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BASE-CATALYZED TRANSFORMATIONS OF IMINIUM PHENYLHYDRAZONES

A NEW CONVENIENT SYNTHESIS OF IMIDAZO[1,2a]AZACYCLOALKANES[1]

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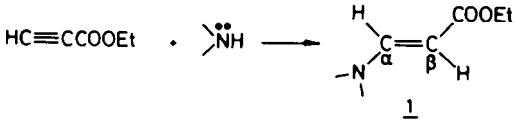
Abstract—β-Enamine esters react with phenyldiazonium fluoroborate to give iminium phenylhydrazone salts which, without isolation, can be converted by a base-catalysed reaction to imidazole derivatives. The latter reaction is critically dependent upon the nature of the base-component of the enamine ester. The mechanism of imidazole formation involves the following sequence of steps: (a) deprotonation of the iminium salt, (b) a symmetry-allowed 1,5-dipolar cyclization of the betaine intermediate and (c) subsequent elimination of aniline, with concomitant aromatization. The scope of the reaction as a facile approach to the synthesis of imidazole derivatives is discussed.

β-Aminoacrylic esters of type **1** can be readily prepared by the addition of secondary amines to ethyl propiolates.[3] These β-enamine esters react with aryldiazonium salts (room temp, MeCN) to yield iminium hydrazone salts which—in many cases—can be isolated as crystalline products. The thermal cyclization of the aryl iminium hydrazones, to cinnoline esters, has been described in the adjoining paper.[4] In this communication we describe the base mediated conversion of the iminium hydrazones to imidazole derivatives.



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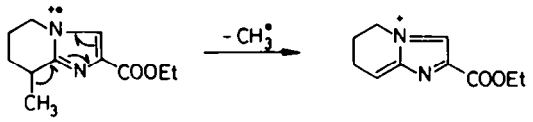
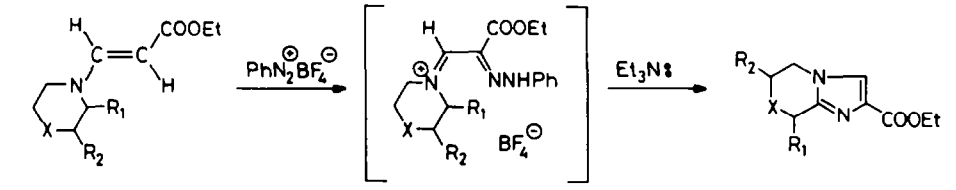
When a solution of the iminium salts **2a–d** (Scheme A), in MeCN, was treated with one equivalent of triethylamine and the mixture refluxed for a couple of hours, fair to good yields (40–70%) of the imidazole derivatives **3a–e** could be isolated after workup. The same products could be isolated when, instead of starting with the isolated salts **2a–d**, mixtures of the corresponding enamine esters and benzenediazonium fluoroborate were allowed to react with triethylamine, after the enamine ester had been consumed (tlc, 1 hr). The preparation of the aforementioned imidazoazacycloalkanes can therefore be achieved in a one-pot reaction. It is noteworthy that the hydrazone **2c**, formed *in situ*, yields a mixture of compounds **3c** and **3d** (2:3), while similarly prepared **2e** did not result in an identifiable product, when treated with the tertiary amine. The structures of the imidazocycloalkanes was assigned on the basis of their spectral and elemental analysis. Distinction between the isomers **3c** and **3d** was made by identification of the AB portion of the ABX pattern for the methylene group next to nitrogen, in the NMR spectrum of **3d** (Experimental). Furthermore, the mass spectrum of **3c** exhibited a M-15 peak, not present in **3d**, which can be ascribed to the expected α-cleavage of the Me group from the parent ion $3c^{+\cdot}$ to result in a stabilized fragment *m/e* 193.



$3c^{+\cdot}$ m/e 193

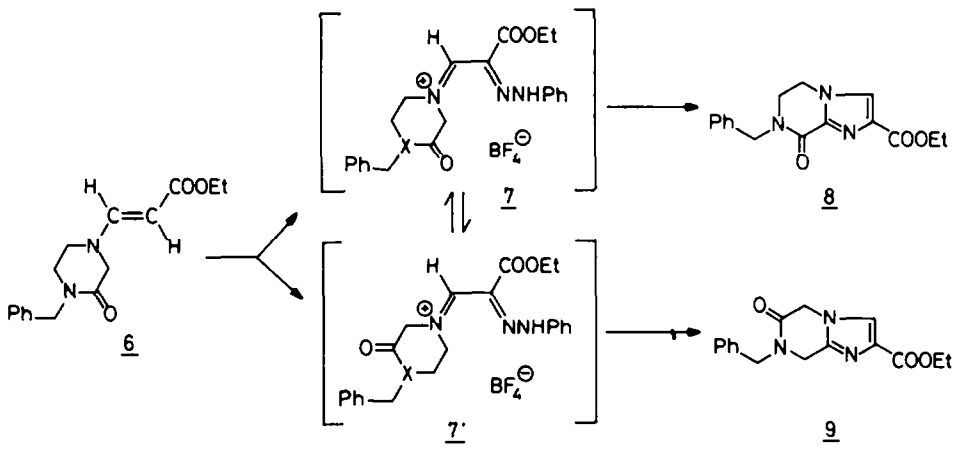
The following mechanism for the formation of the imidazocycloalkanes is proposed (Scheme B). It is visualized that the base abstracts the most acidic proton (=N–NH–) of the iminium salt (Scheme B; **4**→**a**). An intramolecular proton transfer from the α-C (to the iminium nitrogen), that is, process **a**→**b**, results in an intermediate (**b**⟷**b'**), which is poised for a symmetry-allowed disrotatory cyclization to the imidazoline system **c**. Analogous cyclizations have been reported[5a–f] in the literature and, in the context of the present work, special mention may be made of (i) the formation of benzisoxazole by the acid treatment of the oxime of 2-hydroxyaminobenzaldehyde,[5d] (ii) the thermal conversion of osazones to 1-phenyl-1,2,5-triazoles,[5e] and (iii) the synthesis of pyrrolizine esters via the reaction of enamines with dimethyl acetylenedicarboxylate, in methanol.[5f] In the final step of the reaction, aniline is lost from intermediate **c** to yield the imidazoazacycloalkanes **5**.

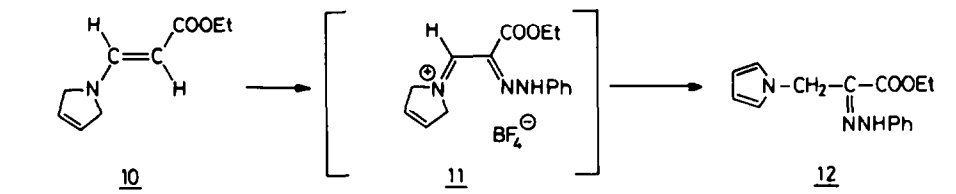
In view of the fact that the salts **2c** and **2e** have been employed *in situ*, the specific structures assigned to them, in terms of the geometry about the C=N$^+$ bond (Scheme A), are arbitrary and represent one set of the two possible isomers. Without further information on this point and on the relative stability of the potentially interconvertible[6] isomers, as well of the intermediates (**a**, **b**⟷**b'**) derived therefrom, under the reaction conditions, it would be expected that **2c** should lead to a mixture of the isomeric imidazoazacycloalkanes **3c** and **3d**. That isomer **3d** is favoured in the mixture suggests the role of steric factors in the cyclization reaction. Presumably, similar factors prevent the formation of any recognizable cyclization product from salt **2e**, where the extra methyl is nearer the reacting site, at least, in one of the isomeric structures.

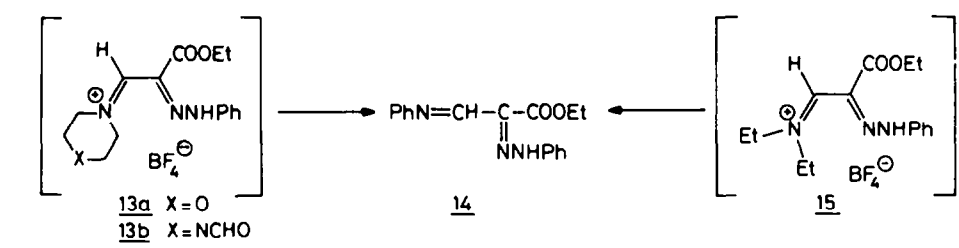


	X	R_1	R_2
2a	–	H	H
2b	CH_2	H	H
2c	CH_2	H	Me
2d	CHMe	H	H
2e	CH_2	Me	H

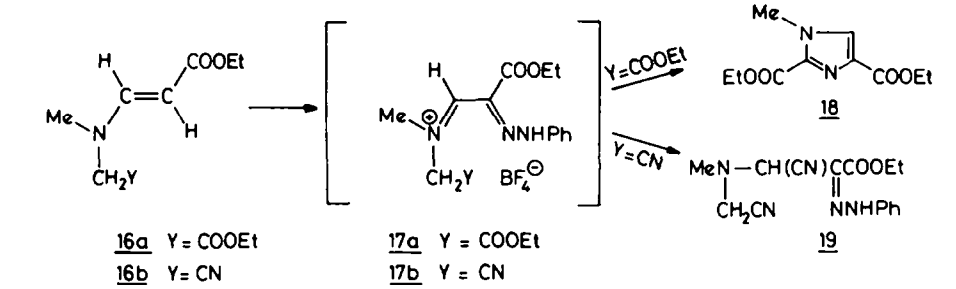
	X	R_1	R_2
3a	–	H	H
3b	CH_2	H	H
3c	CH_2	Me	H
3d	CH_2	H	Me
3e	CHMe	H	H







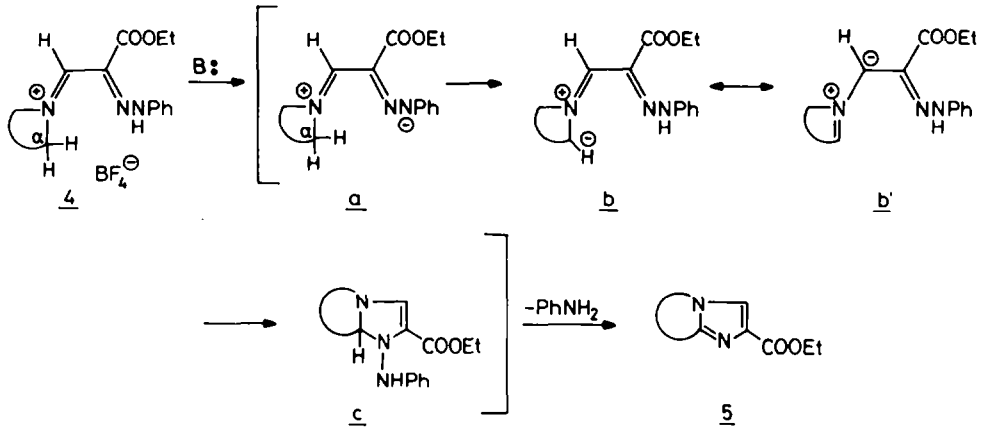
13a X = O
13b X = NCHO



16a Y = COOEt
16b Y = CN

17a Y = COOEt
17b Y = CN

Scheme A



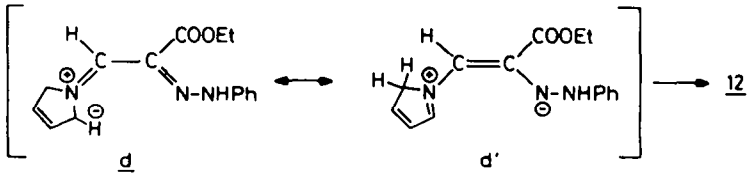
Scheme B

The aforementioned mechanistic sequence (Scheme B) receives support from two further sets of experiments. In one experiment the enamine ester **6**, prepared by the addition of 1-benzyl-2-oxopiperazine[7] to ethyl propiolate, was allowed to react with phenyldiazonium fluoroborate and, the salt **7** (plus, presumably, its geometrical isomer **7'**) formed *in situ*, was treated with triethylamine. While, potentially, two isomeric imidazooxopiperazines are possible from this reaction, only one isomer, namely **8** and the imine **14** (to be discussed in the sequel) could be isolated. No evidence was found for the presence of isomer **9**, in the reaction mixture. The exclusive formation of **8** is consistent with the mechanism described in Scheme B, in which the deprotonation of the α-methylene group in intermediate **a** constitutes a critical step. Such a deprotonation would be favoured from the methylene group between the iminium nitrogen and the CO group of intermediate **7**⟷**7'**, and finally lead to the compound **8**. In the second experiment, the salt **11**, derived from enamine ester **10**, was subjected to the usual basic treatment; whereupon, the hydrazone **12** was obtained (57%). The formation of **12** can be rationalized most adequately, in terms of the generalized Scheme B and is specifically described in Scheme C. The deprotonation process, in case of salt **11**, would result in an ylid intermediate **d**⟷**d'** (Scheme C), which, instead of cyclizing, can stabilize to the pyrrole derivative **12**, via a proton transfer in its betaine form (**d'**). The driving force for this pathway is the aromatization of the pyrroline to the pyrrole moiety, by what amounts to an overall intramolecular redox reaction.

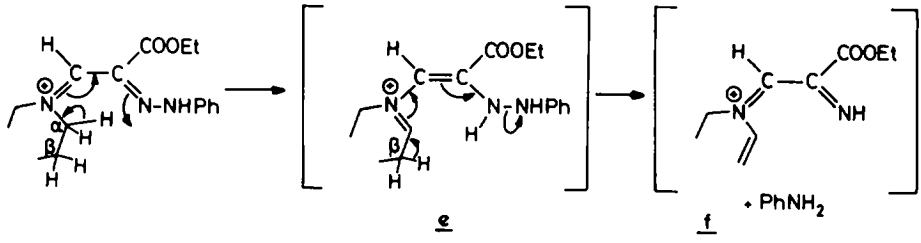
In order to explore the scope of the base-catalyzed cyclization of iminium hydrazones, the reactions of salts **13a, b** and **15** (formed *in situ*) were investigated. However, treatment of the latter products with triethylamine did not result in imidazole formation. Instead, in all three cases, the imine hydrazone **14** was the only product which could be isolated and characterized. Since the preparation of a monocyclic imidazole derivative, via precursor **15**, was not successful, attempts were made to achieve this end by activating the methylene group in the enamine esters (**16a, b**) and, thereby, in the corresponding iminium salts **17a, b**, via introduction of an electronegative group (COOEt or CN). When the reaction mixtures of **16a, b** and phenyldiazonium fluoroborate were, after disappearance of the enamines, allowed to react with triethylamine, **16a** gave the the expected imidazole diester **18** in 38% yield, while **16b** resulted in the formation of the hydrazone ester **19** (23%).

The formation of **14** from a number of precursors (**7**⟷**7'**, **13a, b 15**) argue for a common reaction pathway. In all cases the product (**14**) could be visualized to arise via the reaction of the iminium hydrazone salts with aniline. The latter base replacing the secondary amine moieties of the iminium function. A mechanism for the generation of aniline from **7**⟷**7'**, **13a, b** and **15** is tentatively suggested in Scheme D. A 1,5-hydrogen shift in the salts would result in intermediate **e**, which, following a mechanism analogous to that operative in the formation of osazones (from, e.g. α-hydroxyaldehydes) could fragment into aniline and an unsaturated iminium salt **f**. The latter process, which would be favoured by acidic protons at C(β) (intermediate **e**), is consistent with the fact that, except for **15**, the salts leading to **14**, incorporate an electronegative function next to the *b*-methylene group. The tendency for the fragmentation of **15** to aniline, to finally yield **14**, is not clear. An explanation for the conversion of **15** to **14** via a 1,7-hydrogen (antarafacial) shift in the intermediate of type **e** is not supported by similar anticipated reactions of salts **2a–d**.

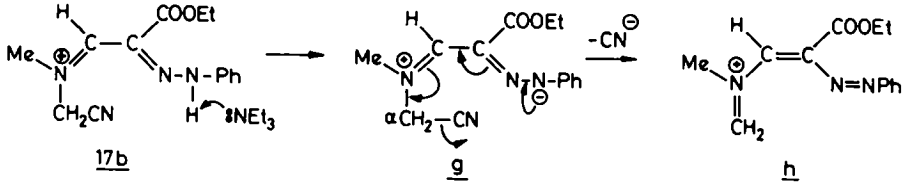
The cyclization of **17a** to **18** has precedent in the conversion of **7** to **8** and must proceed by an analogous mechanism. In this context, the formation of **19** from **17b** is unexpected. However, the cyano group may confer special properties to the intermediate **g** which would be produced from **17b**, upon its reaction with base (Scheme



Scheme C



Scheme D



Scheme E

E). Instead of a proton transfer from the α-methylene group, as in Scheme B, the intermediate (**g**) undergoes stabilization of the negative charge by expulsion of a cyanide ion (**g**→**h**). A similar cyanide ion elimination has been noted for 1-cyano-trans-dimethylamino-4-tertiarybutylcyclohexane.[8] Addition of the liberated cyanide ion to **17b** is visualized as the mechanism of formation of **19**.

EXPERIMENTAL

All m.ps are uncorrected. IR spectra were recorded on a Unicam SP 200 or a Perkin–Elmer 257 spectrometer. The absorptions are given in cm^{-1}. PMR spectra were run on Varian Associates Model A-60, A-60D and HA-100 instruments. The chemical shifts (δ) are given in ppm, using TMS as an internal standard. For the resonance signals the following abbreviations are used: s = singlet, d = doublet, t = triplet, q = quartet and m = multiplet. Spin-spin coupling constants (J) are given in Hertz. Mass spectra were obtained with a Varian Mat-711 spectrometer. Analyses were carried out by Mr. H. Pieters of the Microanalytical Department of this laboratory.

Imidazo[1,2a]*azacycloalkane esters* (**3a–e**)

General procedure. To a soln of the β-amino ester (1 mmol), dissolved in dry MeCN (25 ml), 1 mmol of powdered benzenediazonium tetrafluoroborate was added and the mixture was stirred for 1 hr at room temp. Et_3N (2 mmol) was added and subsequently the soln was refluxed for 2 hr. After evaporation of the solvent the residue was chromatographed on a silica gel column (12 mm × 30 cm). Elution with EtOAc/iPrOH (10:1) yielded the imidazoazacycloalkane ester as a solid, which was recrystallized from EtOAc/diisopropylether. The products **3a–b** could also be obtained by refluxing a soln of **2a–b** (1 mmol) and Et_3N (2 mmol) in MeCN (25 ml) for 2 hr.

Ethyl imidazo-[1,2a]-5,6-*dihydropyrrolo*-2-*carboxylate* (**3a**). M.p. 88–89°; yield 40%. IR ($CHCl_3$): 1705 (C=O); PMR ($CDCl_3$): 1.38 (t, 3H, CH_3), 2.65 (m, 2H, C_6–H), 2.89 (t, 2H, C_7–H, J = 7), 4.03 (t, 2H, C_5–H, J = 7), 4.35 (q, 2H, CH_2–O), 7.57 (s, 1H, C_3–H); MS: *m/e* = 180, (Found: C, 59.92; H, 6.76; N, 15.41. Calc. for $C_9H_{12}N_2O_2$: C, 60.00; H, 6.67; N, 15.56%).

Ethyl imidazo-[1,2a]-5,6,7,8-tetrahydropyridine-2-carboxylate (**3b**). M.p. 59–63°; yield 63%. IR ($CHCl_3$): 1710 (C=O); PMR ($CDCl_3$): 1.38 (t, 3H, CH_3), 1.89 (m, 4H, C_6–H, C_7–H), 2.84 (m, 2H, C_8–H), 3.95 (m, 2H, C_5–H), 4.31 (q, 2H, CH_2–O, 7.41 (s, 1H, C_3–H); MS: *m/e* = 194. (Found: C, 61.75; H, 7.13: N, 14.29. Calc. for $C_{10}H_{14}N_2O_2$: C, 61.86; H, 7.22; N, 14.43%).

Ethyl imidazo-[1,2a]-8-methyl-5,6,7,8-tetrahydropyridino-2-carboxylate (**3c**) and ethyl imidazo-[1,2a]-6-*methyl*-5,6,7,8-*tetrahydropyridino*-2-*carboxylate* (**3d**), yield **3c** 21%. IR ($CHCl_3$): 1710 (C=O); PMR ($CDCl_3$): 1.35 (t, 3H, CH_3–CH_2), 1.43 (d, 3H, CH_3–CH), 2.04 (m, 4H, C_6–H, C_7–H), 2.83 (m, 1H, C_8–H), 3.98 (m, 2H, C_5–H), 4.35 (q, 2H, CH_2–O), 7.44 (s, 1H, C_3–H); MS: *m/e* = 208, 193. (Found: C, 63.28; H, 7.60; N, 13.30. Calc. for $C_{11}H_{16}N_2O_2$: C, 63.46; H, 7.69; N, 13.46%). Yield **3d** 32%; m.p. 66–67°. IR ($CHCl_3$): 1710 (C=O); PMR ($CDCl_3$): 1.11 (d, 3H, CH_3–CH), 1.36 (t, 3H, CH_3–CH_2), 1.62 (m, 1H, C_6–H), 2.05 (m, 2H, C_7–H), 2.90 (m, 2H, C_8–H), 3.78 (AB or ABX-system, 2H, C_5–H, J = 12), 4.35 (q, 2H, CH_2–O), 7.45 (s, 1H, C_3–H); MS: *m/e* = 208. (Found: C, 63.21; H, 7.67; N, 13.57. Calc. for $C_{11}H_{16}N_2O_2$: C, 63.46; H, 7.69; N, 13.46%).

Ethyl imidazo-[1,2a]-7-*methyl*-5,6,7,8-*tetrahydropyridino*-2-*carboxylate* (**3e**). M.p. 98–101°; yield 70%. IR ($CHCl_3$): 1710 (C=O); PMR ($CDCl_3$): 1.14 (d, 3H, CH_3–CH), 1.37 (t, 3H, CH_3–CH_2), 1.70 (m, 1H, C_7–H), 2.03 (m, 2H, C_6–H), 2.73 (ABX, 2H, C_8–H, J_{AB} = 17), 3.96 (m, 2H, C_5–H), 4.35 (q, 2H, CH_2–O), 7.49 (s, 1H, C_3–H); MS: *m/e* = 208. (Found: C, 63.29; H, 7.79; N, 13.51. Calc. for $C_{11}H_{16}N_2O_2$: C, 63.46; H, 7.69; N, 13.46%).

Ethyl imidazo-[1,2a]-7-*benzyl*-8-*oxo*-*piperazino*-2-*carboxylate* (**8**) *and ethyl* 2-*benzenehydrazonyl*-3-*anilineiminopropanoate* (**14**). Starting with **6**, the compds **8** and **14** were prepared according to the same general procedure as described for the synthesis of **3a–e**. After evaporation of the solvent the residue was chromatographed on a silica gel column. Elution with $CHCl_3$/cyclohexane (1:1) yielded **14** (7%), m.p. 84–86°; IR ($CHCl_3$): 1600 (C=C), 1620 (C=N), 1695 (C=O); PMR ($CDCl_3$): 1.41 (t, 3H, CH_3), 4.37 (q, 2H, CH_2), 7.32 (m, 10H, aromatic protons), 8.70, 8.73 (2 × s, 1H, CH=N); MS: *m/e* = 295. (Found: C, 68.98; H, 5.82; N, 14.24. Calc. for $C_{17}H_{17}N_3O_2$: C, 69.15; H, 5.76; N, 14.24%). Compound **14** could also be obtained by the same method as described for the synthesis of **3a–d**, starting with **13a–b** and **15**. Elution with EtOAc/iPrOH (10:1) yielded **8** (28%), m.p. 220–222°; IR (KBr): 1655 (N–C=O), 1710 (C=O); PMR ($CDCl_3$): 1.36 (t, 3H, CH_3), 3.67 (broad t, 2H, C_6–H), 4.29 (broad t, 2H, C_5–H), 4.34 (q, 2H, CH_2–O), 4.76 (s, 2H, CH_2–Ar), 7.30 (s, 5H, aromatic protons), 7.61 (s, 1H, C_3–H); MS: *m/e* = 299. (Found: C, 64.18; H, 5.71; N, 13.97. Calc. for $C_{16}H_7N_3O_3$: C, 64.31; H, 5.69; N, 14.05).

Ethyl 2-*benzenehydrazonyl*-3-*pyrrolopropanoate* (**12**). Starting with **10**, compound **12** was prepared by the general procedure described for the synthesis of **3a–e**. After evaporation of the solvent, the residue was chromatographed on a silica gel column. Elution with $CHCl_3$/cyclohexane (3:1) yielded **12** (57%), m.p. 84–86°; IR (KBr): 1600 (C=C, C=N), 1675 (C=O), 3240 (N–H); PMR ($CDCl_3$): 1.32 (t, 3H, CH_3), 4.24 (q, 2H, CH_2–O), 4.86 (s, 2H, CH_2–N), 6.12, 6.74 (2 × t, 4H, pyrrol protons), 7.25 (m, 5H, aromatic protons), 12.22 (broad s, 1H, N–H); MS: *m/e* = 271. (Found: C, 66.48; H, 6.31; N, 15.46. Calc. for $C_{15}H_{17}N_3O_2$: C, 66.42; H, 6.27; N, 15.50%).

Diethyl 1-methylimidazole-2,4-dicarboxylate (**18**). Starting with **16a** compd **18** was prepared by the general procedure for synthesizing **3a–e**. After evaporation of the solvent the residue was chromatographed on a silica gel thick layer plate (2 mm). Elution with $CHCl_3$/EtOAc (5:1) yielded **18** (38%), m.p. 107–110°; IR ($CHCl_3$): 1705 (arom. –C=O), 1715 (aliph. –C=O); PMR ($CDCl_3$): 1.39, 1.43 (2 × t, 6H, CH_3–CH_2), 4.06 (s, 3H, CH_3–N), 4.39, 4.45 (2 × q, 4H, CH_2–O), 7.69 (s, 1H, C_5–H); MS: *m/e* = 226. (Found: C, 53.25; H, 6.17; N, 12.52. Calc. for $C_{10}H_{14}N_2O_4$: C, 53.09; H, 6.19; N, 12.38%).

Ethyl 2-benzenehydrazonyl-3-cyano-(N-methyl, N-cyanomethyl)-aminopropanoate (**19**). Starting with **16b**, compound **19** was prepared by the general procedure for synthesizing **3a–e**. After evaporation of the solvent, the residue was chromatographed on a silica gel column. Elution with $CHCl_3$/EtOAc (4:1) yielded **19** (23%). IR ($CHCl_3$): 1610 (C=C), 1710 (C=O), 2240 (C≡N); PMR ($CDCl_3$): 1.40 (t, 3H, CH_3–CH_2), 2.84 (s, 3H, CH_3–N), 4.00 (2 × s, 3H, N–CH_2, CH–CN). 4.39 (q, 2H, CH_2–O), 7.50 (m, 5H, aromatic protons); MS: *m/e* = 299.

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