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A Novel Solvent-Free Approach to Imidazole Containing Nitrogen-Bridgehead Heterocycles

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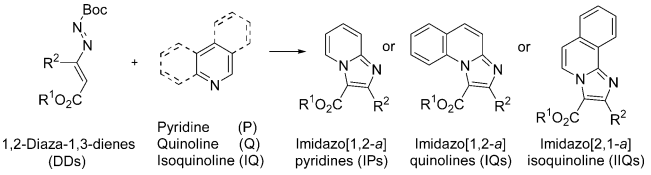
ABSTRACT



A very simple domino reaction under solvent-free conditions of various pyridine-like heterocycles with 1,2-diaza-1,3-dienes produces in good yields imidazo[1,2-*a*]pyridines, imidazo[1,2-*a*]quinolines, and imidazo[2,1-*a*]isoquinolines. The advantage of this one-pot transformation lies in the use of simple pyridine-like compounds without prefunctionalization of the starting heterocycles.

The skeleton of a great number of the biologically active compounds is represented by heterocycles.[1] In this context, the chemistry of imidazo[1,2-*a*]pyridines (IPs) have attracted increasing attention since this nitrogen-bridgehead heterocycle is an important pharmacophore, and it is amply found in many biologically active compounds.[2] For example, IPs show antiprotozoal, anti-inflammatory, antiulcer, antiviral, antibacterial, and antifungal activities.[3] Other therapeutic properties of IPs include melatonin receptor ligands, agonists of benzodiazepine receptors, β-amyloid formation inhibitors, or ligands for detecting β-amyloids.[4] Besides, IPs constitute a novel class of orally active nonpeptide bradykinin B2 receptor antagonists.[5] Drugs containing an IP core such as Alpidem, Necopidem, Saripidem, Zolpidem, Olprinone, Minodronic acid, Divalpon, and Zolimidine are available commercial products (Figure 1).[6] Among the IP benzo-derivatives, imidazo-[1,2-*a*]quinolines (IQs) have been described to be contraceptive, hypotensive, antiallergic, and antiasthmatic agents,[7] while their isomers imidazo[2,1-*a*]isoquinolines (IIQs) show cytotoxic and PARP-1 inhibitory activities.[8]

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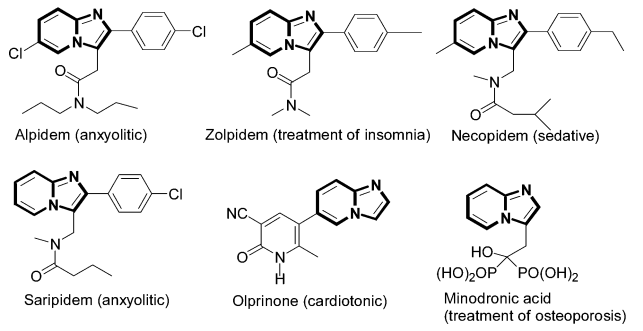


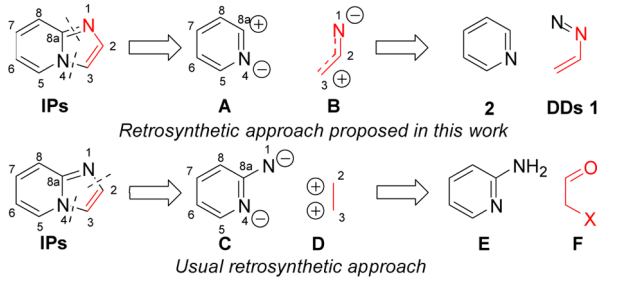
Figure 1. Drugs based on imidazo[1,2-*a*]pyridines.

On the other hand, IPs, IQs, and IIQs have been investigated as biomarkers and photochemical sensors, since they are important organic fluorophores.[9] By virtue of these relevant applications, efficient strategies for their synthesis have been developed.[10] In particular, the most employed method for the synthesis of IPS involves the use of 2-aminopyridines in the coupling reactions with α-halocarbonyl compounds, and in the condensations with aldehydes or isonitriles.[11] Usually, these syntheses require harsh conditions. Some other recent examples include a water-mediated hydroamination,[12] silver-catalyzed cyclization,[13] copper-catalyzed dehydrogenative aminooxygenation,[14] TBAI-catalyzed oxidative coupling,[15] copper-catalyzed aromatic amination,[16] copper-catalyzed three-component coupling,[17] Morita–Baylis–Hilmann reaction,[18] and silver-catalyzed oxidative cross-coupling reaction.[19] Also in all these latter cases various aminopyridine derivatives were employed as starting materials. Recently, Cronin reported an interesting five-step one-pot procedure leading to imidazo-pyridine derivatives that does not require α-amino functionalized starting materials.[20]

Domino processes represent an inviting method for a facile construction of the molecular architecture because they represent an access to the formation of several new bonds in a single manipulation. These processes are operationally simple and minimize the production of chemical waste.[21] From the perspective of green chemistry,[22] domino processes under solvent-free conditions (SFC) are fascinating since they involve the best reaction medium with "no medium".[23]

By exploiting our experience in the field of 1,2-diaza-1,3-dienes (DDs) in the syntheses of several five- and six-membered azaheterocycles,[24] we have thought to plan a more simple methodology for the assembly of IPs, IQs, and IIQs based on their use. In the nitrogen-bridgehead heterocycles construction (Scheme 1) two strategic disconnections of the imidazole core can be envisaged along the N(1)–C(8a) and N(4)–C(3) bonds.

Scheme 1. Comparison between the Retrosynthetic Analysis to Assemble IPs Proposed in This Work and the Most Commonly Employed



Thus, two subunits can be evidenced: a pyridine ring **2**, and an unusual zwitterion **B** bearing an electrophilic center in α-position to the imine moiety, instead of the ordinary nucleophilic site. Fortunately, DDs **1** constitute an umpolung of the classical carbonyl reactivity,[24a] since these neutral compounds enable nucleophilic additions at the terminal carbon atom of the azo-ene system. Thus, the initial conjugate 1,4-addition of the pyridine **2** to DD **1**

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would permit the N(4)−C(3) junction, while the subsequent regioselective intramolecular cyclization would furnish the second connection N(1)−C(8a). It is noteworthy that, in this synthetic approach, the N(1) of the desired IPs derives from the DDs **1**, allowing the use of simple pyridines as starting materials unlike the majority of methods that employ functionalized 2-amino pyridine derivatives, usually obtained via the Chichibabin reaction, or by a regioselective halogenation followed by nucleophilic substitution by ammonia.

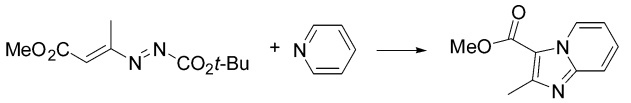
The domino reaction between DDs **1** and pyridine derivatives carried out in this work have confirmed our hypothesis for the construction of IPs **3**. We began our investigation by studying the reaction between DD **1a** and pyridine (P) **2a** chosen as a representative model (Table 1).

Different solvents, such as dichloromethane, tetrahydrofuran, and acetonitrile, were tested, whether at rt or under reflux. In all these cases, IP **3a** was achieved in very moderate yield (Table 1, entries 1−6) and the reactions required 12−24 h. With an incremental increase in the amount of P **2a**, a reduction in yield of IP **3a** was observed, while by increasing the molar ratio of DD **1a** from 1 to 3 equiv, the yield of the IP **3a** slightly improved (Table 1, entries 7, 8). These poor results have led us to extend our investigations to testing solvent-free conditions. To our delight, we have found that under SFC, at rt, by employing 3 equiv of DD **1a**, the reaction time was reduced and the yield was significantly increased (Table 1, entry 11).

A mechanistic hypothesis for this reaction provides a Michael-type nucleophilic attack of the heterocyclic nitrogen of P **2a** to the terminal carbon atom of the azo-ene system of DD **1a**, to form a nonisolable zwitterionic hydrazone intermediate **I**. The proton shift from the C- to N-atom produces the intermediate **II** that is able to promote further nucleophilic attack of the hydrazone sp^2 nitrogen to the formed iminium function leading to the formation of the imidazoline derivative **III**. Final aromatization by elimination of the carbamate residue through cleavage of the N−N bond[25] furnishes the desired IP **3a** (Scheme 2).

With the optimal conditions in hand, the scope of this SFC one-pot reaction was broadened using a range of DDs **1b**−**f** with various Ps **2a**−**c** (Table 2, entries 1−6). The IPs **3b**−**e** derived from P **2a** were obtained in excellent yields (82−92%) (Table 2, entries 1−4), and the reactions were completed in 3.0−5.0 h.[26] An electron-donating group (EDG), such as the methoxy one in the starting Ps **2b**,**c**, significantly reduces the reaction times (1−3 min),[26] and the final IPs **3f**,**g** were achieved in good yields (60, 71%) (Table 2, entries 5, 6).

Table 1. Screening of Different Conditions in the Reaction between DD **1a** and P **2a**

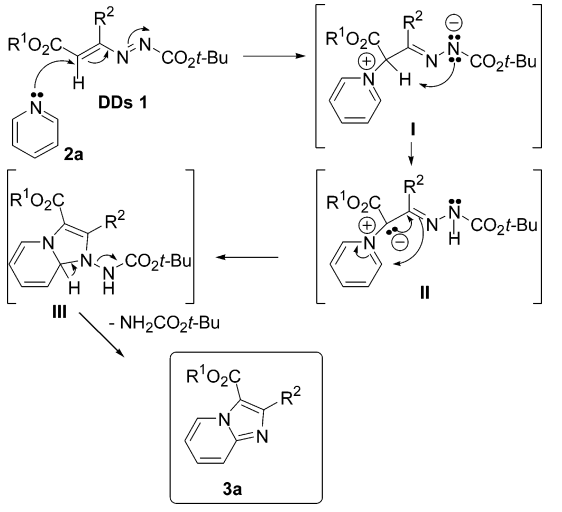


1a **2a** **3a**

entry	solvent	molar ratio **1a**/**2a**	*t* (°C)	**3a** yield (%)[a]	reaction time (h)
1[a]	THF	1/1	rt	10[b]	24
2[a]	CH_3CN	1/1	rt	13[b]	18
3[a]	CH_2Cl_2	1/1	rt	26[b]	18
4[a]	THF	1/1	reflux	13[b]	15
5[a]	CH_3CN	1/1	reflux	13[b]	12
6[a]	CH_2Cl_2	1/1	reflux	26[b]	18
7[a]	CH_2Cl_2	1/3	rt	18[b]	18
8[c]	CH_2Cl_2	3/1	rt	32[d]	15
9[e]	no solvent	1/1	rt	39[b]	8
10[e]	no solvent	1/3	rt	12[b]	10
11[f]	**no solvent**	**3/1**	**rt**	**86**[d]	**3.5**

[a] The reactions were performed at a 0.5 mmol scale of DD **1a** in 5 mL of solvent. [b] Yields of isolated IP **3a** based on DD **1a**. [c] The reactions were performed at a 0.5 mmol scale of P **2a** in 5 mL of solvent. [d] Yields of isolated IP **3a** based on P **2a**. [e] The reactions were performed at a 0.5 mmol scale of DD **1a**. [f] The reactions were performed at a 0.5 mmol scale of P **2a**.

Scheme 2. Plausible Mechanism



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(26) For the detailed reaction times, see Supporting Information.

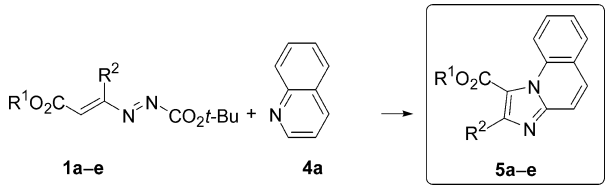
Table 2. One-Pot SFC Synthesis of IPs **3b**–**g**: Reaction Scope with Respect to Ps **2a**–**c**[a]

entry	1	R^1	R^2	2	R^3	R^4	3	yield (%)[b]
1	**1b**	Et	Me	**2a**	H	H	**3b**	87
2	**1c**	*i*-Pr	Me	**2a**	H	H	**3c**	92
3	**1d**	allyl	Me	**2a**	H	H	**3d**	85
4	**1e**	Bn	Me	**2a**	H	H	**3e**	82
5	**1f**	Me	Et	**2b**	H	OMe	**3f**	60
6	**1f**	Me	Et	**2c**	OMe	H	**3g**	71

[a] Reagents and conditions: **1b**–**f** (3.0 mmol), **2a**–**c** (1.0 mmol). [b] Yield of pure isolated products **3** referred to Ps **2a**–**c**.

To further enlarge the scope of this method, we have examined the one-pot SFC reactions between DDs **1a**–**e** and quinoline (Q) **4a.** The corresponding IQs **5a**–**e** were produced in good yields (78–91%) (Table 3, entries 1–5) requiring 3.0–4.5 h.[26]

Table 3. One-Pot SFC Synthesis of IQs **5a**–**e**: Reaction Scope with Respect to Q **4a**.[a]



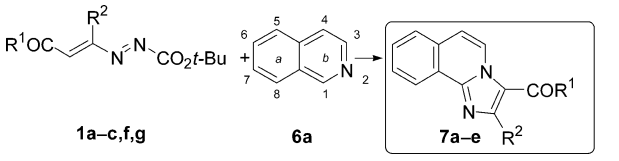
entry	1	R^1	R^2	5	yield (%)[b]
1	**1a**	Me	Me	**5a**	83
2	**1b**	Et	Me	**5b**	78
3	**1c**	*i*-Pr	Me	**5c**	86
4	**1d**	allyl	Me	**5d**	91
5	**1e**	Bn	Me	**5e**	89

[a] Reagents and conditions: **1a**–**e** (3.0 mmol), **4a** (1.0 mmol). [b] Yield of pure isolated products **5** referred to Q **4a**.

Also when the isoquinoline (IQ) **6a** was employed as the starting nucleophile, the SFC reaction with DDs **1a**–**c**,**f**,**g** produced excellent outcomes. The IIQs **7a**–**e** were achieved in very shorts times (0.5–1 min),[26] in excellent yields (85%–96%) (Table 4, entries 1–5), and in a regioselective manner.

In this case, the iminium intermediate **I** has two suitable α positions for the ring closure process (C(1) and C(3)) (Scheme 3). As reported by Cronin,[20] the azaheterocyclization involves only the C(1) site. In this manner, only the aromaticity of the heterocycle *b* is lost during the cyclization process. The absence of singlets in ^{1}H NMR unambiguously confirms the structure of compounds **7a**–**e** (Scheme 3).

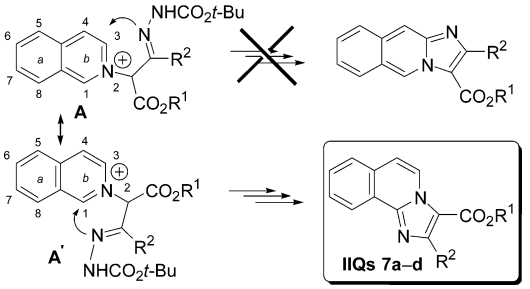
Table 4. One-Pot SFC Synthesis of IIQs **7a**–**e**: Reaction Scope with Respect to IQ **6a**[a]



entry	1	R^1	R^2	7	yield (%)[b]
1	**1a**	OMe	Me	**7a**	91
2	**1b**	OEt	Me	**7b**	92
3	**1c**	O*i*-Pr	Me	**7c**	96
4	**1f**	OMe	Et	**7d**	89
5	**1g**	NMe_2	Me	**7e**	85

[a] Reagents and conditions: **1a**–**c**,**f**,**g** (3.0 mmol), **6a** (1.0 mmol). [b] Yield of pure isolated products **7** referred to IQ **6a**.

Scheme 3. Regioselectivity in the Reaction between DDs **1** and IQ **6a**; ^{1}H NMR spectrum portion of **IIQ 7b**



In conclusion, we report a novel and very simple solvent- and metal-free methodology that leads to the synthesis of a range of imidazo-pyridine-like derivatives such as imidazo[1,2-*a*]pyridines, imidazo[1,2-*a*]quinolines, and imidazo[2,1-*a*]isoquinoline starting from simple pyridine, quinoline, and isoquinoline derivatives. The synthetic route that combines the advantages of the domino reactions with the solvent-free conditions is itself completely different from the previous ones and avoids the prefunctionalization of the starting heterocycles.

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Supporting Information Available. Experimental procedures and characterization data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.