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One-Pot Synthesis of Imidazole-4-Carboxylates by Microwave-Assisted 1,5-Electrocyclization of Azavinyl Azomethine Ylides

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Abstract

Diversely functionalized imidazole-4-carboxylates were synthesized by microwave-assisted 1,5-eletrocyclization of 1,2-diaza-1,3-diene-derived azavinyl azomethine ylides. 1,2-Diaza-1,3-dienes were treated with primary aliphatic or aromatic amines and subjected to microwave irradiation in the presence of aldehydes. 3-Alkyl- and 3-arylimidazole-4-carboxylates were prepared in good yields through a one-pot multicomponent procedure. Modulation of the substituents at C-2, N-3 and C-5 was possible, and 2-unsubstituted imidazoles were obtained when paraformaldehyde was used.

Keywords

Azomethine ylides; Electrocyclic reactions; Microwave chemistry; Multicomponent reactions; Nitrogen heterocycles

Introduction

The field of organic synthesis has witnessed a dramatic surge in the application of microwave irradiation as an alternative to conventional heating. In most cases, microwave heating has resulted in drastic reduction of reaction times, improvement of workup procedures and, ultimately, increased product yields in comparison to classical heating.[1] To date, microwave irradiation has been applied successfully to a broad array of reaction types,[1] and has become a standard tool in organic synthesis. Microwave-enhanced cycloadditions have also been reported,[2] including [3 + 2] cycloadditions of azomethine ylides.[3]

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Supporting information for this article is available on the WWW under http://www.eurjoc.org/ or from the author.

Supporting Information (see footnote on the first page of this article): Experimental procedure for the preparation of non-commercially available aldehydes (and spectral data thereof) used for the synthesis of imidazole-4-carboxylates **2l–n** and ^{1}H and ^{13}C NMR spectra for DDs **1c–f** and imidazoles **2a–w**.

Recently, we have reported the successful synthesis of α-imidazol-1-yl esters via 1,5-electrocyclization of azavinyl azomethine ylides that were ultimately derived from 1,2-diaza-1,3-dienes (henceforth DDs)[4] and aziridines[5] or by sequential reaction with α-aminoesters and aldehydes.[6] In particular, conjugated azavinyl azomethine ylides were generated by refluxing DD-derived α-aminoester hydrazones in toluene in the presence of aldehydes, and were found to undergo an original 1,5-electrocyclization to imidazoles.[5,6] To follow up our work, we envisioned replacing α-aminoesters with primary aliphatic or aromatic amines, which would allow a more general access to simpler imidazole-4-carboxylates in a one-pot fashion without the need of isolating reaction intermediates. Initial attempts with α-aminohydrazones under the same reactions conditions[5,6] did provide the desired imidazole-4-carboxylates in very modest yields. Since charged chemical species or intermediates are well known to benefit from microwave irradiation, as in the case of 1,3-dipolar cycloadditions,[3] we reasoned that our 1,5-electrocyclization of DD-derived azavinyl azomethine ylides could be likewise enhanced by employing microwave heating.

Results and Discussion

DDs **1a–b** were reacted with the appropriate amine in acetonitrile at r.t. until complete decolouration occurred. In the case of DD **1a**, the compound was freshly prepared from the parent chlorohydrazone by preliminary treatment with triethylamine in acetonitrile at rt, and used as such without further purification for the following reaction. Subsequent treatment with paraformaldehyde in a sealed vessel under microwave irradiation at 150 °C for 20 min afforded 2-unsubstituted 3*H*-imidazole-4-carboxylates **2a–i** generally in good yields (Table 1), with the exception of **2f** (Table 1, entries 11 and 12), most presumably due to partial loss of the *tert*-butyl substituent at nitrogen under the reaction conditions employed. Yields with DD **1b** were generally comparable to those with in situ generated **1a**. Aliphatic and aromatic amines (Table 1, entries 1–14 and 15–18, respectively) performed equally well. When (*R*)-α-phenylethylamine was used (Table 1, entries 7 and 8), enantiomerically pure imidazole **2d** was recovered (ee > 95%). Using microwave irradiation, the reaction resulted in higher yields and shorter reaction times than with conventional heating, i.e. refluxing in toluene. In particular, yields for imidazoles **2a** and **2e** were in the 51–55% range under classical conditions, but rose to 71–77% when microwave heating was employed.

Encouraged by the success with paraformaldehyde, we sought to extend the scope of this one-pot protocol by varying the aldehyde partner. Treatment of DD **1b** and in situ generated **1a** with benzylamine in acetonitrile at r.t. and subsequent microwave heating in the presence of aliphatic or aromatic aldehydes under the same reaction conditions afforded 2-substituted 3-benzyl imidazole-4-carboxylates **2j–o** in moderate to good yields (Table 2). In the case of butanal and phenylacetaldehyde, yields were excellent with in situ prepared **1a** (Table 2, entries 1 and 4), but dropped when DD **1b** was used (entries 2 and 5). When butanal was replaced with its dimethyl acetal, imidazole **2j** was still obtained, albeit in lower yield (Table 2, entry 3). Yields were only moderate with benzaldehyde, either by using **1a** or **1b** as the starting material (Table 2, entries 10 and 11).

When benzylamine and either paraformadehyde or butanal were added simultaneously, rather than sequentially, to freshly formed DD **1a**, and the resulting solution was subjected immediately to microwave irradiation, imidazoles **2a** or **2j** were isolated in 71 and 70% yield, respectively. Strictly speaking, therefore, the whole process displays a multicomponent character, as all reagents can be mixed at the same time without affecting the reaction outcome and, importantly, with comparable overall yields.

Whilst simple variations of the aldehyde or amine partners allowed the access to imidazoles 4-carboxylates with different functionalities at C-2 and N-3, respectively, modulation of the

substituent at C-5 required the use of an appropriate DD as the starting material. Therefore, additional DDs **1c–f** were allowed to react with benzylamine or allylamine in the presence of paraformaldehyde under the same conditions. 5-Alkyl and 5-arylimidazole-4-carboxylates **2p–w** were isolated in moderate to good yields (Table 3). In particular, yields were higher for imidazoles **2p–s** having an ethyl or a propyl side chain (Table 3, entries 1–4), whereas DD **1f** gave 5-phenylimidazoles **2v,w** only in moderate yields (Table 3, entries 7,8). Use of benzylamine or allylamine always resulted in comparable yields, except for DD **1e** which afforded the corresponding 5-methoxycarbonylmethyl-imidazoles in good yield only for the latter (Table 3, entries 5,6).

A rationale mechanism for the formation of imidazole-4-carboxylates **2a–w** is depicted in Scheme 1. Michael-type 1,4-conjugate addition of DDs **1a–f** (either as an isolated compound or in situ generated from the corresponding chlorohydrazone by treatment with TEA in the case of **1a,c**) with the primary amine gives α-aminohydrazone **A**[4e] which in turn condenses with the aldehyde partner to yield iminium ion **B**. Microwave-assisted heating may result in the formation of conjugated azavinyl azomethine ylide[7,8] **C** which undergoes 1,5-electrocyclization to 2,3-dehydroimidazole-4-carboxylate **D** and, eventually, aromatization with loss of carbamate or urea, thus affording the desired 3*H*-imidazole-4-carboxylates **2a–w**, by analogy to the formation of DD-derived α-imidazol-1-yl esters we have recently disclosed.[5,6]

Microwave irradiation has been already employed for the preparation of aryl or alkyl 2,4,5-trisubstituted and 1,2,4,5-tetrasubstituted imidazoles.[9,10] In particular, a three-component reaction between 1,2-diketones and aldehydes in the presence of ammonium acetate was used for the synthesis of 2,4,5-triaryl- and -trialkylimidazoles,[9] whereas a four-component variant that also included aliphatic or aromatic amines gave 1,2,4,5-tetrasubstituted imidazoles.[9b–c,i,10] In most of these cases, however, the resulting imidazole products displayed a rather low degree of functionalization that preclude further chemistries. The present method, by contrast, allows the preparation of functionalized imidazoles whose substituents are amenable to subsequent manipulations, especially in the framework of target-driven multistep syntheses.

Conclusions

We have reported a significant extension of the 1,5-electrocyclization of conjugated azavinyl azomethine ylides[5,6] to substituted imidazole-4-carboxylates by one-pot sequential reaction between DDs and primary amines, followed by microwave-assisted heating in the presence of aldehydes. The method is efficient and straightforward and does not require isolation of intermediates. Moreover, appropriate choice of the amine, aldehyde and DD partners makes possible the modulation of substituents at the N-3, C-2 and C-5 atoms of the final product, respectively. Noteworthily, the reaction can be also performed in a multicomponent fashion by simply mixing the three partners at r.t. and subjecting them to microwave irradiation. Such a one-pot multicomponent approach is most flexible and useful for the synthesis of functionalized imidazole-4-carboxylates starting from readily available materials such as aliphatic or aromatic primary amines and aldehydes, and nicely adds to the variety of available methods to access the biologically important and pharmaceutically relevant imidazole skeleton.[11]

Experimental Section

General Methods

Microwave-assisted reactions were performed in sealed glass vials using a temperature- and pressure-controlled single-mode microwave reactor (CEM, Discover LabMate) equipped

with a 300 W power source. Temperature and pressure were set at 150 °C and 150 psi, respectively, power source at 150 W. Such values were reached within 5 min and were maintained for further 20 min by means of IR sensor thermal control and pressure feedback control. Commercial grade acetonitrile was used without further purification as reaction solvent. 1,2-Diaza-1,3-dienes (DDs) **1a–b** were synthesized as already described and occur both as a mixture of *E*/*Z* isomers.[12] Whereas DD **1b** is a shelf-stable red crystalline compound,[12b] DD **1a**[12a] is a somewhat unstable red liquid that tends to decompose upon prolonged storage. Therefore, **1a** was always generated in situ by treatment of the parent chlorohydrazone with triethylamine in acetonitrile at rt, and the resulting red solution was used as such for the subsequent chemistry without further purification. 1,2-Diaza-1,3-dienes (DDs) **1c–f** were synthesized according to the procedure described below. Amines and aldehydes were purchased from Sigma-Aldrich and used as received, except for thiophen-2-yl-acetaldehyde, phenoxyacetaldehyde and 2-phenoxypropanal (used for the synthesis of imidazole-4-carboxylates **2l**, **2m** and **2n**, respectively) which were prepared by reduction of the parent methyl ester with DIBALH by analogy to a literature procedure[13] (see Supporting Information). Chromatographic purification of compounds was performed on silica gel (60–200 μm) using the appropriate eluant as specified; commercially grade light petroleum/ethyl acetate mixtures were used for such purpose. Pre-loaded (0.25 mm) glass supported silica gel plates (Kieselgel 60, Merck) were used for TLC analysis and compounds were visualized by exposure to UV light and by dipping the plates in 1% $Ce(SO_4)•4H_2O$, 2.5% $(NH_4)_6Mo_7O_{24}•4H_2O$ in 10% sulphuric acid followed by heating on a hot plate. Melting points were determined in open capillary tubes and are uncorrected. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ solution at 25 °C on Bruker 200 or 400 MHz instruments. Multiplicity is given as s = singlet, d = doublet, t = triplet, q = quartet, sex = sextet, m = multiplet and br = broad signal, and chemical shifts (δ) are reported in ppm downfield from tetramethylsilane as internal standard. Coupling constants ($^3J_{H,H}$) are given in Hz. COSY, HSQC and HMBC experiments were performed to aid in the assignment of ^1H and ^{13}C resonances. Mass spectra were recorded in the EI mode (70 eV). For elemental analyses, a Carlo Erba Elemental Analyzer (model 1110) was used. The enantiomeric excess (ee) of imidazole **2d** was determined by chiral HPLC analysis (Jasco PU-980) using a Lux Cellulose-1 column (5 μm; 250 × 4.6 mm; Phenomenex, Torrance, CA, US). The mobile phase consisted of *n*-hexane/isopropanol 9:1 (v/v) under isocratic elution at a flow rate of 0.7 mL min^{-1} at 20 °C; samples were dissolved in *n*-hexane/isopropanol 1:1 (v/v) and injection volume was 20 μL. Detection was performed at 254 nm using a variable wavelength detector (Jasco UV-1575). Accuracy was within ±5%.

1,2-Diaza-1,3-dienes (DDs) 1c–f were synthesized as follows

Procedure for the synthesis of DDs 1c–e—Commercially available methyl 2-chloro-3-oxopentanoate (5 mmol), or freshly prepared (see below) ethyl 2-chloro-3-oxo-hexanoate (5 mmol) or dimethyl 2-chloro-3-oxopentanedioate (5 mmol) were added to a magnetically stirred solution of semicarbazide hydrochloride (5 mmol, pretreated with an equimolecular amount of sodium acetate) or methyl carbazate (5 mmol) in tetrahydrofuran (50 mL, **1c**) or methanol (50 mL, **1d,e**). The reaction was magnetically stirred at r.t. until the disappearance of the reagents (TLC). The reaction solvent was evaporated under reduced pressure, the crude α-chloro-hydrazone was dissolved in ethyl acetate and washed with aqueous saturated solution of sodium carbonate (50 mL×2) and with an aqueous solution of sodium hydroxide (1%, 50 mL×1, only for **1c,d**). Ethyl acetate was removed under reduced pressure and the crude residue purified by chromatography on silica gel column, affording DDs **1c–e**.

Ethyl 2-chloro-3-oxo-hexanoate or dimethyl 2-chloro-3-oxopentanedioate required for the synthesis of DDs **1d,e,** were prepared from the parent ethyl 3-oxo-hexanoate (5 mmol) or

dimethyl 3-oxopentanedioate (5 mmol) by chlorination with sulfuryl chloride (SO_2Cl_2) (5.5 mmol.). The reaction was performed in dichloromethane (10 mL) at r.t. under magnetic stirring for 15–30 min (monitored by TLC and/or ^{1}H-NMR). Thereafter, the reaction mixture was washed with brine (5×30 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure affording the desired α-chloro hydrazone as a colourless oil.

Procedure for the synthesis of DD 1f—Ethyl 3 oxo-3-phenylpropanoate (5 mmol) was treated with 1 equiv. of *tert* butyl carbazate (5 mmol) and a catalytic amount of *p*-toluenesulfonic acid in the minimum amount of tetrahydrofuran (5 mL). The reaction mixture was allowed to react at r.t. for 48 h: the desired hydrazone separates as a white solid, which was recovered by filtration and washed with light petroleum ether. The hydrazone was then dissolved in dichloromethane and 1.1 equiv. of sulfuryl chloride was added at r.t. and the resulting solution was allowed to react for 30 min under magnetical stirring. Thereafter the reaction mixture was washed with brine (5×30 mL), and the organic layer was dried over magnesium sulfate, filtered and concentrated under reduced pressure to give α-chloro hydrazone as a pale yellow oil.

Finally, addition of N,N-diisopropylethylamine (1.0 equiv.) to a magnetically stirred solution of the α-chloro hydrazone in the minimum amount of dichloromethane at r.t. for 5 min assisted to the 1,2-diaza-1,3-diene formation. The resulting red-orange solution was directly purified by column chromatography (cyclohexane/ethyl acetate 90:10) to give **DD 1f** as a somewhat unstable red liquid that tends to decompose upon storage.

4-Methoxycarbonyl-3-ethyl-1-metoxycarbonyl-1,2-diaza-1,3-diene (1c)—DD **1c** was isolated (540 mg, 54%) by column chromatography (cyclohexane/ethyl acetate 90:10). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.84 (s, 1H, C*H*), 4.03 (s, 3H, OC*H*$_3$), 3.83 (s, 3H, OC*H*$_3$), 2.83 (q, *J* = 7.6 Hz, 2H, C*H*$_2$CH$_3$), 1.01 (t, *J* = 7.6 Hz, 3H, CH$_2$C*H*$_3$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.4 (*C*O$_2$CH$_3$), 165.7 (N*C*O$_2$CH$_3$), 162.7 (*C*-3), 131.1 (*C*-4), 54.9 (O*C*H$_3$), 52.0 (O*C*H$_3$), 17.7 (*C*H$_2$), 12.2 (*C*H$_3$) ppm. MS (EI): *m/z* (%) = 200 (M^+, 1), 167 (2), 149 (5), 125 (10), 111 (22), 97 (38), 83 (39), 69 (60), 57 (100). $C_8H_{12}N_2O_4$ (200.08): calcd. C 48.00, H 6.04, N 13.99; found C 47.81, H 6.31, N 14.23

4-Ethoxycarbonyl-3-propyl-1-aminocarbonyl-1,2-diaza-1,3-diene (1d)—DD **1d** was isolated (499 mg, 47%) by column chromatography (cyclohexane/ethyl acetate 65:35). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.87 (s, 1H, C*H*), 6.23 and 6.02 (br, 2H, N*H*$_2$), 4.29 (q, *J* = 7.2 Hz, 2H, CH$_3$C*H*$_2$O), 2.85 (t, *J* = 7.6 Hz, 2H, C*H*$_2$CH$_2$CH$_3$), 1.43 (sex, *J* = 7.6 Hz, 2H, CH$_2$C*H*$_2$C*H*$_3$), 1.37 (t, *J* = 7.6 Hz, 3H, CH$_2$CH$_2$C*H*$_3$), 0.91 (t, *J* = 7.2 Hz, 3H, C*H*$_3$CH$_2$O) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.4 (*C*O$_2$CH$_2$CH$_3$), 165.4 (N*C*O$_2$NH$_2$), 161.1 (*C*-3), 132.1 (*C*-4), 61.1 (O*C*H$_2$CH$_3$), 26.3 (*C*H$_2$CH$_2$CH$_3$), 21.3 (CH$_2$*C*H$_2$CH$_3$), 14.1 (2*C*H$_3$) ppm. MS (EI): *m/z* (%) = 170 (3), 141 (27), 125 (72), 113 (50), 99 (60), 85 (24), 67 (66), 55 (100). $C_9H_{15}N_3O_3$ (213.11): calcd. C 50.69, H 7.09, N 19.71; found C 50.47, H 7.33, N 19.63.

4-Methoxycarbonyl-3-(2-methoxy-2-oxoethyl)-1-aminocarbonyl-1,2-diaza-1,3-diene (1e)—DD **1e** was isolated (492 mg, 43%) by column chromatography (cyclohexane/ethyl acetate 40:60). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.21 (s, 1H, C*H*), 6.28 and 6.02 (br, 2H, N*H*$_2$), 4.03 (s, 3H, C*H*$_3$O), 3.86 (s, 3H, C*H*$_3$O), 3.66 (s, 2H, C*H*$_2$CO$_2$Me) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.1 (CH$_2$*C*O$_2$CH$_3$), 165.5 (*C*O$_2$CH$_3$), 161.2 (N*C*O$_2$NH$_2$), 158.9 (*C*-3), 135.2 (*C*-4), 52.3 (2O*C*H$_3$), 30.4 (*C*H$_2$) ppm. MS (EI): *m/z* (%) = 155 (68), 126 (56), 98 (100), 85 (70), 68 (58), 59 (100). $C_8H_{11}N_3O_5$ (229.07): calcd. C 41.92, H 4.84, N 18.33; found C 42.07, H 4.67, N 18.09.

4-Ethoxycarbonyl-3-phenyl-1-*tert*-butoxycarbonyl-1,2-diaza-1,3-diene (1f)—DD **1f** was isolated (851 mg, 56%) by column chromatography (cyclohexane/ethyl acetate 90:10). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.42– 7.37 (m, 3H, C*H*Ar), 7.24–7.20 (m, 2H, C*H*Ar), 6.92 (s, 1H, C*H*), 4.11 (q, J = 7.2 Hz, 2H, OCH_2CH$_3$), 1.59 (s, 9H, (CH_3)$_3$), 1.12 (t, J = 7.2 Hz, 3H, OCH$_2$CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.8 (*C*O$_2$CH$_2$CH$_3$), 163.0 (N*C*O$_2$*t*-Bu), 161.2 (*C*-3), 134.2 (*C*HAr), 130.4 (*C*-4), 129.4 (*C*HAr), 129.0 (*C*HAr), 127.8 (*C*HAr), 85.6 (*C*(CH$_3$)$_3$), 60.9 (O*C*H$_2$CH$_3$), 27.7 ((*C*H$_3$)$_3$), 13.8 (*C*H$_3$) ppm. MS (EI): *m/z* (%) = 176 (27), 21(16), 131 (100), 103 (64), 77 (30). $C_{16}H_{20}N_2O_4$ (304.14): calcd. C 63.14, H 6.62, N 9.20; found C 63.01, H 6.85, N 9.04.

Typical Procedure for the Synthesis of Imidazole-4-carboxylates from DDs 1a,c (Method A)

2-Chloro-3-(ethoxycarbonylhydrazono)-butanoic acid ethyl ester[12] (0.6 mmol) or 2-Chloro-3-(methoxycarbonylhydrazono)-pentanoic acid methyl ester (0.6 mmol) is dissolved in acetonitrile (2 mL) in a microwave glass vial and treated with TEA (84 μL, 0.6 mmol) at r.t. under magnetic stirring to give a red solution. The primary amine (0.63 mmol) is added and the resulting solution is stirred until complete decolouration, whereupon the aldehyde (1.2 mmol) is added. The vessel containing the pale yellow mixture is then sealed and heated under microwave irradiation at 150 °C for 20 min. After removal of the solvent in vacuo, purification by column chromatography affords the desired imidazole.

Typical Procedure for the Synthesis of Imidazole-4-carboxylates from DDs 1b,d–f (Method B)

A solution of DD **1b**[12b]**,d–f** (0.54 mmol) in acetonitrile (2 mL) in a microwave glass vial equipped with a stir bar is treated with the amine (0.57 mmol) at r.t. until complete decolouration. The aldehyde (1.08 mmol) is added, and the vessel with the resulting light yellow mixture is sealed and heated under microwave irradiation at 150 °C for 20 min. The solvent is evaporated under reduced pressure and the crude residue is purified by column chromatography to yield the desired imidazole-4-carboxylate.

Ethyl 3-benzyl-5-methyl-3*H*-imidazole-4-carboxylate (2a)—Imidazole **2a** was isolated (method A: 114 mg, 78; method B: 101 mg, 77%) by column chromatography (light petroleum/ethyl acetate 50:50) as a pale yellow solid, mp 54–56 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.72 (s, 1H, *H*-2), 7.33 (m, 3H, *H*-3′–*H*-5′), 7.18 (m, 2H, *H*-2′, *H*-6′), 5.52 (s, 2H, CH_2Ph), 4.30 (q, J = 7.1 Hz, 2H, CH$_3$CH_2O), 2.56 (s, 3H, CH_3C), 1.34 (t, J = 7.1 Hz, 3H, CH_3CH$_2$O) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.7 (*C*=O), 147.6 (*C*-5), 140.0 (*C*-2), 136.3 (*C*-1′), 128. 9 (*C*-3′, *C*-5′), 128.1 (*C*-4′), 127.2 (*C*-2′, *C*-6′), 118.8 (*C*-4), 60.5 (CH$_3$*C*H$_2$O), 50.9 (*C*H$_2$Ph), 15.6 (*C*H$_3$), 14.2 (*C*H$_3$CH$_2$O) ppm. MS (EI): *m/z* (%) = 244 (M^+, 14), 198 (12), 109 (8), 91 (100), 65 (10). $C_{14}H_{16}N_2O_2$ (244.12): calcd. C 68.83, H 6.60, N 11.47; found C 70.12, H 6.92, N 11.79.

Ethyl 3-allyl-5-methyl-3*H*-imidazole-4-carboxylate (2b)—Imidazole **2b** was isolated (method A: 100 mg, 86%; method B: 65 mg, 62%) by column chromatography (light petroleum/ethyl acetate 50:50) as a yellow liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.48 (s, 1H, *H*-2), 5.93 (ddt, J = 17.1, 10.3, 5.5 Hz, 1H, CH$_2$C*H*), 5.14 (ddd, J = 10.3, 2.6, 1.2 Hz, 1H, H_{cis}), 5.01 (ddd, J = 17.1, 2.6, 1.6 Hz, 1H, H_{trans}), 4.82 (dt, J = 5.5, 1.4 Hz, 2H, NCH_2), 4.26 (q, J = 7.1 Hz, 2H, CH$_3$CH_2O), 2.44 (s, 3H, CH_3C), 1.31 (t, J = 7.1 Hz, 3H, CH_3CH$_2$O) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.9 (*C*=O), 148.0 (*C*-5), 139.9 (*C*-2), 133.3 (NCH$_2$*C*H), 118.5 (*C*-4), 117.7 (CH*C*H$_2$), 60.3 (CH$_3$*C*H$_2$O), 49.4 (*C*H$_2$N), 15.8 (*C*H$_3$C), 14.3 (*C*H$_3$CH$_2$O) ppm. MS (EI): *m/z* (%) = 194 (M^+, 68), 165 (58), 149 (67), 121 (78), 109 (33), 94 (25), 80 (21), 67 (24), 54 (22), 41 (100). $C_{10}H_{14}N_2O_2$ (194.11): calcd. C 61.84, H 7.27, N 14.42; found C 62.09, H 7.07, N 14.71.

Ethyl 5-methyl-3-prop-2-ynyl-3*H*-imidazole-4-carboxylate (2c)—Imidazole **2c** was isolated (method A: 96 mg, 83%; method B: 64 mg, 62%) by column chromatography (light petroleum/ethyl acetate 70:30) as a pale yellow solid, mp 56–58 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.51 (s, 1H, *H*-2), 4.82 (d, *J* = 2.5 Hz, 2H, NCH_2), 4.10 (q, *J* = 7.1 Hz, 2H, CH_3CH_2O), 2.27 (t, *J* = 2.5 Hz, 1H, C≡C*H*), 2.24 (s, 3H, CH_3C), 1.14 (t, *J* = 7.1 Hz, 3H, CH_3CH_2O) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.00 (*C*=O), 148.6 (*C*-5), 139.6 (*C*-2), 118.4 (*C*-4), 76.8 (*C*≡CH), 74.9 (C≡*C*H), 60.5 (CH_3CH_2O), 37.1 (NCH_2), 15.8 (CH_3C), 14.3 (CH_3CH_2O) ppm. MS (EI): *m/z* (%) = 192 (M^+, 19), 163 (100), 147 (28), 136 (20), 119 (11), 109 (29), 92 (13), 65 (17), 52 (16), 39 (55). $C_{10}H_{12}N_2O_2$ (192.09): calcd. C 62.49, H 6.29, N 14.57; found C 62.74, H 6.44, N 14.80.

Ethyl (3*R*)-5-methyl-3-(1-phenylethyl)-3*H*-imidazole-4-carboxylate (2d)—Imidazole **2d** was isolated (method A: 116 mg, 75%; method B: 112 mg, 80%) by column chromatography (light petroleum/ethyl acetate 50:50) as a pale yellow liquid, $[\alpha]_D$ +48.3 (*c* 1.5, CH_2Cl_2), ee 98% (by chiral HPLC analysis). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.66 (s, 1H, *H*-2), 7.25 (m, 3H, *H*-3′–*H*-5′), 7.10 (d, *J* = 7.1 Hz, 2H, *H*-2′, *H*-6′), 6.27 (q, *J* = 7.1 Hz, 1H, NC*H*), 4.22 (q, *J* = 7.1 Hz, 1H, CH_3CH), 4.20 (q, *J* = 7.1 Hz, 1H, CH_3CH_2O), 2.45 (s, 3H, CH_3C), 1.78 (d, *J* = 7.1 Hz, 3H, CH_3CH), 1.26 (t, *J* = 7.1 Hz, 3H, CH_3CH_2O) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.9 (*C*=O), 147.8 (*C*-5), 141.3 (*C*-1′), 137.7 (*C*-2), 128.8 (*C*-3′, *C*-5′), 127.9 (*C*-4′), 126.2 (*C*-2′, *C*-6′), 118.8 (*C*-4), 60.4 (CH_3CH_2O), 55.9 (N*C*H), 22.3 (NCHCH_3), 15.8 (CH_3C), 14.2 (CH_3CH_2O) ppm. MS (EI): *m/z* (%) = 258 (M^+, 5), 154 (8), 105 (100), 77 (15). $C_{15}H_{18}N_2O_2$ (258.14): calcd. C 69.74, H 7.02, N 10.84; found C 70.02, H 7.30, N 11.04.

Ethyl 3-*sec*-butyl-5-methyl-3*H*-imidazole-4-carboxylate (2e)—Imidazole **2e** was isolated (method A: 105 mg, 83%; method B: 81 mg, 71%) by column chromatography (light petroleum/ethyl acetate 50:50) as a pale yellow liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.67 (s, 1H, *H*-2), 5.05 (m, 1H, C*H*), 4.30 (q, *J* = 7.1 Hz, 2H, CH_3CH_2O), 2.47 (s, 3H, CH_3C), 1.77 (m, 2H, CH_3CH_2CH), 1.43 (d, *J* = 6.8 Hz, 3H, CH_3CH), 1.35 (t, *J* = 7.1 Hz, 3H, CH_3CH_2O), 0.85 (t, *J* = 7.4 Hz, 3H, CH_3CH_2CH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.2 (*C*=O), 147.4 (*C*-5), 136.9 (*C*-2), 118.6 (*C*-4), 60.3 (CH_3CH_2O), 54.0 (CH_3CH_2CH), 30.6 (CH_3CH_2CH), 21.2 (CH_3CH), 15.9 (CH_3C), 14.3 (CH_3CH_2O), 10.3 (CH_3CH_2CH) ppm. MS (EI): *m/z* (%) = 210 (M^+, 39), 181 (8), 165 (14), 154 (17), 137 (25), 125 (95), 109 (100), 82 (17), 54 (17), 41 (27). $C_{11}H_{18}N_2O_2$ (210.14): calcd. C 62.83, H 8.63, N 13.32; found C 63.18, H 8.95, N 13.56.

Ethyl 3-*tert*-butyl-5-methyl-3*H*-imidazole-4-carboxylate (2f)—Imidazole **2f** was isolated (method A: 56 mg, 44%; method B: 57 mg, 50%) by column chromatography (light petroleum/ethyl acetate 50:50) as a pale yellow liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.73 (s, 1H, *H*-2), 4.30 (q, *J* = 7.1 Hz, 2H, CH_3CH_2O), 2.44 (s, 3H, CH_3C), 1.68 (s, 9H, $(CH_3)_3C$), 1.36 (t, *J* = 7.1 Hz, 3H, CH_3CH_2O) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.6 (*C*=O), 149.1 (*C*-5), 137.4 (*C*-2), 120.0 (*C*-4), 60.6 (CH_3CH_2O), 58.7 (($CH_3)_3C$), 30.1 (($CH_3)_3C$), 16.5 (CH_3C), 14.3 (CH_3CH_2O) ppm. MS (EI): *m/z* (%) = 210 (M^+, 10), 154 (89), 125 (100), 109 (81), 82 (22), 57 (55), 41 (47). $C_{11}H_{18}N_2O_2$ (210.14): calcd. C 62.83, H 8.63, N 13.32; found C 63.04, H 8.88, N 13.65.

Ethyl 3-[2-(4-methoxyphenyl)-2-oxo-ethyl]-5-methyl-3*H*-imidazole-4-carboxylate (2g)—Imidazole **2g** was isolated (method A: 136 mg, 75%; method B: 113 mg, 69%) by column chromatography (light petroleum/ethyl acetate 50:50) as a pale yellow solid, mp 116–118 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.11 (s, 1H, *H*-2), 7.97 (d, *J* = 8.9 Hz, 3H, *H*-3′,*H*-5′), 6.98 (d, *J* = 8.9 Hz, 2H, *H*-2′, *H*-6′), 5.79 (s, 2H, CH_2CO), 4.22 (q, *J* = 7.1 Hz, 2H, CH_3CH_2O), 3.88 (s, 3H, CH_3O), 2.57 (s, 3H, CH_3C), 1.25 (t, *J* = 7.1 Hz, 3H,

C*H*$_3$CH$_2$O) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 189.9 (*C*OCH$_2$), 164.4 (*C*-4′), 160.6 (C=O), 145.4 (*C*-5), 140.4 (*C*-2), 130.4 (*C*-3′, *C*-5′), 127.3 (C-1′), 119.3 (C-4), 114.2 (*C*-2′, *C*-6′), 60.8 (CH$_3$*C*H$_2$O), 55.6 (*C*H$_3$O), 53.3 (*C*H$_2$CO), 14.9 (*C*H$_3$C), 14.2 (*C*H$_3$CH$_2$O) ppm. MS (EI): *m/z* (%) = 302 (M^+, 3), 135 (100), 92 (7), 77 (11). $C_{16}H_{18}N_2O_4$ (302.13): calcd. C 63.56, H 6.00, N 9.27; found C 63.66, H 6.25, N 9.50.

Ethyl 5-methyl-3-phenyl-3*H*-imidazole-4-carboxylate (2h)—Imidazole **2h** was isolated (method A: 111 mg, 80%; method B: 39 mg, 31%) by column chromatography (light petroleum/ethyl acetate 50:50) as a pale yellow solid, mp 47–49 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.63 (s, 1H, *H*-2), 7.44 (m, 3H, *H*-3′–*H*-5′), 7.27 (m, 2H, *H*-2′, *H*-6′), 4.15 (q, *J* = 7.1 Hz, 2H, CH$_3$C*H*$_2$O), 2.58 (s, 3H, C*H*$_3$C), 1.13 (t, *J* = 7.1 Hz, 3H, C*H*$_3$CH$_2$O) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.1 (*C*=O), 147.7 (*C*-5), 140.0 (*C*-2), 137.1 (*C*-1′), 128.89 (*C*-3′, *C*-5′), 128.86 (*C*-4′), 126.3 (*C*-2′, *C*-6′), 120.3 (*C*-4), 60.4 (CH$_3$*C*H$_2$O), 15.2 (*C*H$_3$C), 14.0 (*C*H$_3$CH$_2$O) ppm. MS (EI): *m/z* (%) = 230 (M^+, 59), 201 (63), 185 (49), 158 (29), 130 (30), 104 (18), 77 (100), 51 (45). $C_{13}H_{14}N_2O_2$ (230.11): calcd. C 67.81, H 6.13, N 12.17; found C 68.11, H 6.30, N 12.44.

Ethyl 3-(4-dimethylaminophenyl)-5-methyl-3*H*-imidazole-4-carboxylate (2i)—Imidazole **2i** was isolated (method A: 125 mg, 76%; method B: 103 mg, 70%) by column chromatography (petroleum/ethyl acetate 50:50) as a pale brown solid, mp 96–98 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.66 (s, 1H, *H*-2), 7.11 (d, *J* = 9.0, 2H, *H*-3′, *H*-5′), 6.71 (d, *J* = 9.0, 2H, *H*-2′, *H*-6′), 4.19 (q, *J* = 7.1 Hz, 2H, CH$_3$C*H*$_2$O), 3.00 (s, 6H, N(C*H*$_3$)$_2$), 2.59 (s, 3H, C*H*$_3$C), 1.20 (t, *J* = 7.1 Hz, 3H, C*H*$_3$CH$_2$O) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.0 (*C*=O), 150.7 (*C*-4′), 146.0 (*C*-5), 139.7 (*C*-2), 126.9 (*C*-2′, *C*-6′), 125.4 (*C*-1′), 120.7 (*C*-4), 111.7 (*C*-3′, *C*-5′), 60.5 (CH$_3$*C*H$_2$O), 40.5 (N(*C*H$_3$)$_2$), 15.0 (*C*H$_3$C), 14.1 (*C*H$_3$CH$_2$O) ppm. MS (EI): *m/z* (%) = 273 (M^+, 100), 227 (15), 200 (29), 173 (17), 159 (38), 147 (70), 132 (31), 121 (40), 113 (17), 105 (21), 86 (19), 77 (28), 42 (19). $C_{15}H_{19}N_3O_2$ (273.15): calcd. C 65.91, H 7.01, N 15.37; found C 66.33, H 7.45, N 15.60.

Ethyl 3-benzyl-5-methyl-2-propyl-3*H*-imidazole-4-carboxylate (2j)—Imidazole **2j** was isolated (method A: 149 mg, 87% using butanal, 84 mg, 49% using 1,1-dimethoxybutane; method B: 57 mg, 37%) by column chromatography (light petroleum/ethyl acetate 70:30) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.05 (m, 3H, *H*-3′–*H*-5′), 6.73 (d, *J* = 7.2 Hz, 2H, *H*-2′, *H*-6′), 5.29 (s, 2H, NC*H*$_2$Ph), 3.99 (q, *J* = 7.1 Hz, 2H, CH$_3$C*H*$_2$O), 2.37 (t, *J* =7.9 Hz, 2H, CH$_3$CH$_2$C*H*$_2$), 2.28 (s, 3H, C*H*$_3$C), 1.46 (m, *J* =7.7 Hz, 2H, CH$_3$C*H*$_2$CH$_2$), 1.04 (t, *J* = 7.1 Hz, 3H, C*H*$_3$CH$_2$O), 0.69 (t, *J* = 7.3 Hz, 3H, C*H*$_3$CH$_2$CH$_2$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.1 (*C*=O), 152.4 (*C*-2), 147.1 (*C*-5), 137.2 (*C*-1′), 128.7 (*C*-3′, *C*-5′), 127.4 (*C*-4′), 125.8 (*C*-2′, *C*-6′), 118.4 (*C*-4), 60.1 (CH$_3$*C*H$_2$O), 48.1 (N*C*H$_2$), 29.0 (CH$_3$CH$_2$*C*H$_2$), 21.3 (*C*H$_3$CH$_2$CH$_2$), 15.8 (*C*H$_3$C), 14.2 (*C*H$_3$CH$_2$O), 13.9 (*C*H$_3$CH$_2$CH$_2$) ppm. MS (EI): *m/z* (%) = 286 (M^+, 9), 257 (13), 167 (11), 91 (100), 65 (12). $C_{17}H_{22}N_2O_2$ (286.17): calcd. C 71.30, H 7.74, N 9.78; found C 71.67, H 7.90, N 10.02.

Ethyl 2,3-dibenzyl-5-methyl-3*H*-imidazole-4-carboxylate (2k)—Imidazole **2k** was isolated (method A: 159 mg, 79%; method B: 86 mg, 48%) by column chromatography (light petroleum/ethyl acetate 70:30) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.30–7.19 (m, 6H, *H*-3′–*H*-5′, *H*-3″–*H*-5″), 7.13 (m, 2H, *H*-2′, *H*-6′), 6.89 (m, 2H, *H*-2″, *H*-6″), 5.41 (s, 2H, NC*H*$_2$Ph), 4.23 (q, *J* = 7.1 Hz, 2H, CH$_3$C*H*$_2$O), 4.06 (s, 2H, CC*H*$_2$Ph), 2.57 (s, 3H, C*H*$_3$C), 1.27 (t, *J* = 7.1 Hz, 3H, C*H*$_3$CH$_2$O) ppm. ^{13}C NMR (400 MHz, $CDCl_3$): δ = 160.8 (*C*=O), 150.2 (*C*-2), 146.3 (*C*-5), 136.6 (*C*-1″), 135.7 (*C*-1′), 128.9 (*C*-3′, *C*-5′), 128. 8 (*C*-3″, *C*-5″), 128.4 (*C*-2′, *C*-6′), 127.5 (*C*-4″), 127.1 (*C*-4′), 125.8 (*C*-2″, *C*-6″), 119.2 (*C*-4), 60.4 (CH$_3$*C*H$_2$O), 48.4 (N*C*H$_2$Ph), 33.4 (C*C*H$_2$Ph), 15.6 (*C*H$_3$C), 14.2 (*C*H$_3$CH$_2$O) ppm.

MS (EI): *m/z* (%) = 334 (M^+, 14), 243 (12), 215 (9), 167 (13), 91 (100), 65 (13). $C_{21}H_{22}N_2O_2$ (334.17): calcd. C 75.42, H 6.63, N 8.38; found C 75.60, H 6.77, N 8.61.

Ethyl 3-benzyl-5-methyl-2-thiophen-2-ylmethyl-3*H*-imidazole-4-carboxylate (2l)—Imidazole **2l** was isolated (method A: 102 mg, 50%; method B: 74 mg, 40%) by column chromatography (light petroleum/ethyl acetate 70:30) as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.31–7.21 (m, 3H, *H*-3′–*H*-5′), 7.14 (dd, *J* = 5.1, 1.1 Hz, 1H, *H*-5′), 6.93 (d, *J* = 7.0 Hz, 2H, *H*-2″, *H*-6″), 6.88 (dd, *J* = 5.1, 3.6 Hz, 1H, *H*-4′), 6.75 (dd, *J* = 3.6, 1.1 Hz, 1H, *H*-3′), 5.49 (s, 2H, NCH_2Ph), 4.23 (q, *J* = 7.1 Hz, 2H, CH_3CH_2O), 4.17 (s, 2H, CCH_2–C-2′), 2.54 (s, 3H, CH_3C), 1.28 (t, *J* = 7.1 Hz, 3H, CH_3CH_2O) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.1 (C=O), 149.6 (*C*-2), 147.2 (*C*-5), 138.2 (*C*-2′), 136.8 (*C*-1′), 128.8 (*C*-3″, *C*-5″), 127.4 (*C*-4′), 127.0 (*C*-4″), 125.9 (*C*-3′), 125.8 (*C*-2″, *C*-6″), 124.7 (*C*-5′), 119.2 (*C*-4), 60.2 (CH_3CH_2O), 48.4 (NCH_2), 28.4 (CCH_2–C-2′), 16.0 (CH_3C), 14.2 (CH_3CH_2O) ppm. MS (EI): *m/z* (%) = 340 (M^+, 13), 249 (11), 173 (15), 91 (100), 65 (13). $C_{19}H_{20}N_2O_2S$ (340.12): calcd. C 67.03, H 5.92, N 8.23, S 9.42; found C 66.72, H 6.25, N 8.39, S 9.18.

Ethyl 3-benzyl-5-methyl-2-phenoxymethyl-3*H*-imidazole-4-carboxylate (2m)—Imidazole **2m** was isolated (method A: 156 mg, 74%) by column chromatography (light petroleum/ethyl acetate 70:30) as a brown solid, mp 51–53 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.28–7.22 (m, 5H, *H*-3′, *H*-5′, *H*-3″–*H*-5″), 7.01–6.93 (m, 3H, *H*-4′, *H*-2″, *H*-6″), 6.90 (d, *J* = 8.0 Hz, 2H, *H*-2′, *H*-6′), 5.69 (s, 1H, NCH_2Ph), 5.05 (s, 2H, CCH_2O), 4.25 (q, *J* = 7.1 Hz, 2H, CH_3CH_2O), 2.54 (s, 3H, CH_3C), 1.27 (t, *J* = 7.1 Hz, 3H, CH_3CH_2O) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.9 (*C*=O), 157.8 (*C*-1′), 147.0 (*C*-2), 146.6 (*C*-5), 137.0 (*C*-1″), 129. 6 (*C*-3′, *C*-5′), 128.7 (*C*-3″, *C*-5″), 127.4 (*C*-4″), 126.1 (*C*-2″, *C*-6″), 121.6 (*C*-4′), 120.3 (*C*-4), 114.8 (*C*-2′, *C*-6′), 62.5 (CCH_2O), 60.4 (CH_3CH_2O), 48.8 (NCH_2Ph), 15.9 (CH_3C), 14.2 (CH_3CH_2O) ppm. MS (EI): *m/z* (%) = 305 ([M – EtO]$^+$, 1), 257 (18), 211 (19), 183 (2), 115 (3), 91 (100), 77 (3), 65 (12), 39 (4). $C_{21}H_{22}N_2O_3$ (350.16): calcd. C 71.98, H 6.33, N 7.99; found C 72.30, H 6.55, N 8.28.

Ethyl 3-benzyl-5-methyl-2-(1-phenoxyethyl)-3*H*-imidazole-4-carboxylate (2n)—Imidazole **2n** was isolated (Method A: 133 mg, 61%) by column chromatography (light petroleum/ethyl acetate 70:30) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.25–7.16 (m, 5H, *H*-3′, *H*-5′, *H*-3″–*H*-5″), 6.95–6.85 (m, 3H, *H*-4′, *H*-2″, *H*-6″), 6.81 (d, *J* = 8.0 Hz, 2H, *H*-2′, *H*-6′), 5.78 (d, *J* = 16.3 Hz, 1H, CH_2Ph), 5.58 (d, *J* = 16.3 Hz, 1H, CH_2Ph), 5.50 (q, *J* = 6.6 Hz, 1H, CH_3CH), 4.19 (q, *J* = 7.1 Hz, 2H, CH_3CH_2O), 2.55 (s, 3H, CH_3C), 1.65 (d, *J* = 6.6 Hz, 3H, CH_3CH), 1.23 (t, *J* = 7.1 Hz, 3H, CH_3CH_2O) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.8 (*C*=O), 157.1 (*C*-1′), 150.3 (*C*-2), 146.9 (*C*-5), 137.4 (*C*-1″), 129.6 (*C*-3′, *C*-5′), 128.6 (*C*-3″, *C*-5″), 127.2 (*C*-4″), 125.7 (*C*-2″, *C*-6″), 121.6 (*C*-4′), 120.0 (*C*-4), 115.6 (*C*-2′, *C*-6′), 69.7 (CH_3CH), 60.3 (CH_3CH_2O), 48.6 (CH_2Ph), 19.3 (CH_3CH), 15.9 (CH_3C), 14.2 (CH_3CH_2O) ppm. MS (EI): *m/z* (%) = 364 (M^+, 1), 319 (1), 271 (26), 225 (5), 135 (4), 91 (100), 65 (11), 39 (5). $C_{22}H_{24}N_2O_3$ (364.18): calcd. C 72.50, H 6.64, N 7.69; found C 72.33, H 6.90, N 7.88.

Ethyl 3-benzyl-5-methyl-2-phenyl-3*H*-imidazole-4-carboxylate (2o)—Imidazole **2o** was isolated (method A: 96 mg, 50%; method B: 76 mg, 44%) by column chromatography (light petroleum/ethyl acetate 70:30) as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.52 (m, 2H, *H*-2′, *H*-6′), 7.42–7.33 (m, 3H, *H*-3′–*H*-5′), 7.31–7.20 (m, 3H, *H*-3″–*H*-5″), 6.95 (d, *J* = 7.2 Hz, 2H, *H*-2″, *H*-6″), 5.58 (s, 2H, NCH_2Ph), 4.22 (q, *J* = 7.1 Hz, 2H, CH_3CH_2O), 2.61 (s, 3H, CH_3C), 1.24 (t, *J* = 7.1 Hz, 3H, CH_3CH_2O) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.1 (*C*=O), 151.5 (*C*-2), 148.2 (*C*-5), 138.1 (*C*-1″), 134.0 (*C*-1′), 129.9 (*C*-4′), 129.4 (*C*-2′, *C*-6′), 128.82 (*C*-3′, *C*-5′), 128.78 (*C*-3″, *C*-5″), 127.4

(*C*-4″), 125.8 (*C*-2″, *C*-6″), 119.7 (*C*-4), 60.4 (CH_3CH_2O), 49.8 (NCH_2), 16.0 (CH_3C), 14.3 (CH_3CH_2O) ppm. MS (EI): *m/z* (%) = 320 (M^+, 12), 274 (3), 115 (4), 104 (6), 91 (100), 65 (8). $C_{20}H_{20}N_2O_2$ (320.15): calcd. C 74.98, H 6.29, N 8.74; found C 75.18, H 6.33, N 8.92.

Methyl 3-benzyl-5-ethyl-3*H*-imidazole-4-carboxylate (2p)—Imidazole **2p** was isolated (method A: 101 mg, 69%) by column chromatography (light petroleum/ethyl acetate 50:50 to 40:60) as a pale yellow oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.53 (s, 1H, *H*-2), 7.39–7.23 (m, 3H, *H*-3′–*H*-5′), 7.20–7.08 (m, 2H, *H*-2′, *H*-6′), 5.46 (s, 2H, CH_2Ph), 3.80 (s, 3H, OCH_3), 2.90 (q, *J* = 7.5 Hz, 2H, CH_3CH_2C), 1.25 (t, *J* = 7.5 Hz, 3H, CH_3CH_2C) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 161.3 (*C*=O), 154.2 (*C*-5), 140.7 (*C*-2), 136.6 (*C*-1′), 128.8 (*C*-3′, *C*-5′), 127.9 (*C*-4′), 127.1 (*C*-2′, *C*-6′), 117.8 (*C*-4), 51.2 (CH_2Ph), 50.6 (OCH_3), 22.8 (CH_3CH_2C), 13.5 (CH_3CH_2C) ppm. MS (EI): *m/z* (%) = 244 (M^+, 51), 229 (9), 197 (12), 153 (13), 121 (43), 91 (100), 65 (43). $C_{14}H_{16}N_2O_2$ (244,12) calcd. C 68.83, H 6.60, N 11.47; found C 69.06, H 6.68, N 11.58.

Methyl 3-allyl-5-ethyl-3*H*-imidazole-4-carboxylate (2q)—Imidazole **2q** was isolated (method A: 91 mg, 78%) by column chromatography (light petroleum/ethyl acetate 50:50 to 40:60) as a pale yellow oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.48 (s, 1H, *H*-2), 5.96 (ddt, *J* = 17.0, 10.3, 5.5, 1H, NCH_2CH), 5.18 (ddd, *J* = 10.3, 2.4, 1.3 Hz, 1H, H_{cis}), 5.04 (ddd, *J* = 17.0, 2.6, 1.6 Hz, 1H, H_{trans}), 4.85 (dt, *J* = 5.5, 1.3 Hz, 2H, NCH_2), 3.84 (s, 3H, CH_3O), 2.87 (q, *J* = 7.5 Hz, 2H, CH_3CH_2C), 1.22 (t, *J* = 7.5 Hz, 3H, CH_3CH_2C) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.3 (*C*=O), 154.0 (*C*-5), 140.3 (*C*-2), 133.3 (NCH_2CH), 117.7 ($NCHCH_2$), 117.6 (*C*-4), 51.2 (NCH_2), 49.4 (OCH_3), 22.7 (CH_3CH_2C), 13.6 (CH_3CH_2C) ppm. MS (EI): *m/z* (%) = 194 (M^+, 64), 179 (82), 163 (20), 149 (11), 135 (22), 121 (100), 41 (33). $C_{10}H_{14}N_2O_2$ (194.11): calcd. C 61.84, H 7.27, N 14.42; found C 61.95, H 7.40, N 14.70.

Ethyl 3-benzyl-5-propyl-3*H*-imidazole-4-carboxylate (2r)—Imidazole **2r** was isolated (method B: 134 mg, 87%) by column chromatography (light petroleum/ethyl acetate 50:50 to 40:60) as a colourless oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.50 (s, 1H, *H*-2), 7.37–7.20 (m, 3H, *H*-3′–*H*-5′), 7.16–7.04 (m, 2H, *H*-2′, *H*-6′), 5.44 (s, 2H, CH_2Ph), 4.24 (q, *J* = 7.1 Hz, 2H, CH_3CH_2O), 2.86 (t, *J* = 7.4 Hz, 2H, $CH_3CH_2CH_2C$), 1.70 (sext, *J* = 7.4 Hz, 2H, $CH_3CH_2CH_2C$), 1.28 (t, *J* = 7.1 Hz, 3H, CH_3CH_2O), 0.95 (t, *J* = 7.4 Hz, 3H, $CH_3CH_2CH_2C$) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 161.9 (*C*=O), 152.8 (*C*-5), 140.6 (*C*-2), 136.7 (*C*-1′), 128.7 (*C*-3′, *C*-5′), 127.8 (*C*-4′), 127.0 (*C*-2′, *C*-6′), 118.4 (*C*-4), 60.2 (CH_3CH_2O), 50.5 (CH_2Ph), 31.5 ($CH_3CH_2CH_2C$), 22.8 ($CH_3CH_2CH_2C$), 14.1 (CH_3CH_2O), 13.9 ($CH_3CH_2CH_2C$) ppm. MS (EI): *m/z* (%) = 272 (M^+, 4), 244 (22), 197 (6), 153 (5), 91 (100), 65 (6). $C_{16}H_{20}N_2O_2$ (272.15) calcd. C 70.56, H 7.40, N 10.29; found C 70.79, H 7.49, N 10.46.

Ethyl 3-Allyl-5-propyl-3*H*-imidazole-4-carboxylate (2s)—Imidazole **2s** was isolated (method B: 102 mg, 81%) by column chromatography (light petroleum/ethyl acetate 50:50 to 40:60) as a pale yellow oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.46 (s, 1H, *H*-2), 5.96 (ddt, *J* = 17.0, 10.3, 5.5, 1H, NCH_2CH), 5.17 (dd, *J* = 10.3, 1.1 Hz, 1H, H_{cis}), 5.02 (dd, *J* = 17.0, 1.1 Hz, 1H, H_{trans}), 4.85 (d, *J* = 5.5 Hz, 2H, NCH_2), 4.29 (q, *J* = 7.1 Hz, 2H, CH_3CH_2O), 2.83 (t, *J* = 7.4 Hz, 2H, $CH_3CH_2CH_2C$), 1.67 (sext, *J* = 7.4 Hz, 2H, $CH_3CH_2CH_2C$), 1.34 (t, *J* = 7.1 Hz, 3H, CH_3CH_2O), 0.93 (t, *J* = 7.4 Hz, 3H, $CH_3CH_2CH_2C$) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 160.9 (*C*=O), 152.5 (*C*-5), 140.1 (*C*-2), 133.4 (NCH_2CH), 117.6 (2 x *C*-4, $NCHCH_2$), 60.1 (CH_3CH_2O), 49.3 (NCH_2), 31.4 ($CH_3CH_2CH_2C$), 22.7 ($CH_3CH_2CH_2C$), 14.2 (CH_3CH_2O), 13.9 ($CH_3CH_2CH_2C$) ppm. MS (EI): *m/z* (%) = 222 (M^+, 11), 207 (10), 194 (100), 177 (9), 165 (29), 149 (29), 135 (33) 125 (35) 109 (40) 41

(44). $C_{12}H_{18}N_2O_2$ (222.14): calcd. C 64.84, H 8.16, N 12.60; found C 65.02, H 8.37, N 12.67.

Methyl 3-benzyl-5-methoxycarbonylmethyl-3*H*-imidazole-4-carboxylate (2t)— Imidazole **2t** was isolated (method B: 97 mg, 59%) by column chromatography (light petroleum/ethyl acetate 50:50 to 70:30) as a whitish solid, mp 68–71 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.55 (s, 1H, *H*-2), 7.42–7.23 (m, 3H, *H*-3′–*H*-5′), 7.21–7.10 (m, 2H, *H*-2′, *H*-6′), 5.48 (s, 2H, CH_2Ph), 3.96 (s, 2H, CH_2CO$_2$CH$_3$), 3.79 (s, 3H, CH_3O), 3.71 (s, 3H, CH_3O) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 170.9 (CH$_2$*C*=O), 160.6 (*C*=O), 144.5 (*C*-5), 140.8 (*C*-2), 136.1 (*C*-1′), 128.9 (*C*-3′, *C*-5′), 128.1 (*C*-4′), 127.3 (*C*-2′, *C*-6′), 119.8 (*C*-4), 52.0 (*C*H$_2$Ph), 51.4 (O*C*H$_3$), 50.7 (O*C*H$_3$), 35.7 (*C*H$_2$CO$_2$CH$_3$) ppm. MS (EI): *m/z* (%) = 288 (M^+, 22), 228 (8), 197 (5), 121 (35), 91 (100), 65 (13). $C_{15}H_{16}N_2O_4$ (288.11) calcd. C 62.49, H 5.59, N 9.72; found C 62.80, H 5.40, N 9.96.

Methyl 3-allyl-5-methoxycarbonylmethyl-3*H*-imidazole-4-carboxylate (2u)— Imidazole **2u** was isolated (method B: 92 mg, 68%) by column chromatography (light petroleum/ethyl acetate 50:50 to 40:60) as a colourless oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.55 (s, 1H, *H*-2), 6.00 (ddt, *J* = 17.0, 10.3, 5.6, 1H, NCH$_2$C*H*), 5.24 (ddd, *J* = 10.3, 2.3, 1.3 Hz, 1H, H_{cis}), 5.11 (ddd, *J* = 17.0, 2.5, 1.5 Hz, 1H, H_{trans}), 3.96 (s, 2H, CH_2CO$_2$CH$_3$), 3.84 (s, 3H, CH_3O), 3.71 (s, 3H, CH_3O) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.0 (CH$_2$*C*=O), 160.6 (*C*=O), 144.3 (*C*-5), 140.4 (*C*-2), 132.9 (NCH$_2$*C*H), 119.6 (*C*-4), 118.2 (NCH*C*H$_2$), 52.1 (N*C*H$_2$), 51.5 (O*C*H$_3$), 49.6 (O*C*H$_3$), 35.8 (*C*H$_2$CO$_2$CH$_3$) ppm. MS (EI): *m/z* (%) = 238 (M^+, 19), 206 (7), 179 (100), 147 (20), 119 (35), 41 (67). $C_{11}H_{14}N_2O_4$ (238.10): calcd. C 55.46, H 5.92, N 11.76; found C 55.87, H 5.68, N 12.09.

Methyl 3-benzyl-5-phenyl-3*H*-imidazole-4-carboxylate (2v)—Imidazole **2v** was isolated (method B: 99 mg, 57%) by column chromatography (light petroleum/ethyl acetate 50:50 to 40:60) as a whitish solid, mp 99–101 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.75–7.60 (m, 2H, *H*-2″, *H*-6″), 7.66 (s, 1H, *H*-2), 7.48–7.27 (m, 6H, *H*-3′–*H*-5′, *H*-3″–*H*-5″), 7.22 (d, *J* = 7.8 Hz, 2H, *H*-2′, *H*-6′), 5.54 (s, 2H, CH_2Ph), 4.18 (q, *J* = 7.1 Hz, 2H, CH$_3$CH_2O), 1.12 (t, *J* = 7.1 Hz, 3H, CH_3CH$_2$O) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 160.7 (*C*=O), 149.6 (*C*-5), 141.0 (*C*-2), 136.4 (*C*-1′), 134.3 (*C*-1″), 129.5 (*C*-2″, *C*-6″), 128.9 (2 x *C*), 128.09, 128.06, 127.6 (*C*-2′, *C*-6′), 127.2 (2 x *C*), 118.6 (*C*-4), 60.7 (CH$_3$*C*H$_2$O), 50.8 (*C*H$_2$Ph), 13.8 (*C*H$_3$CH$_2$O) ppm. MS (EI): *m/z* (%) = 306 (M^+, 44), 260 (7), 233 (11), 171 (6), 91 (100), 65 (14). $C_{19}H_{18}N_2O_2$ (306.14) calcd. C 74.49, H 5.92, N 9.14; found C 74.77, H 5.77, N 9.33.

Methyl 3-allyl-5-phenyl-3*H*-imidazole-4-carboxylate (2w)—Imidazole **2w** was isolated (method B: 90 mg, 62%) by column chromatography (light petroleum/ethyl acetate 70:30 to 40:60) as a pale yellow oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.78–7.59 (m, 3H, *H*-2′, *H*-6′, *H*-2), 7.50–7.30 (m, 3H, *H*-3′–*H*-5′), 6.06 (ddt, *J* = 17.0, 11.0, 5.5, 1H, NCH$_2$C*H*), 5.28 (dd, *J* = 11.0, 0.9 Hz, 1H, H_{cis}), 5.17 (dd, *J* = 17.0, 0.9 Hz, 1H, H_{trans}), 4.95 (d, *J* = 5.5 Hz, 2H, NCH_2), 4.24 (q, *J* = 7.1 Hz, 2H, CH$_3$CH_2O), 1.20 (t, *J* = 7.1 Hz, 3H, CH_3CH$_2$O) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 160.7 (*C*=O), 149.4 (*C*-5), 140.5 (*C*-2), 134.4 (*C*-1′), 133.2 (NCH$_2$*C*H), 129.5 (*C*-3′, *C*-5′), 128.0 (*C*-4′), 127.5 (*C*-2′, *C*-6′), 118.4 (*C*-4), 118.1 (CH*C*H$_2$), 60.6 (CH$_3$*C*H$_2$O), 49.6 (*C*H$_2$Ph), 13.8 (*C*H$_3$CH$_2$O) ppm. MS (EI): *m/z* (%) = 256 (M^+, 100), 209 (43), 183 (86), 171 (27), 89 (43), 41 (44). $C_{15}H_{16}N_2O_2$ (256.12): calcd. C 70.29, H 6.29, N 10.93; found C 70.65, H 6.02, N 10.83.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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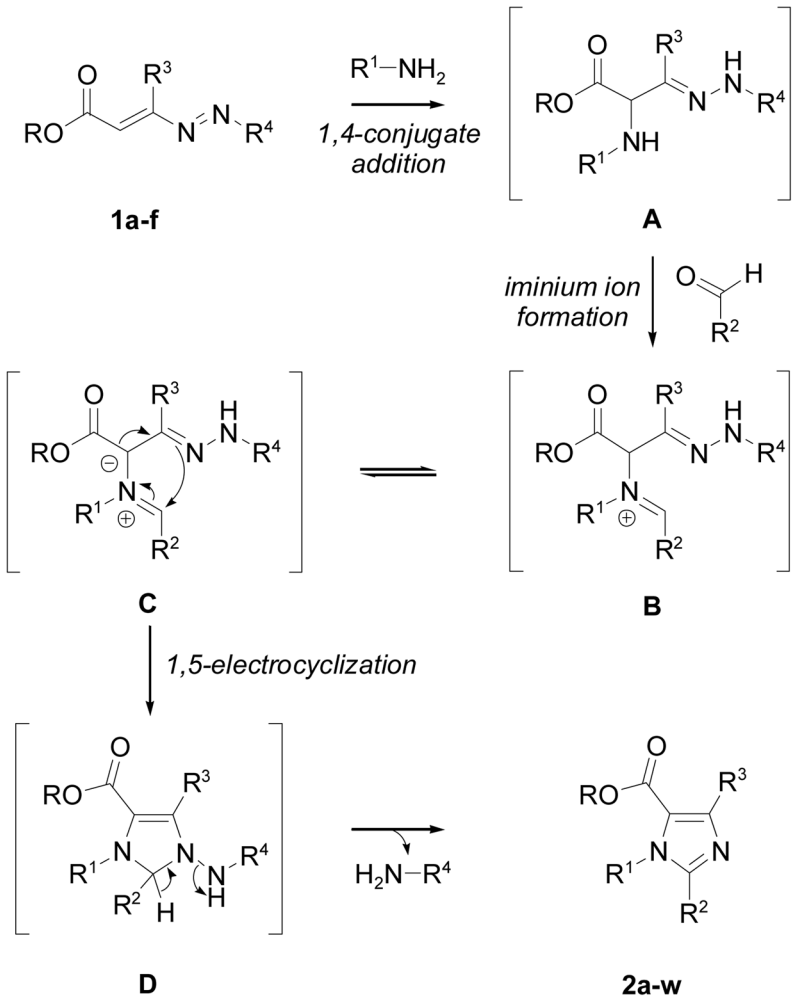
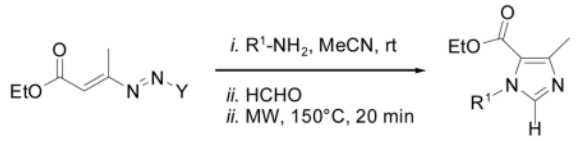


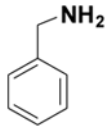
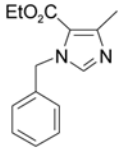
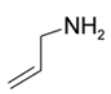
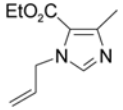
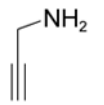
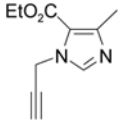
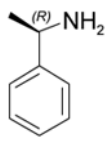
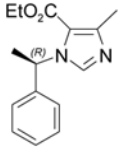
Scheme 1.
Postulated mechanism for the formation of imidazole-4-carboxylates **2a–w** from DDs **1a–f**.

Table 1

One-pot synthesis of 2-unsubstituted 3*H*-imidazole-4-carboxylates **2a–i**.



1a-b **2a-i**

Entry	DD 1	DD Y	Amine	Imidazole	2	Yield[a] (%)
1	**1a**[b]	COOEt			**2a**	78
2	**1b**	$CONH_2$				77
3	**1a**[b]	COOEt			**2b**	86
4	**1b**	$CONH_2$				62
5	**1a**[b]	COOEt			**2c**	83
6	**1b**	$CONH_2$				62
7	**1a**[b]	COOEt			**2d**	75
8	**1b**	$CONH_2$				80

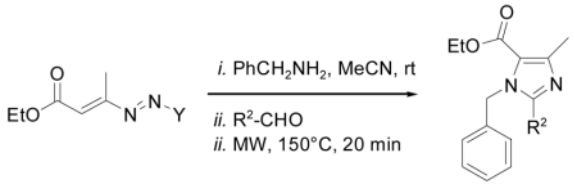
Entry	DD 1	Y	Amine	Imidazole	2	Yield[a] (%)
9	1a[b]	COOEt			2e	83
10	1b	$CONH_2$				71
11	1a[b]	COOEt			2f	44
12	1b	$CONH_2$				50
13	1a[b]	COOEt			2g	75
14	1b	$CONH_2$				69
15	1a[b]	COOEt			2h	80
16	1b	$CONH_2$				31
17	1a[b]	COOEt			2i	76
18	1b	$CONH_2$				70

[a] Isolated yield (after silica gel chromatography) based on starting material, viz. DD **1b** or the corresponding chlorohydrazone in the case of **1a**.

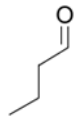
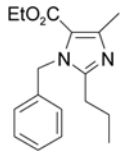
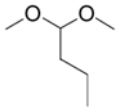
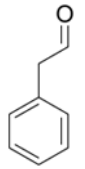
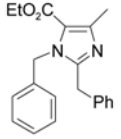
[b] DD **1a** was prepared in situ from the parent chlorohydrazone and used without further purification.

Table 2

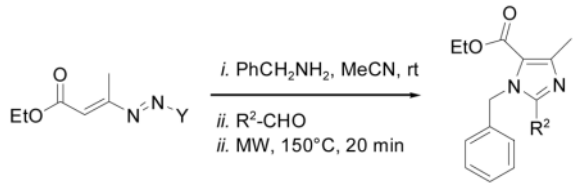
One-pot synthesis of 2-substituted 3-benzyl-3*H*-imidazole-4-carboxylates **2j–o**.



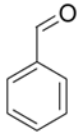
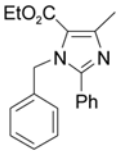
1a-b **2j-o**

Entry	DD		Aldehyde	Imidazole	2	Yield[a] (%)
	1	Y				
1	**1a**[b]	COOEt			**2j**	87
2	**1b**	$CONH_2$				37
3	**1a**[b]	COOEt				49
4	**1a**[b]	COOEt			**2k**	79
5	**1b**	$CONH_2$				48

Entry	DD 1	DD Y	Aldehyde	Imidazole	2	Yield[a] (%)
6	1a[b]	COOEt			2l	50
7	1b	$CONH_2$				40
8	1a[b]	COOEt			2m	74
9	1a[b]	COOEt			2n	61



1a-b **2j-o**

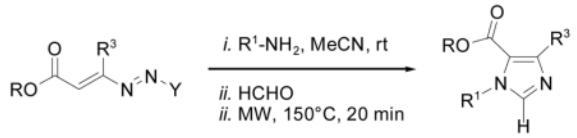
Entry	DD		Aldehyde	Imidazole	2	Yield[a] (%)
	1	Y				
10	**1a**[b]	COOEt			**2o**	50
11	**1b**	$CONH_2$				44

[a]Isolated yield (after silica gel chromatography) based on starting material, viz. DD **1b** or the corresponding chlorohydrazone in the case of **1a**.

[b]DD **1a** was prepared in situ from the parent chlorohydrazone and used without further purification.

Table 3

One-pot synthesis of 2-unsubstituted 3*H*-imidazole-4-carboxylates **2p–w** using benzyamine or allylamine.



1c-f **2p-w**

Entry	DD 1	Imidazole	2	Yield[a] (%)
1	**1c**[b]		**2p**	69
2	**1c**[b]		**2q**	78
3	**1d**		**2r**	87
4	**1d**		**2s**	81

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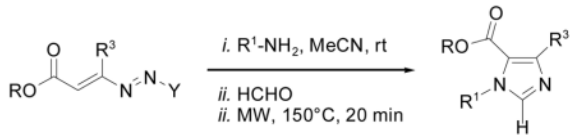
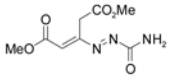
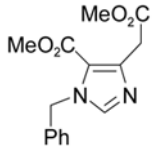
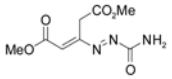
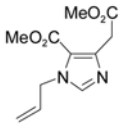
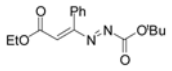
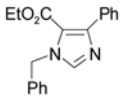
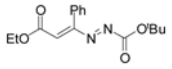
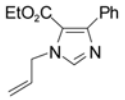


1c-f **2p-w**

Entry	DD 1		Imidazole	2	Yield[a] (%)
5	**1e**			**2t**	59
6	**1e**			**2u**	68
7	**1f**			**2v**	57
8	**1f**			**2w**	62

[a]Isolated yield (after silica gel chromatography) based on starting material, viz. DD **1d–f** or the corresponding chlorohydrazone in the case of **1c**.

[b]DD **1c** was prepared in situ from the parent chlorohydrazone and used without further purification.