (s), 171.5 (s). IR: ν_{max} = 3440, 3338, 3223, 1744, 1726, 1624 cm^{-1}. MS: *m*/*z* (%) = 364 [M$^+$] (1), 233 (13), 202 (17), 188 (14), 173 (16), 158 (14), 144 (9), 130 (23), 121 (83), 106 (100). Anal. calcd for $C_{18}H_{28}N_4O_4$: C, 59.32; H, 7.74; N, 15.37. Found: C, 59.42; H, 7.89; N, 15.23.

*tert-Butyl 2-{2-[(2-Aminobenzyl)amino]-3-isopropoxy-1-methyl-3-oxopropylidene}hydrazinecarboxylate (**3h**).* White powder from ethyl acetate; mp 144—6 °C. ^{1}H NMR ($CDCl_3$): δ = 1.23 and 1.25 (2d, *J* = 6.4 Hz, 6H), 1.50 (s, 9H), 1.75 (s, 3H), 2.12 (br s, 1H), 3.69 and 3.78 (AB-system, *J* = 12.4 Hz, 2H), 4.05 (s, 1H), 4.38 (br s, 2H), 5.07 (sept, *J* = 6.4 Hz, 1H), 6.63—6.67 (m, 2H), 6.98—7.08 (m, 2H), 7.64 (2s, 1H). ^{13}C NMR ($CDCl_3$): δ = 12.3 (q), 21.6 (q), 28.1 (q), 50.3 (t), 67.1 (d), 69.1 (d), 81.2 (s), 115.6 (d), 117.7 (d), 119.8 (s), 128.5 (d), 130.3 (d), 146.5 (s), 147.2 (s), 152.4 (s), 170.2 (s). IR: ν_{max} = 3465, 3375, 3135, 1752, 1735, 1617 cm^{-1}. MS: *m*/*z* (%) = 378 [M$^+$] (1), 289 (3), 247 (10), 233 (4), 216 (11), 202 (7), 189 (4), 174 (8), 159 (24), 142 (6), 130 (20), 121 (46), 106 (100). Anal. calcd for $C_{19}H_{30}N_4O_4$: C, 60.30; H, 7.99; N, 14.80. Found: C, 60.44; H, 7.85; N, 14.93.

General Procedure for the Synthesis of 2,5,6,7-Tetrahydro-1H-1,4-diazepin-2-ones ***4a*****—*****o***. To a solution of diamines **2a**—**c** (1.0 mmol) in EtOH (2 mL) magnetically stirred at room temperature was added a solution of 1,2-diaza-1,3-dienes **1a**—**f** (1.0 mmol) in EtOH (3 mL). The disappearance of the red color of **1a**—**f** occurred within 1 min, and, at this point of the reaction, the TLC analysis revealed the presence of α-aminohydrazones **3** as major products. After 1.0—8.0 h, compounds **3** were converted into the corresponding 2,5,6,7-tetrahydro-1*H*-1,4-diazepin-2-ones **4a**—**o** that in part crystallized from the reaction medium, while the remaining part was obtained by flash chromatography (silica, 10% methanol—90% ethyl acetate as eluant). Spectroscopic data for 2,5,6,7-tetrahydro-1*H*-1,4-diazepin-2-ones **4a**—**o** are given below.

*tert-Butyl 2-[1-(2-Oxo-2,5,6,7-tetrahydro-1H-1,4-diazepin-3-yl)-ethylidene]hydrazinecarboxylate (**4a**).* White powder from ethanol; mp 248—50 °C. ^{1}H NMR (DMSO-d_6): δ = 1.41 (s, 9H), 1.81 (qi, *J* = 6.8 Hz, 2H), 2.02 (s, 3H), 2.85 (q, *J* = 6.0 Hz, 2H), 3.53 (t, *J* = 6.4 Hz, 2H),

8.19 (t, J = 6.0 Hz, 1H), 10.05 (s, 1H). ^{13}C NMR (DMSO-d_6): δ = 11.5 (q), 28.0 (q), 28.1 (t), 36.0 (t), 47.7 (t), 79.8 (s), 147.1 (s), 152.2 (s), 166.5 (s), 167.2 (s). IR: ν_{max} = 3230, 1739, 1708, 1678, 1648 cm^{-1}. MS: m/z (%) = 268 [M$^+$] (1), 212 (29), 195 (24), 167 (49), 150 (13), 139 (100), 111 (94). Anal. calcd for $C_{12}H_{20}N_4O_3$: C, 53.72; H, 7.51; N, 20.88. Found: C, 53.88; H, 7.59; N, 20.61.

*1-(2-Oxo-2,5,6,7-tetrahydro-1H-1,4-diazepin-3-yl)-1-ethanone N-Phenylsemicarbazone (**4b**).* White powder from ethanol; mp 182−4 °C. ^{1}H NMR (DMSO-d_6): δ = 1.85 (qi, J = 6.4 Hz, 2H), 2.07 (s, 3H), 2.91 (q, J = 6.0 Hz, 2H), 3.59 (t, J = 6.0 Hz, 2H), 7.03 (t, J = 7.6 Hz, 1H), 7.32 (t, J = 7.6 Hz, 2H), 7.42 (d, J = 8.4 Hz, 2H), 8.42 (t, J = 6.0 Hz, 1H), 8.57 (s, 1H), 10.28 (br s, 1H). ^{13}C NMR (DMSO-d_6): δ = 10.9 (q), 28.0 (t), 36.0 (t), 48.0 (t), 118.3 (d), 122.7 (d), 129.0 (d), 138.3 (s), 143.9 (s), 152.4 (s), 165.8 (s), 166.3 (s). IR: ν_{max} = 3362, 3255, 3183, 1697, 1668, 1612 cm^{-1}. MS: m/z (%) = 287 [M$^+$] (17), 195 (4), 167 (64), 140 (100), 111 (79). Anal. calcd for $C_{14}H_{17}N_5O_2$: C, 58.52; H, 5.96; N, 24.38. Found: C, 58.39; H, 6.09; N, 24.51.

*Benzyl 2-[1-(2-Oxo-2,5,6,7-tetrahydro-1H-1,4-diazepin-3-yl)ethylidene] hydrazinecarboxylate (**4c**).* White powder from ethanol; mp 230−2. ^{1}H NMR (DMSO-d_6): δ = 1.80 (qi, J = 6.4 Hz, 2H), 2.02 (s, 3H), 2.90 (q, J = 6.0 Hz, 2H), 3.53 (t, J = 6.4 Hz, 2H), 5.16 (s, 2H), 7.32−7.41 (m, 5H), 8.21 (t, J = 6.8 Hz, 1H), 10.43 (br s, 1H). ^{13}C NMR (DMSO-d_6): δ = 11.6 (q), 28.1 (t), 36.0 (t), 47.8 (t), 66.1 (t), 127.9 (d), 128.0 (d), 128.4 (d), 136.4 (s), 148.0 (s), 153.3 (s), 165.4 (s), 167.1 (s). IR: ν_{max} = 3398, 3229, 1740, 1711, 1685, 1646 cm^{-1}. MS: m/z (%) = 302 [M$^+$] (3), 225 (5), 211 (3), 196 (2), 167 (95), 152 (4), 139 (100), 111 (92). Anal. calcd for $C_{15}H_{18}N_4O_3$: C, 59.59; H, 6.00; N, 18.53. Found: C, 59.61; H, 6.03; N, 18.61.

*1-(2-Oxo-2,5,6,7-tetrahydro-1H-1,4-diazepin-3-yl)-1-ethanone Semicarbazone (**4d**).* White powder from ethanol; mp 233−5 °C. ^{1}H NMR (DMSO-d_6): δ = 1.82 (qi, J = 6.8 Hz, 2H), 1.99 (s, 3H), 2.87 (q, J = 6.4 Hz, 2H), 3.54 (t, J = 6.4 Hz, 2H), 5.82 and 6.51 (2br s, 2H), 8.23 (t, J = 6.4 Hz, 1H), 9.89 (s, 1H). ^{13}C NMR (DMSO-d_6): δ = 10.8 (q), 28.0 (t), 36.0 (t), 47.8 (t), 142.8 (s), 156.3 (s), 165.8 (s), 166.6 (s). IR: ν_{max} = 3460, 3192, 1718, 1704, 1683, 1635 cm^{-1}. MS: m/z (%) = 211 [M$^+$] (1), 167 (83), 151 (44), 139 (85), 111 (100). Anal. calcd for $C_8H_{13}N_5O_2$: C, 45.49; H, 6.20; N, 33.16. Found: C, 45.38; H, 6.39; N, 33.01.

*1-(2-Oxo-2,5,6,7-tetrahydro-1H-1,4-diazepin-3-yl)-1-propanone Semicarbazone (**4e**).* White powder from ethanol; mp 196−8 °C. ^{1}H NMR (DMSO-d_6): δ = 0.90 (t, J = 7.6 Hz, 3H), 1.80 (qi, J = 6.4 Hz, 2H), 2.58 (q, J = 7.6 Hz, 2H), 2.84 (q, J = 6.4 Hz, 2H), 3.53 (t, J = 6.4 Hz, 2H), 5.86 and 6.56 (2br s, 2H), 8.20 (t, J = 6.4 Hz, 1H), 10.02 (s, 1H). ^{13}C NMR (DMSO-d_6): δ = 10.0 (q), 16.8 (t), 28.0 (t), 36.1 (t), 47.8 (t), 146.9 (s), 156.4 (s), 165.8 (s), 165.9 (s). IR: ν_{max} = 3463, 3201, 1708, 1687, 1654 cm^{-1}. MS: m/z (%) = 225 [M$^+$] (1), 181 (81), 164 (21), 153 (45), 110 (100). Anal. calcd for $C_9H_{15}N_5O_2$: C, 47.99; H, 6.71; N, 31.09. Found: C, 48.03; H, 6.79; N, 31.11.

*1-(6-Methyl-2-oxo-2,5,6,7-tetrahydro-1H-1,4-diazepin-3-yl)-1-ethanone N-Phenylsemicarbazone (**4f**).* Pink powder from ethanol; mp 178−80 °C. ^{1}H NMR (DMSO-d_6): δ = 0.91 (d, J = 7.2 Hz, 3H), 2.06 (s, 3H), 2.15 (sex., J = 6.0 Hz, 1H), 2.61 (dt, J = 14.8 Hz, J = 5.6 Hz, 1H), 2.98 (dt, J = 14.8 Hz, J = 5.6 Hz, 1H), 3.20 (dd, J = 9.0 Hz, J = 8.4 Hz, 1H), 3.70 (dd, J = 10.2 Hz, J = 6.0 Hz, 1H), 7.03 (t, J = 7.6 Hz, 1H), 7.32 (t, J = 8.4 Hz, 2H), 7.42 (d, J = 8.4 Hz, 2H), 8.53 (t, J = 6.0 Hz, 1H), 8.59 (s, 1H), 10.04 (br s, 1H). ^{13}C NMR (DMSO-d_6): δ = 11.0 (q), 16.5 (q), 34.6 (d), 42.9 (t), 55.0 (t), 118.3 (d), 122.7 (d), 129.0 (d), 138.4 (s), 144.0 (s), 152.4 (s), 165.8 (s), 169.3 (s). IR: ν_{max} = 3451, 3327, 3195, 3066, 1705, 1654 cm^{-1}. MS: m/z (%) = 301 [M$^+$] (23), 209 (6), 181 (63), 167 (11), 154 (100), 139 (22), 125 (69), 111 (57). Anal. calcd for $C_{15}H_{19}N_5O_2$: C, 59.79; H, 6.36; N, 23.24. Found: C, 59.89; H, 6.49; N, 23.11.

*tert-Butyl 2-[1-(6-Methyl-2-oxo-2,5,6,7-tetrahydro-1H-1,4-diazepin-3-yl)ethylidene]hydrazinecarboxylate (**4g**).* Pink powder from ethanol; mp 242−4 °C. ^{1}H NMR (DMSO-d_6): δ = 0.87 (d, J = 6.8 Hz, 3H), 1.44 (s, 9H), 1.98 (s, 3H), 2.13 (sex., J = 5.6 Hz, 1H), 2.54 (dt, J = 14.4 Hz, J = 4.8 Hz, 1H), 2.89 (dt, J = 14.4 Hz, J = 6.0 Hz, 1H), 3.11 (dd, J = 10.8 Hz, J = 7.2 Hz, 1H), 3.62 (dd, J = 10.4 Hz, J = 5.6 Hz, 1H), 8.32 (t, J = 6.0 Hz, 1H), 10.06 (s, 1H). ^{13}C NMR (DMSO-d_6): δ = 11.5 (q), 16.4 (q), 28.0 (q), 34.6 (d), 42.8 (t), 54.8 (t), 79.9 (s), 147.1 (s), 152.2 (s), 165.5 (s), 167.3 (s). IR: ν_{max} = 3397, 3240, 1746, 1723,1685, 1651 cm^{-1}. MS: m/z (%) = 283 [M$^+$] (1), 267 (3), 226 (25), 209 (20), 181 (45), 153 (100), 139 (19), 125 (49), 110 (35). Anal. calcd for $C_{13}H_{22}N_4O_3$: C, 55.30; H, 7.85; N, 19.84. Found: C, 55.18; H, 7.99; N, 19.66.

*Benzyl 2-[1-(6-Methyl-2-oxo-2,5,6,7-tetrahydro-1H-1,4-diazepin-3-yl)-ethylidene]hydrazinecarboxylate (**4h**).* White powder from ethanol; mp 110−2 °C. ^{1}H NMR (DMSO-d_6): δ = 0.89 (d, J = 6.8 Hz, 3H), 2.02 (s, 3H), 2.14 (sex., J = 5.6 Hz, 1H), 2.48−2.61 (m, 1H), 2.92 (dt, J = 14.4 Hz, J = 7.6 Hz, 1H), 3.15 (dd, J = 8.8 Hz, J = 8.0 Hz, 1H), 3.65 (dd, J = 10.6 Hz, J = 6.4 Hz, 1H), 5.18 (s, 2H), 7.33−7.40 (m, 5H), 8.36 (t, J = 6.8 Hz, 1H), 10.47 (br s, 1H). ^{13}C NMR (DMSO-d_6): δ = 11.6 (q), 16.4 (q), 34.6 (d), 42.8 (t), 54.8 (t), 66.1 (t), 127.9 (d), 128.0 (d), 128.4 (d), 136.4 (s), 148.1 (s), 153.3 (s), 165.4 (s), 167.1 (s). IR: ν_{max} = 3390, 3221, 1744, 1717, 1682, 1645 cm^{-1}. MS: m/z (%) = 316 [M$^+$] (1), 239 (9), 224 (20), 196 (56), 183 (12), 167 (75), 151 (19), 139 (31), 126 (35), 108 (100). Anal. calcd for $C_{16}H_{20}N_4O_3$: C, 60.75; H, 6.37; N, 17.71. Found: C, 60.64; H, 6.43; N, 17.65.

*1-(6-Methyl-2-oxo-2,5,6,7-tetrahydro-1H-1,4-diazepin-3-yl)-1-ethanone Semicarbazone (**4i**).* Pink powder from ethanol; mp 148−50 °C. ^{1}H NMR (DMSO-d_6): δ = 0.89 (d, J = 6.8 Hz, 3H), 1.99 (s, 3H), 2.15 (sex., J = 5.2 Hz, 1H), 2.56 (dt, J = 14.8 Hz, J = 4.4 Hz, 1H), 2.92 (dt, J = 14.8 Hz, J = 8.0 Hz, 1H), 3.14 (dd, J = 8.4 Hz, J = 8.0 Hz, 1H), 3.65 (dd, J = 10.6 Hz, J = 6.0 Hz, 1H), 5.92 and 6.66 (2br s, 2H), 8.35 (t, J = 6.0 Hz, 1H), 9.90 (s, 1H). ^{13}C NMR (DMSO-d_6): δ = 10.8 (q), 16.5 (q), 34.6 (d), 42.9 (t), 54.9 (t), 142.9 (s), 156.4 (s), 165.8 (s), 166.7 (s). IR: ν_{max} = 3451, 3193, 1725, 1705, 1694, 1655 cm^{-1}. MS: m/z (%) = 225 [M$^+$] (1), 209 (2), 181 (68), 165 (4), 153 (100), 139 (6), 125 (43), 110 (14). Anal. calcd for $C_9H_{15}N_5O_2$: C, 47.99; H, 6.71; N, 31.09. Found: C, 48.08; H, 6.79; N, 31.16.

*1-(6-Methyl-2-oxo-2,5,6,7-tetrahydro-1H-1,4-diazepin-3-yl)-1-propanone Semicarbazone (**4j**).* Pink powder from ethanol; mp 190−2 °C. ^{1}H NMR (DMSO-d_6): δ = 0.89 (d, J = 8.4 Hz, 3H), 1.03 (t, J = 7.2 Hz, 3H), 2.16 (sex., J = 6.0 Hz, 1H), 2.48−2.61 (m, 3H), 2.92 (dt, J = 14.8 Hz, J = 7.2 Hz, 1H), 3.18 (dd, J = 9.0 Hz, J = 9.2 Hz, 1H), 3.62 (dd, J = 8.0 Hz, J = 6.0 Hz, 1H), 5.90 and 6.63 (2br s, 2H), 8.33 (t, J = 5.6 Hz, 1H), 10.05 (s, 1H). ^{13}C NMR (DMSO-d_6): δ = 10.0 (q), 16.4 (q), 16.9 (t), 34.6 (d), 43.0 (t), 54.9 (t), 146.9 (s), 156.4 (s), 165.8 (s), 165.9 (s). IR: ν_{max} = 3399, 3191, 1703, 1687 cm^{-1}. MS: m/z (%) = 240 [M$^+$] (1), 224 (4), 195 (24), 179 (42), 164 (37), 149 (23), 138 (32), 126 (78), 111 (100). Anal. calcd for $C_{10}H_{17}N_5O_2$: C, 50.20; H, 7.16; N, 29.27. Found: C, 50.33; H, 7.09; N, 29.44.

*1-(6,6-Dimethyl-2-oxo-2,5,6,7-tetrahydro-1H-1,4-diazepin-3-yl)-1-ethanone N-Phenylsemicarbazone (**4k**).* Pink powder from ethanol; mp 216−8 °C. ^{1}H NMR (DMSO-d_6): δ = 0.91 (s, 6H), 2.04 (s, 3H), 2.58 (d, J = 6.0 Hz, 2H), 3.28 (s, 2H), 7.01 (t, J = 7.2 Hz, 1H), 7.30 (t, J = 7.2 Hz, 2H), 7.40 (d, J = 7.6 Hz, 2H), 8.57 (s, 1H), 8.65 (t, J = 6.0 Hz, 1H), 10.38 (br s, 1H). ^{13}C NMR (DMSO-d_6): δ = 10.9 (q), 24.4 (q), 39.9 (s), 48.5 (t), 60.4 (t), 118.3 (d), 122.7 (d), 128.9 (d), 138.4 (s), 144.0 (s), 152.4 (s), 165.6 (s), 166.4 (s). IR: ν_{max} = 3325, 3196, 3086, 1702, 1662, 1599 cm^{-1}. MS: m/z (%) = 315 [M$^+$] (17), 285 (1), 223 (5), 195 (43), 176 (15), 167 (100), 153 (11), 139 (29), 119 (32), 110 (30). Anal. calcd for $C_{16}H_{21}N_5O_2$: C, 60.94; H, 6.71; N, 22.21. Found: C, 61.02; H, 6.85; N, 22.43.

*tert-Butyl 2-[1-(6,6-Dimethyl-2-oxo-2,5,6,7-tetrahydro-1H-1,4-diazepin-3-yl)ethylidene]hydrazinecarboxylate (**4l**).* Pink powder from ethanol; mp 220−4 °C. ^{1}H NMR (DMSO-d_6): δ = 0.88 (s, 6H), 1.44 (s, 9H), 1.98 (s, 3H), 2.52 (d, J = 6.4 Hz, 2H), 3.22 (s, 2H), 8.45 (t, J = 6.0 Hz, 1H), 10.06 (s, 1H). ^{13}C NMR (DMSO-d_6): δ = 11.5 (q), 24.4

(q), 28.0 (q), 39.9 (s), 48.5 (t), 60.1 (t), 79.8 (s), 147.2 (s), 152.2 (s), 165.4 (s), 167.3 (s). IR: ν_{max} = 3255, 1746, 1720,1688, 1651 cm^{-1}. MS: m/z (%) = 296 [M$^+$] (1), 281 (2), 240 (19), 223 (18), 195 (31), 179 (6), 167 (100), 153 (18), 139 (35), 124 (20), 110 (45). Anal. calcd for $C_{14}H_{24}N_4O_3$: C, 56.74; H, 8.16; N, 18.90. Found: C, 56.88; H, 8.23; N, 18.66.

*Benzyl 2-[1-(6,6-Dimethyl-2-oxo-2,5,6,7-tetrahydro-1H-1,4-diazepin-3-yl)ethylidene]hydrazinecarboxylate (**4m**).* Pink powder from ethanol; mp 90−2 °C. ^{1}H NMR (DMSO-d_6): δ = 0.90 (s, 6H), 2.03 (s, 3H), 2.55 (d, J = 6.0 Hz, 2H), 3.25 (s, 2H), 5.19 (s, 2H), 7.33−7.42 (m, 5H), 8.51 (t, J = 6.0 Hz, 1H), 10.48 (br s, 1H). ^{13}C NMR (DMSO-d_6): δ = 11.7 (q), 24.5 (q), 39.9 (s), 48.6 (t), 60.2 (t), 66.2 (t), 128.0 (d), 128.1 (d), 128.5 (d), 136.4 (s), 148.2 (s), 153.5 (s), 165.4 (s), 167.2 (s). IR: ν_{max} = 3399, 3223, 1749, 1717, 1690 cm^{-1}. MS: m/z (%) = 330 [M$^+$] (1), 239 (6), 206 (19), 191 (100), 128 (19), 108 (49). Anal. calcd for $C_{17}H_{22}N_4O_3$: C, 61.80; H, 6.71; N, 16.96. Found: C, 61.69; H, 6.55; N, 17.02.

*1-(6,6-Dimethyl-2-oxo-2,5,6,7-tetrahydro-1H-1,4-diazepin-3-yl)-1-ethanone Semicarbazone (**4n**).* Scarlet powder from ethanol; mp 208−10 °C. ^{1}H NMR (DMSO-d_6): δ = 0.91 (s, 6H), 1.99 (s, 3H), 2.55 (d, J = 6.4 Hz, 2H), 3.25 (s, 2H), 5.92 and 6.67 (2br s, 2H), 8.49 (t, J = 6.0 Hz, 1H), 9.88 (br s, 1H). ^{13}C NMR (DMSO-d_6): δ = 10.8 (q), 24.5 (q), 39.8 (s), 48.5 (t), 60.2 (t), 142.9 (s), 156.3 (s), 165.6 (s), 166.7 (s). IR: ν_{max} = 3450, 3294, 3204, 1690, 1655 cm^{-1}. MS: m/z (%) = 240 [M$^+$] (1), 224 (3), 209 (3), 195 (54), 178 (10), 167 (100), 153 (8), 139 (21), 124 (19), 113 (48). Anal. calcd for $C_{10}H_{17}N_5O_2$: C, 50.20; H, 7.16; N, 29.27. Found: C, 50.29; H, 7.19; N, 29.46.

*1-(6,6-Dimethyl-2-oxo-2,5,6,7-tetrahydro-1H-1,4-diazepin-3-yl)-1-propanone Semicarbazone (**4o**).* Scarlet powder from ethanol; mp 176−8 °C. ^{1}H NMR (DMSO-d_6): δ = 0.89 (s, 6H), 0.92 (t, J = 7.2 Hz, 3H), 2.45−2.59 (m, 4H), 3.23 (s, 2H), 5.88 and 6.62 (2br s, 2H), 8.45 (t, J = 6.4 Hz, 1H), 10.05 (s, 1H). ^{13}C NMR (DMSO-d_6): δ = 10.1 (q), 16.9 (t), 24.4 (q), 39.8 (s), 48.5 (t), 60.2 (t), 146.9 (s), 156.4 (s), 165.9 (s), 166.1 (s). IR: ν_{max} = 3432, 3203, 3159, 1711, 1664, 1596 cm^{-1}. MS: m/z (%) = 253 [M$^+$] (1), 209 (91), 181 (100), 167 (23), 153 (32), 139 (19), 110 (92). Anal. calcd for $C_{11}H_{19}N_5O_2$: C, 52.16; H, 7.56; N, 27.65. Found: C, 52.27; H, 7.48; N, 27.49.

*General Procedure for the Synthesis of Alkyl 5H-1,4-Benzodiazepine-3-carboxylates **5a**−**d**.* A solution of α-aminohydrazones **3e**−**h** (1.0 mmol) in toluene (5 mL) was refluxed for 3.0−5.0 h, until the corresponding alkyl 5*H*-1,4-benzodiazepine-3-carboxylates **5a**−**d** were formed. After flash chromatography (silica, 10% ethyl acetate− 90% cyclohexane as eluant), compounds **5a**−**c** were obtained as oils, while **5d** was crystallized from cyclohexane−ethyl acetate. Spectroscopic data for alkyl 5*H*-1,4-benzodiazepine-3-carboxylates **5a**−**d** are given below.

*Ethyl 2-Methyl-5H-1,4-benzodiazepine-3-carboxylate (**5a**).* Red oil. ^{1}H NMR ($CDCl_3$): δ = 1.34 (t, J = 7.2 Hz, 3H), 2.54 (s, 3H), 4.30 (q, J = 7.2 Hz, 2H), 4.63 (br s, 2H), 7.22−7.39 (m, 4H). ^{13}C NMR ($CDCl_3$): δ = 14.0 (q), 25.6 (q), 54.5 (t), 62.4 (t), 125.7 (d), 127.1 (d), 128.1 (d), 128.8 (s), 128.9 (d), 146.8 (s), 154.9 (s), 162.6 (s), 163.2 (s). IR: ν_{max} = 1731, 1633 cm^{-1}. ESI$^+$: m/z = 231 [M + H]$^+$. Anal. calcd for $C_{13}H_{14}N_2O_2$: C, 67.81; H, 6.13; N, 12.17. Found: C, 67.98; H, 6.29; N, 12.01.

*Methyl 2-Methyl-5H-1,4-benzodiazepine-3-carboxylate (**5b**).* Orange oil. ^{1}H NMR ($CDCl_3$): δ = 2.43 (s, 3H), 3.72 (s, 3H), 4.62 (br s, 2H), 7.12−7.27 (m, 4H). ^{13}C NMR ($CDCl_3$): δ = 25.6 (q), 53.0 (q), 54.5 (t), 125.6 (d), 127.1 (d), 128.0 (d), 128.6 (s), 128.9 (d), 146.7 (s), 154.3 (s), 162.9 (s), 163.1 (s). IR: ν_{max} = 1749, 1729, 1640 cm^{-1}. ESI$^+$: m/z = 217 [M + H]$^+$. Anal. calcd for $C_{12}H_{12}N_2O_2$: C, 66.65; H, 5.59; N, 12.96. Found: C, 66.88; H, 5.33; N, 13.02.

*Methyl 2-Ethyl-5H-1,4-benzodiazepine-3-carboxylate (**5c**).* Orange oil. ^{1}H NMR ($CDCl_3$): δ = 1.27 (t, J = 7.2 Hz, 3H), 2.88 (q, J = 7.6 Hz, 2H), 3.85 (s, 3H), 4.82 (br s, 2H), 7.25−7.41 (m, 4H). ^{13}C NMR ($CDCl_3$): δ = 11.1 (q), 31.5 (t), 53.1 (q), 54.6 (t), 125.7 (d), 127.0 (d), 128.1 (d), 128.8 (s), 129.0 (d), 147.9 (s), 154.5 (s), 163.1 (s), 168.0 (s). IR: ν_{max} = 1752, 1738, 1640 cm^{-1}. MS: m/z (%) = 230 [M$^+$] (34), 191 (4), 171 (6), 145 (30), 130 (100), 117 (33). Anal. calcd for $C_{13}H_{14}N_2O_2$: C, 67.81; H, 6.13; N, 12.17. Found: C, 67.66; H, 6.28; N, 12.31.

*Isopropyl 2-Methyl-5H-1,4-benzodiazepine-3-carboxylate (**5d**).* Yellow powder from cyclohexane−ethyl acetate; mp 112−4 °C. ^{1}H NMR ($CDCl_3$): δ = 1.28 (d, J = 6.0 Hz, 6H), 2.48 (s, 3H), 4.25 (br s, 2H), 5.1 (sept, J = 6.4 Hz, 1H), 7.20−7.36 (m, 4H). ^{13}C NMR ($CDCl_3$): δ = 21.4 (q), 25.4 (q), 54.3 (t), 70.2 (d), 125.6 (d), 126.9 (d), 128.0 (d), 128.7 (s), 128.8 (d), 146.7 (s), 155.2 (s), 162.1 (s), 163.1 (s). IR: ν_{max} = 1724, 1645, 1605 cm^{-1}. MS: m/z (%) = 244 [M$^+$] (37), 229 (4), 202 (11), 186 (16), 157 (26), 130 (100), 116 (19), 103 (10). Anal. calcd for $C_{14}H_{16}N_2O_2$: C, 68.83; H, 6.60; N, 11.47. Found: C, 68.99; H, 6.49; N, 11.51.

*General Procedure for the Synthesis of 4-[(3-Aminopropyl)-(methyl)amino]-1H-pyrazol-3-ones **6a**−**d**.* To a solution of *N*-methyl-1,3-diaminopropane **2e** (1.0 mmol) in dichloromethane (2 mL) magnetically stirred at room temperature was added a solution of 1,2-diaza-1,3-dienes **1a**,**b**,**g**,**i** (1.0 mmol) in dichloromethane (3 mL). The disappearance of the red color of **1a**,**b**,**g**,**i** occurred within 0.1−0.2 h and products **6a**−**d** directly crystallized from the reaction solvent. Spectroscopic data for 4-[(3-aminopropyl)(methyl)amino]-1*H*-pyrazol-3-ones **6a**−**d** are given below.

*tert-Butyl 4-[(3-Aminopropyl)(methyl)amino]-3-methyl-5-oxo-2,5-dihydro-1H-pyrazole-1-carboxylate (**6a**).* Pink powder from dichloromethane; mp 95−7 °C. ^{1}H NMR ($CDCl_3$): δ = 1.49−1.57 (m, 4H), 1.61 (s, 9H), 2.16 (s, 3H), 2.52 (s, 3H), 2.77−2.83 (m, 2H), 2.85−2.92 (m, 2H), 8.94 (br s, 1H). ^{13}C NMR ($CDCl_3$): δ = 15.8 (q), 24.1 (t), 38.0 (t), 40.7 (t), 54.7 (q), 82.5 (s), 113.0 (s), 150.6 (s), 150.7 (s), 160.4 (s). IR: ν_{max} = 3443, 3219, 1732, 1648 cm^{-1}. MS: m/z (%) = 284 [M$^+$] (1), 256 (4), 226 (6), 211 (8), 184 (32), 167 (15), 153 (18), 140 (100), 126 (64), 111 (29). Anal. calcd for $C_{13}H_{24}N_4O_3$: C, 54.91; H, 8.51; N, 19.70. Found: C, 54.88; H, 8.59; N, 19.81.

*4-[(3-Aminopropyl)(methyl)amino]-3-methyl-5-oxo-N-phenyl-2,5-dihydro-1H-pyrazole-1-carboxamide (**6b**).* Pink powder from dichloromethane; mp 132−4 °C. ^{1}H NMR (DMSO-d_6): δ = 1.58−1.61 (m, 2H), 2.00 (s, 3H), 2.04 and 2.31 (2br s, 2H), 2.61 (s, 3H), 2.63−2.93 (m, 4H), 6.99 (t, J = 7.6 Hz, 1H), 7.28 (t, J = 8.0 Hz, 2H), 7.48 (d, J = 8.0 Hz, 2H), 8.03 (br s, 1H), 12.66 (s, 1H). ^{13}C NMR (DMSO-d_6): δ = 16.3 (q), 25.1 (t), 38.3 (t), 43.1 (t), 54.5 (q), 108.4 (s), 118.8 (d), 122.2 (d), 128.9 (d), 139.2 (s), 148.3 (s), 149.8 (s), 160.1 (s). IR: ν_{max} = 3338, 3184, 1725, 1690, 1662, 1599 cm^{-1}. MS: m/z (%) = 303 [M$^+$] (2), 277 (9), 234 (7), 221 (14), 210 (26), 188 (53), 176 (37), 166 (23), 151 (22), 140 (70), 119 (100), 111 (62). Anal. calcd for $C_{15}H_{21}N_5O_2$: C, 59.39; H, 6.98; N, 23.09. Found: C, 59.48; H, 6.89; N, 23.01.

*tert-Butyl 4-[(3-Aminopropyl)(methyl)amino]-3-ethyl-5-oxo-2,5-dihydro-1H-pyrazole-1-carboxylate (**6c**).* Pink powder from dichloromethane; mp 128−30 °C. ^{1}H NMR ($CDCl_3$): δ = 1.17 (t, J = 7.2 Hz, 3H), 1.42 (br s, 2H), 1.48−1.50 (m, 2H), 1.62 (s, 9H), 2.50−2.55 (m, 5H), 2.61−2.82 (m, 2H), 2.87−2.94 (m, 2H), 8.96 (br s, 1H). ^{13}C NMR ($CDCl_3$): δ = 13.6 (q), 22.7 (t), 26.9 (t), 37.4 (t), 39.5 (t), 53.9 (q), 82.2 (s), 112.3 (s), 150.8 (s), 155.8 (s), 160.3 (s). IR: ν_{max} = 3316, 3186, 1729, 1638 cm^{-1}. MS: m/z (%) = 298 [M$^+$] (3), 267 (8), 235 (30), 197 (19), 180 (24), 168 (29), 134 (42), 128 (49), 115 (100). Anal. calcd for $C_{14}H_{26}N_4O_3$: C, 56.35; H, 8.78; N, 18.78. Found: C, 56.42; H, 8.69; N, 18.66.

*Methyl 4-[(3-Aminopropyl)(methyl)amino]-3-methyl-5-oxo-2,5-dihydro-1H-pyrazole-1-carboxylate (**6d**).* Pink powder from dichloromethane; mp 150−2 °C. ^{1}H NMR ($CDCl_3$): δ = 1.52−1.64 (m, 4H), 2.19 (s, 3H), 2.59 (s, 3H), 2.89−2.96 (m, 4H), 3.89 (s, 3H), 8.69 (br s, 1H). ^{13}C NMR ($CDCl_3$): δ = 15.2 (q), 24.2 (t), 38.9 (t), 41.5 (t), 53.0 (q), 55.7 (q), 112.3 (s), 151.5 (s), 151.6 (s), 160.4 (s). IR: ν_{max} = 3450, 3282, 1739, 1648 cm^{-1}. MS: m/z (%) = 242 [M$^+$] (21), 211 (29), 198

(36), 184 (10), 166 (21), 154 (7), 140 (100), 111 (19). Anal. calcd for $C_{10}H_{18}N_4O_3$: C, 49.57; H, 7.49; N, 23.13. Found: C, 49.48; H, 7.53; N, 23.25.

General Procedure for the Synthesis of Bis-α-aminohydrazones ***7a,b***. To a solution of 1,2-diaza-1,3-dienes **1a,b** (2.0 mmol) in acetonitrile (3 mL) magnetically stirred at room temperature, a solution of *N,N′*-dimethyl-1,3-diaminopropane **2f** (1 mmol) in acetonitrile (2 mL) was added. At the disappearance of the red color of **1a,b** that occurred within 5 min, products **7a,b** were obtained simply by evaporation of the reaction solvent; **7a** was obtained as yellow oil, while **7b** was crystallized from diethyl ether−petroleum ether (bp 40−60 °C). Spectroscopic data for bis-α-aminohydrazones **7a,b** are given below.

*Di-tert-Butyl 5,11-Bis(ethoxycarbonyl)-4,6,10,12-tetramethyl-2,3,6,10,13,14-hexaazapentadeca-3,12-diene-1,15-dioate (**7a**).* Yellow oil. ^{1}H NMR ($CDCl_3$): δ = 1.24 (t, J = 7.2 Hz, 6H), 1.47 (s, 18H), 1.60−1.64 (m, 2H), 1.85 (s, 6H), 2.25 (s, 6H), 2.39−2.45 (m, 4H), 3.90 (s, 2H), 4.12−4.19 (m, 4H), 7.63 (br s, 2H). ^{13}C NMR ($CDCl_3$): δ = 12.2 (q), 13.8 (q), 27.8 (q), 38.4 (t), 51.8 (t), 53.2 (t), 60.2 (q), 73.7 (d), 80.5 (s), 148.0 (s), 152.3 (s), 169.8 (s). IR: ν_{max} = 3390, 3205, 1740, 1685 cm^{-1}. MS: m/z (%) = 586 [M$^+$] (6), 513 (3), 343 (12), 312 (24), 286 (40), 274 (32), 244 (13), 213 (100). Anal. calcd for $C_{27}H_{50}N_6O_8$: C, 55.27; H, 8.59; N, 14.32. Found: C, 55.38; H, 8.69; N, 14.21.

*Dimethyl 1,15-Dianilino-4,6,10,12-tetramethyl-1,15-dioxo-2,3,6,10,13,14-hexaazapentadeca-3,12-diene-5,11-dicarboxylate (**7b**).* Yellow powder from diethyl ether−light petroleum (bp 40−60 °C); mp 68−70 °C. ^{1}H NMR ($CDCl_3$): δ = 1.65−1.69 (m, 2H), 2.00 (s, 6H), 2.34 (s, 6H), 2.54−2.63 (m, 4H), 3.74 (s, 6H), 4.00 (s, 2H), 7.02−7.04 (m, 2H), 7.25−7.31 (m, 4H), 7.43−7.47 (m, 4H), 8.06 (s, 2H), 8.95 (br s, 2H). ^{13}C NMR ($CDCl_3$): δ = 13.5 (q), 38.5 (t), 50.1 (t), 51.5 (t), 51.9 (q), 73.7 (d), 119.1 (d), 123.3 (d), 128.9 (d), 137.9 (s), 146.7 (s), 153.5 (s), 170.6 (s). IR: ν_{max} = 3368, 3193, 1742, 1690, 1651 cm^{-1}. MS: m/z (%) = 596 [M$^+$] (1), 356 (4), 326 (3), 294 (100). Anal. calcd for $C_{29}H_{40}N_8O_6$: C, 58.37; H, 6.76; N, 18.78. Found: C, 58.58; H, 6.89; N, 18.95.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information. Figures giving ^{1}H NMR and ^{13}C NMR spectral data for compounds **3a−h**, **4a−o**, **5a−d**, **6a−d**, and **7a,b**. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: lucia.decrescentini@uniurb.it.

■ ACKNOWLEDGMENT

This work was supported by the financial assistance from the Ministero dell'Istruzione, dell'Università e della Ricerca (MIUR)-Roma (PRIN 2007), and Università degli Studi di Urbino.

■ REFERENCES

(1) Horton, D. A.; Boune, G. T.; Smythe, M. L. *Chem. Rev.* **2003**, *103*, 893–930.

(2) Evans, B. E.; Rittle, K. E.; Block, M. G.; DiPardo, R. M.; Freidinger, R. M.; Whitter, W. L.; Lundell, G. F.; Veber, D. F.; Anderson, P. S.; Chang, R. S. L.; Lotti, V. J.; Cerino, D. J.; Chen, T. B.; Kling, P. J.; Kunkel, K. A.; Springer, J. P.; Hirshfield, J. *J. Med. Chem.* **1988**, *31*, 2235–2246.

(3) Costantino, L.; Barlocco, D. *Curr. Med. Chem.* **2006**, *13*, 65–85.

(4) (a) Berezhnoy, D.; Gibbs, T. T.; Farb, D. H. *Mol. Pharmacol.* **2009**, *76*, 440–450. (b) Kadriu, B.; Guidotti, A.; Costa, E.; John, M.; Auta, J. *Toxicol. Sci.* **2011**, *120*, 136–145. (c) Bianchi, M. T. *Curr. Neuropharmacol.* **2010**, *8*, 10–17. (d) Alhambra, C.; Becker, C.; Blake, T.; Chang, A. (H.-F.); Damewood, J. R., Jr.; Daniels, T.; Dembofsky, B. T.; Gurley, D. A.; Hall, J. E.; Herzog, K. J.; Horchler, C. L.; Ohnmacht, C. J.; Schmiesing, R. J.; Dudley, A.; Ribadeneira, M.; Knappenberger, K. S.; Maciag, C.; Stein, M. M.; Chopra, M.; Liu, X. F.; Christian, E. P.; Arriza, J. L.; Chapdelaine, M. J. *Bioorg. Med. Chem.* **2011**, *19*, 2927–2938.

(5) (a) Johnston, S. R. D. *Drugs* **2003**, *6*, 72–78. (b) Rahman, K. M.; Vassoler, H.; James, C. H.; Thurston, D. E. *Med. Chem. Lett.* **2010**, *1*, 29–39.

(6) Weitz, I. S.; Pellegrini, M.; Mierke, D. F.; Chorev, M. *J. Org. Chem.* **1997**, *62*, 2527–2534.

(7) Ramanathan, S. K.; Keeler, J.; Lee, H.-L.; Reddy, D. S.; Lushington, G.; Aubé, J. *Org. Lett.* **2005**, *7*, 1059–1062.

(8) Iden, H.; Lubell, W. D. *Org. Lett.* **2006**, *8*, 3425–3428.

(9) Kesheva Murthy, K. S.; Knaus, E. E. *Drug Dev. Res.* **1999**, *46*, 155–162.

(10) Hirano, S.; Ichikawa, S.; Matsuda, A. *J. Org. Chem.* **2008**, *73*, 569–577.

(11) Isono, K. *J. Antibiot.* **1988**, *41*, 1711–1739 .

(12) (a) Wattanasin, S.; Albert, R.; Ehrhardt, C.; Roche, D.; Sabio, M.; Hommel, U.; Welzenbach, K.; Weitz-Schmidt, G. *Biorg. Med. Chem. Lett.* **2003**, *13*, 499–502. (b) Wattanasin, S.; Kallen, J.; Myers, S.; Guo, Q.; Sabio, M.; Ehrhardt, C.; Albert, R.; Hommel, U.; Welzenbach, K.; Weitz-Schmidt, G. *Biorg. Med. Chem. Lett.* **2005**, *15*, 1217–1220.

(13) (a) Nadin, A.; Sanchez Lopez, J. M.; Owens, A. P.; Howells, D. M.; Talbot, A. C.; Harrison, T. *J. Org. Chem.* **2003**, *68*, 2844–2852. (b) Marcaccini, S.; Miliciani, M.; Pepino, R. *Tetrahedron Lett.* **2005**, *46*, 711–713.

(14) Ho, W.; Kukla, M. J.; Breslin, H. J.; Ludovici, D. W.; Grous, P. P.; Diamond, C. J.; Miranda, M.; Rodgers, J. D.; Ho, C. Y.; De Clercq, E.; Pauwels, R.; Andries, K.; Janssen, M. A. C.; Janssen, P. A. J. *J. Med. Chem.* **1995**, *38*, 771–793.

(15) (a) Katritzky, A. R.; Xu, Y.-J.; He, H.-Y. *J. Chem. Soc., Perkin Trans. 1* **2002**, 592–598. (b) Welmaker, G. S.; Sebalski, J. E. *Tetrahedron Lett.* **2004**, *45*, 4851–4854.

(16) Nakajima, N.; Isobe, T.; Irisa, S.; Ubukata, M. *Heterocycles* **2003**, *59*, 107–113.

(17) Iden, H. S.; Lubell, W. D. *J. Org. Chem.* **2007**, *72*, 8980–8983.

(18) Iden, H. S.; Lubell, W. D. *J. Comb. Chem.* **2008**, *10*, 691–699.

(19) Van Berkom, L. W. A.; De Gelder, R.; Sheeren, H. W. *Eur. J. Org. Chem.* **2005**, *S*, 907–917.

(20) Gravier-Pelletier, C.; Charvet, I.; Le Merrer, Y.; Depezay, J. C. *J. Carbohydr. Chem.* **1997**, *16*, 129–141.

(21) Balsells, J.; Waters, M.; Hansen, K.; Kieczykowski, G. R.; Song, Z. J. *Synthesis* **2007**, *18*, 2779–2781.

(22) Alajarín, M.; Vidal, A.; Tovar, F. *Tetrahedron* **2005**, *61*, 1531–1537.

(23) Vokv, M. V.; Golovach, N. M.; Sukach, V. A.; Chernyuk, O. N.; Manoilenko, O. V. *Russ. J. Org. Chem.* **2010**, *46*, 480–484.

(24) For reviews on the chemistry of 1,2-diaza-1,3-dienes, see: (a) Attanasi, O. A.; De Crescentini, L.; Filippone, P.; Mantellini, F.; Santeusanio, S. *Arkivoc* **2002**, *xi*, 274–292. (b) Attanasi, O. A.; De Crescentini, L.; Favi, G.; Filippone, P.; Mantellini, F.; Perrulli, F. R.; Santeusanio, S. *Eur. J. Org. Chem.* **2009**, 3109–3127.

(25) For the electrophilicity parameters E of DDs, see: Kanzian, T.; Nicolini, S.; De Crescentini, L.; Attanasi, O. A.; Ofial, A. R.; Mayr, H. *Chem.—Eur. J.* **2010**, *16*, 12008−12016 and references cited therein.

(26) For selected recent articles on the chemistry of 1,2-diaza-1,3-dienes, see: (a) Boeckman, R. K., Jr.; Ge, P.; Reed, J. E. *Org. Lett.* **2001**, *3*, 3651–3653. (b) Kramp, G. J.; Kim, M.; Gais, H.-J.; Vermeeren, C. *J. Am. Chem. Soc.* **2005**, *127*, 17910–17920. (c) Palacios, F.; Aparicio, D.; López, Y.; de los Santos, J. M. *Tetrahedron* **2005**, *61*, 2815–2830. (d) Attanasi, O. A.; De Crescentini, L.; Favi, G.; Nicolini, S.; Perrulli, F. R.; Santeusanio, S. *Org. Lett.* **2011**, *13*, 353–355. (e) Boga, C.; Zanna, N.; Attanasi, O. A.; Baccolini, G.; De Crescentini, L.; Forlani, L.; Mantellini,

F.; Nicolini, S.; Micheletti, G.; Tozzi, S. *Eur. J. Org. Chem.* **2011**, 1326–1334. (f) Attanasi, O. A.; Bianchi, L.; De Crescentini, L.; Favi, G.; Mantellini, F. *Eur. J. Org. Chem.* **2011**, 2924–2927.

(27) Aparicio, D.; Attanasi, O. A.; Filippone, P.; Ignacio, R.; Lillini, S.; Mantellini, F.; Palacios, F.; de los Santos, J. M. *J. Org. Chem.* **2006**, *71*, 5897–5905.

(28) Attanasi, O. A.; Berretta, S.; De Crescentini, L.; Favi, G.; Giorgi, G.; Mantellini, F.; Nicolini, S. *Adv. Synth. Catal.* **2011**, *353*, 595–605.

(29) McDougall, R. H.; Malik, H. *J. Chem. Soc. C* **1969**, 2044–2051.

(30) Knapp, S.; Morriello, G. J.; Nandan, S. R.; Emge, T. J.; Doss, G. A.; Mosley, R. T.; Chen, L. *J. Org. Chem.* **2001**, *66*, 5822–5831.

(31) (a) Randles, K. R.; Storr, R. C. *J. Chem. Soc., Chem. Commun.* **1984**, 1485–1486. (b) Wasserman, H. H.; Long, Y. O.; Parr, J. *Tetrahedron Lett.* **2003**, *44*, 361–363. (c) Hamann, L. G.; Ding, C. Z.; Miller, A. V.; Madsen, C. S.; Wang, P.; Stein, P. D.; Pudzianowski, A. T.; Green, D. W.; Monshizadegan, H.; Atwal, K. S. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 1031–1034.

(32) DDs **1a**−**i** were synthesized from the corresponding chlorohydrazones by treatment with base, see: (a) Sommer, S. *Tetrahedron Lett.* **1977**, *18*, 117–120. (b) Attanasi, O. A.; Filippone, P.; Mei, A.; Santeusanio, S. *Synthesis* **1984**, 671–672. (c) Attanasi, O. A.; Filippone, P.; Mei, A.; Santeusanio, S. *Synthesis* **1984**, 873–874. (d) South, M. S.; Jakuboski, T. L.; Westmeyer, M. D.; Dukesherer, D. R. *J. Org. Chem.* **1996**, *61*, 8921–8934.

(33) (a) Johsi, B. S.; Likhate, M. A.; Viswanathan, N. *Indian J. Chem., Sect. B: Org. Chem. Incl. Med. Chem.* **1984**, *23*, 114–6. (b) Hossain, M. M.; Islam, R. M.; Saha, S. K.; Islam, M. K. *Tetrahedron Lett.* **2010**, *51*, 1155–57.

(34) *Progress in Heterocyclic Chemistry*; Gribble, G. W.; Joule, J. A., Eds.; Elsevier: Oxford, 2003−2010; Vol. 15−22.