Studies on the Reactivity of α-Cyano-α-isocyanoalkanoates – Versatile Synthons for the Assembly of Imidazoles

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Dedicated to Professor Dr. *Werner Schroth*, Halle/Saale, on the occasion of his 70th birthday

The reactivity and the synthetic potential of α-cyano-α-isocyanoalkanoates **2** were investigated. Interestingly, reaction of **2** with alkoxides gave (alkoxy)(alkyl)imidazoles **5**, whereas the analogous thiolates led to different products, namely substituted 4*H*-imidazoles **7**, together with compounds **6**, which formed by addition of thiolate to the isocyano group. Primary amines reacted, on one hand, in the same manner as thiolates to form of 4*H*-imidazoles **10**, and, on the other hand, cleavage of the molecule to the proposed unstable aminoimidazole **8** and the carbamate **9** was observed. Secondary amines add selectively to the isocyano group to form compounds **11**. Like simple isocyanides, α-cyano-α-isocyanoalkanoates **2** can be subjected to [4 + 1] cycloadditions and multicomponent reactions of the *Passerini* type. Mechanisms for the described reactions are discussed.

Introduction. – In previous publications, we reported on the synthesis of α-cyano-α-isocyanoalkanoates **2** [1] (*Scheme 1*) and their application to the preparation of 5,5-disubstituted 2,4-dithiohydantoins [2].

Scheme 1

1 **2**

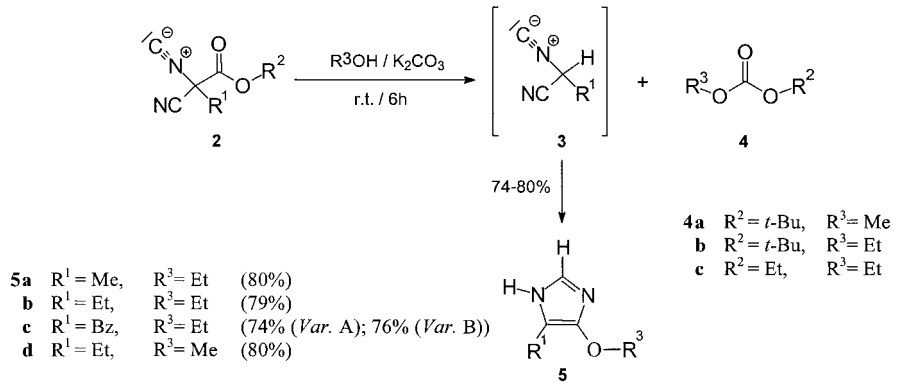
a R^1 = Me, R^2 = *t*-Bu
b R^1 = Et, R^2 = *t*-Bu
c R^1 = Bz, R^2 = *t*-Bu
d R^1 = Bz, R^2 = Et

To further explore the reactivity of compounds of type **2** and their application to the synthesis of heterocycles, we chose to investigate the reaction of **2** with various nucleophiles. Since α-cyano-α-isocyanoalkanoates **2** contain numerous functional groups, they should be suitable precursors for the assembly of more complex systems, especially for substituted five-membered azacycles like imidazoles.

Results and Discussion. – *Schöllkopf* and *Handke* reported on the reaction of (cyano)(isocyano)alkanes with alkoxides yielding (alkoxy)(alkyl)imidazoles of type **5**

[3] (*Scheme 2*). α-Cyano-α-isocyanoalkanoates **2**, containing no α-H-atom, should give alkoxy-substituted 4*H*-imidazoles under analogous conditions. However, on reaction of **2** with alkoxides, compounds **5** were obtained (*Scheme 2*).

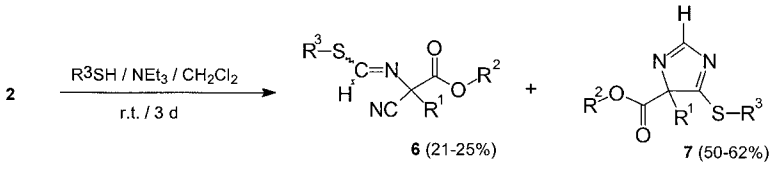
Scheme 2



The formation of **5** can be explained by nucleophilic attack of the alkoxide ion at the C=O group followed by cleavage of the C–C bond between the C(α)-atom and the ester-carbonyl C-atom under formation of alkyl carbonate **4** and (cyano)(isocyano)alkanes **3** as intermediates. The latter reacted to give the isolated product **5**, similar to the work published by *Schöllkopf* and *Handke* [3]. The by-product **4** could be isolated and characterized spectroscopically. The spectroscopic data of **5a** are identical to those published in [3]; products **5b**–**d** could be unambiguously identified by their spectral data.

To determine whether other nucleophiles also cleave the C–C bond, **2** was reacted with thiolates, as well as with primary and secondary amines. In contrast to alkoxides, ethylthiolate – generated from EtSH and Et_3N – reacted with **2** in CH_2Cl_2 to form **6** and **7** (*Scheme 3*).

Scheme 3



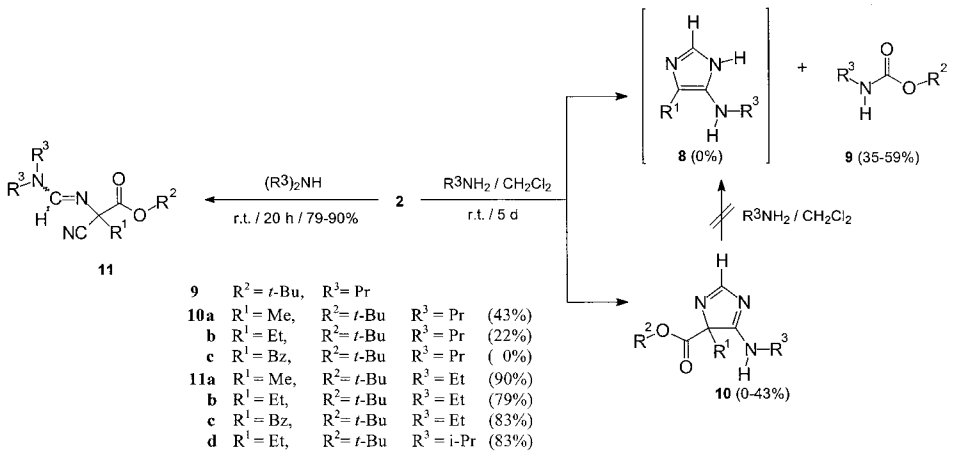
a R^1 = Me, R^2 = *t*-Bu R^3 = Et (**6**: 24%, **7**: 50%)
b R^1 = Et, R^2 = *t*-Bu R^3 = Et (**6**: 21%, **7**: 62%)
c R^1 = Bz, R^2 = *t*-Bu R^3 = Et (**6**: 25%, **7**: 51%)

4*H*-Imidazole **7** is the product of a nucleophilic attack of thiolate ion on the CN group and subsequent ring closure with the isocyano C-atom. This mechanism seems plausible and is supported by the molecular structure of **7**, which was determined by standard spectroscopic methods and by a selective INEPT-NMR experiment.

As already observed by *Schöllkopf* and *Handke* [3] and *Saegusa et al.* [4][5], thiolates add to the isocyano C-atom, leading to thioimino esters **6**, which, in the present case, could also be isolated and characterized as by-products. As opposed to alkoxides, thiolates attack parallel to the isocyanido and the CN C-atom. They do not cleave the C–C bond as observed with alkoxides.

When **2** was reacted with amines, a wide range of products was obtained, depending on the nature of the amine. Secondary amines furnished the addition products **11** which were formed by selective attack on the isocyano group (*Scheme 4*) [6][7]. Primary amines, however, showed a completely different behavior. On the one hand, the CN group was attacked by the same mechanism observed with the thiolates, leading to substituted 4*H*-imidazoles **10**, the molecular structures of which could be determined spectroscopically and by selective INEPT-NMR experiments. On the other hand, the amines cleaved the C–C bond as observed with alkoxides. The resulting carbamate **9** could be isolated and clearly identified, whereas the corresponding aminoimidazole **8**, proposed as the second product, decomposed spontaneously. When **2c** was subjected to the same conditions, exclusively the corresponding cleavage product **9** was formed, supposedly because of steric constraints. The spectroscopic data of 4*H*-imidazoles **10** are generally similar to those of 4*H*-imidazoles **7**.

Scheme 4



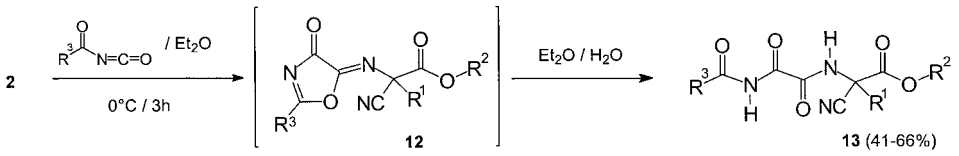
9	R^2 = *t*-Bu,	R^3 = Pr		
10a	R^1 = Me,	R^2 = *t*-Bu	R^3 = Pr	(43%)
b	R^1 = Et,	R^2 = *t*-Bu	R^3 = Pr	(22%)
c	R^1 = Bz,	R^2 = *t*-Bu	R^3 = Pr	(0%)
11a	R^1 = Me,	R^2 = *t*-Bu	R^3 = Et	(90%)
b	R^1 = Et,	R^2 = *t*-Bu	R^3 = Et	(79%)
c	R^1 = Bz,	R^2 = *t*-Bu	R^3 = Et	(83%)
d	R^1 = Et,	R^2 = *t*-Bu	R^3 = i-Pr	(83%)

There are two possible pathways for the formation of products **8** and **9**. One is cleavage of the C–C bond by the amine in the α-cyano-α-isocyanoalkanoate **2** or in the 4*H*-imidazole **10**. Both mechanisms lead to the same reaction products.

To verify the proposed mechanism, we tried to react 4*H*-imidazole **10b** in the presence of the amine. After stirring for 48 h at room temperature, no reaction was observed, providing evidence that compound **10** is not an intermediate in the formation of **8** and **9** (*Scheme 4*).

It is known that isocyanides undergo [4 + 1] cycloadditions with aromatic acyl isocyanates [13–17]. Therefore, we treated **2** with various aromatic acyl isocyanates in Et_2O at low temperature. The expected cycloaddition products **12** are unstable, and only their hydrolysis products **13** could be isolated (*Scheme 5*).

Scheme 5



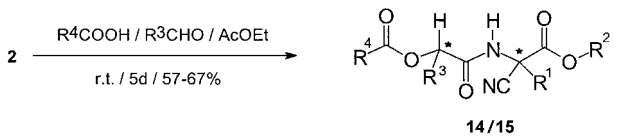
a R^1 = Bz, R^2 = Et, R^3 = Ph (41%)
b R^1 = Bz, R^2 = Et, R^3 = 4-Cl–C_6H_4 (54%)
c R^1 = Bz, R^2 = *t*-Bu, R^3 = Ph (47%)
d R^1 = Bz, R^2 = *t*-Bu, R^3 = 4-Cl–C_6H_4 (66%)

The characterization of **13** may serve as a proof for the intermediate formation of **12**. $^1H\{^{13}C\}$-NOE, $^1H\{^1H\}$-NOE, and selective decoupling experiments served to establish the structure of **13** and allowed complete assignment of the signals in the NMR spectra.

The high tendency of isocyanides to undergo cycloaddition and multicomponent reactions – like the *Passerini* [8–10] and the *Ugi-4CC* reactions [11][12] – is documented in the literature[1]). We decided to investigate whether α-cyano-α-isocyanoalkanoates **2** would react in this way like simple isocyanides.

Application of these reactions to α-cyano-α-isocyanoalkanoates **2** should be of particular interest because of the large variety of substituents on **2**, leading to novel compounds with potential applications in drug research. To evaluate the potential of **2** for such reactions, Cl_3CCOOH and isobutanal were chosen as other components because of their high reactivity. These two components were allowed to react with various derivatives of **2**. Because an additional chiral center was formed during the *Passerini* reaction with the asymmetric α-cyano-α-isocyanoalkanoates **2**, the formation of a mixture of both diastereoisomers **14/15** was observed (*Scheme 6*).

Scheme 6



a R^1 = Me, R^2 = *t*-Bu, R^3 = i-Pr, R^4 = Cl-CH_2 (**14**: 50%, **15**: 17%)
b R^1 = Et, R^2 = *t*-Bu, R^3 = i-Pr, R^4 = Cl-CH_2 (**14**: 34%, **15**: 23%)
c R^1 = Bz, R^2 = *t*-Bu, R^3 = i-Pr, R^4 = Cl-CH_2 (**14**: 33%, **15**: 30%)

The NMR spectra of the crude products proved the presence of two stereoisomers. Fortunately, the diastereoisomeric compounds could be separated by fractional crystallization from Et_2O. No efforts have been made to determine the absolute configurations of the separated isomers.

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[1]) The *Passerini* reaction and the *Ugi-4CC* reaction can be used to synthesize depsipeptides and tripeptides in a one-pot reaction.

Conclusion. – The synthetic potential of α-cyano-α-isocyanoalkanoates **2** was explored by reacting them with various nucleophiles, by cycloaddition, and by using them in multicomponent reactions. Different nucleophiles showed different reactivities, and plausible mechanisms are proposed. The α-cyano-α-isocyanoalkanoates **2** proved to be a versatile class of compounds, and further work in this direction is in progress.

We thank *BASF AG*, *Bayer AG*, and *Hoechst AG*, the *Fonds der Chemischen Industrie*, as well as the *Deutsche Forschungsgemeinschaft* for support of this work. Thanks go to *Hewlett-Packard* for providing UV/VIS spectrometers. We would also like to thank Dr. *W. Kramer* and Ms. *U. Hertle* for NMR spectra, Mr. *H. Rudy* and Mr. *P. Weyrich* for elemental analysis and mass spectra. Dr. *R. Faust* is warmly thanked for many helpful discussions and Dr. *M. Winter* for help with the manuscript.

Experimental Part

General. All reactions were carried out under Ar in flame-dried glassware. CH_2Cl_2 was freshly distilled from CaH_2; Et_2O, THF, and benzene were distilled from Na/benzophenone before use. Column chromatography (CC): silica gel (60–200 mesh) from *ICN-Biomedicals*. M.p.: *Reichert* melting-point microscope; uncorrected. UV/VIS Spectra: MeCN solns.; *Hewlett Packard HP 8453 UV/VIS ChemStation* and *Hewlett Packard HP 8452A* diode array spectrophotometer: λ in nm (log ε). IR Spectra: KBr pellets or films; *Perkin-Elmer PE 1600 FT-IR* spectrophotometer, $\tilde{\nu}$ in cm^{-1}. ^{1}H-NMR Spectra: at 250.13 MHz on *Bruker WM-250* spectrometer; at 360.12 Hz on *Bruker AM-360* spectrometer, and at 299.95 MHz on *Varian XL 300* spectrometer; δ in ppm rel. to TMS, J in Hz. ^{13}C-NMR Spectra: at 62.89, 90.56, and 75.43 MHz on the same spectrometers (the degree of substitution was determined by J-modulated spin-echo experiments). MS: *Varian MAT-311 A* spectrometer at 70 eV; m/z (rel. %). Elemental analyses: *Foss-Heraeus Vario EL*; all compounds gave satisfactory analyses (C, H, S $\pm$ 0.3%).

Ethyl 2-Cyano-2-formamido-3-phenylpropanoate (**1d**). Compound **1d** was obtained from a soln. of Na (0.25 g, 10.86 mmol) in EtOH (10 ml), *tert*-butyl 2-cyano-2-formamidoacetate (1.7 g, 10.86 mmol) in EtOH (3 ml), and $PhCH_2I$ (2.84 g, 13 mmol) in EtOH (8 ml) as described in [1]. Recrystallization from EtOH: 4.8 g (73%) of **1d**. Colorless crystals. M.p. 83–85° (EtOH). (KBr): 3311*s* (NH), 2988*m*, 2936*m*, 2244*w* (CN), 1747*s* (CO), 1690*s* (CHO), 1670*s* (CHO), 1506*s*, 1385*m*, 1267*s*, 1082*m*, 1047*m*, 773*m*, 708*s*. ^{1}H-NMR ($CDCl_3$): 1.23 (*t*, ^3J = 7.2, *Me*CH_2); 3.40 (*d*, ^2J = 13.4, 1 H, PhCH_2); 3.55 (*d*, ^2J = 13.4, 1 H, PhCH_2); 4.22 (*q*, ^3J = 7.2, MeCH_2); 7.04 (*s*, NH); 7.22–7.36 (*m*, 5 arom. *H*); 8.19 (*s*, CHO). ^{13}C-NMR ($CDCl_3$): 13.7 (*Me*CH_2); 41.5 (Ph*C*H_2); 56.7 (*C*CO); 63.9 (Me*C*H_2); 115.6 (CN); 128.4, 128.7, 129.9, 131.2 (arom. C); 160.5 (CHO); 165.0 (CO). FAB-MS (NBA matrix): 247 (90, $[M+H]^+$); 91 (100, $[C_7H_7]^+$).

Ethyl 2-Cyano-2-isocyano-3-phenylpropanoate (**2d**). To a soln. of **1d** (0.615 g, 2.5 mmol) in CH_2Cl_2 (7.5 ml) were added, under stirring at −78°, Et_3N (1.75 ml) at once and trichloromethyl chloroformate (diphosgene; 0.3 g, 0.183 ml) dropwise during 10 min. The soln. turned slightly brown, and a white precipitate was formed. After stirring for 15 min. at −78°, the mixture was allowed to warm to r.t., and H_2O (25 ml) was added. The org. layer was separated, washed with H_2O, and dried with Na_2SO_4. The resulting soln. was filtered over silica (15 × 1 cm), and the pure product **2d** was obtained as a soln. in CH_2Cl_2. Compound **2d** can be stored at −25° for a few months. Yield: 342 mg (60%). R_f (hexane/AcOEt 3:1) 0.49. IR (film): 3066*m*, 3035*m*, 2986*m*, 2940*w*, 2256*w* (CN), 2140*s* (NC), 1766*s* (CO), 1456*m*, 1370*m*, 1265*s*, 1094*m*, 852*m*, 738*s*, 701*m*. ^{1}H-NMR (CH_2Cl_2): 1.30 (*t*, ^3J = 7.5, *Me*CH_2); 3.49 (*s*, PhCH_2); 4.32 (*q*, ^3J = 7.5, MeCH_2); 7.30–7.45 (*m*, 5 arom. *H*). ^{13}C-NMR (CH_2Cl_2): 13.5 (MeCH_2); 44.8 (Ph*C*H_2); 53.8 (*C*H_2Cl_2); 65.6 (Me*C*H_2); 112.4 (CN); 128.9; 129.1; 130.3; 130.4 (arom. C); 161.0 (NC); 166.5 (*C*O). FAB-MS (NBA matrix) 229 (4, $[M+H]^+$), 91 (100, $[C_7H_7]^+$). FAB-MS (LiCl matrix): 235 (25, $[M+Li]^+$). HR-MS ($C_{13}H_{12}N_2O_2$): 228.0899 (calc. 228.0899).

4-Alkoxy-5-alkylimidazoles **5**. *General Procedure*. α-Cyano-α-isocyanoalkanoates **2a**–**d** (1 mmol) were dissolved in 6 ml of the corresponding alcohol, and anh. K_2CO_3 (21 mg, 1.5 mmol) was added at r.t. under stirring. After additional stirring for 6 h, the mixture turned pale-yellow. The residue was filtered off, washed with alcohol, and the resulting alcoholic soln. was evaporated. Recrystallization of the remaining solid from cyclohexane yielded the pure products as fine colorless needles.

4-Ethoxy-5-methylimidazole (**5a**). tert-*Butyl 2-cyano-2-isocyanopropanoate* (**2a**; 180 mg, 1 mmol) in EtOH yielded 102 mg (80%) of **5a**. M.p. 92–93° (C_6H_{12}) ([3]: 93°).

4-Ethoxy-5-ethylimidazole (**5b**): From tert-*butyl 2-cyano-2-isocyanobutanoate* (**2b**; 194 mg, 1 mmol) in EtOH: 111 mg (79%) of **5b**. M.p. 97–99° (C_6H_{12}). IR (KBr): 3123*m*, 3038*m*, 2972*s*, 2934*s*, 2835*m*, 2676*m*, 1616*s*, 1472*m*, 1384*m*, 1306*m*, 1138*m*, 1050*s*, 972*m*. ^{1}H-NMR ($CDCl_3$): 1.18 (*t*, ^3J = 7.7, *Me*CH_2); 1.31 (*t*, ^3J = 7.1, *Me*CH_2O); 2.57 (*q*, ^3J = 7.7, MeCH_2); 4.16 (*q*, ^3J = 7.1, MeCH_2O); 7.17 (*s*, H–C(2)); 9.05 (*s*, NH). ^{13}C-NMR ($CDCl_3$): 13.8 (*Me*CH_2); 15.1 (*Me*CH_2O); 16.5 (Me*C*H_2); 66.9 (Me*C*H_2O); 113.1 (C(5)); 127.8 (C(2)); 149.7 (C(4)). EI-MS (61°): 140 (43, M^+), 112 (20, $[M - C_2H_4]^+$), 97 (100 $[M - C_2H_4Me]^+$). HR-MS ($C_7H_{12}N_2O$): 140.0949 (calc. 140.0950).

5-Benzyl-4-ethoxyimidazole (**5c**). *Procedure A:* Compound **2d** (228 mg, 1 mmol) in EtOH yielded 150 mg (74%) of **5c**. M.p. 121–123° (AcOEt; subl. at 105°). *Procedure B:* From tert-*butyl 2-cyano-2-isocyano-3-phenylpropanoate* (**2c**, 256 mg, 1 mmol) in EtOH gave 154 mg (76%) of **5c**. M.p. 121–123° (AcOEt; subl. at 105°). IR (KBr): 3110*m*, 3030*s*, 2977*s*, 2883*s*, 2832*s*, 2733*m*, 2640*m*, 1615*s*, 1473*s*, 1375*m*, 1243*m*, 1101*s*, 1039*s*, 960*m*, 722*s*. ^{1}H-NMR ($CDCl_3$): 1.29 (*t*, ^3J = 7.1, *Me*CH_2O); 3.87 (*s*, PhCH_2); 4.15 (*q*, ^3J = 7.1, MeCH_2O); 6.99 (*s*, H–C(2)); 7.13–7.25 (*m*, 5 arom. H); 9.95 (*s*, NH). ^{13}C-NMR ($CDCl_3$): 15.2 (*Me*CH_2O); 29.2 (Ph*C*H_2); 66.3 (Me*C*H_2O); 109.1 (C(5)); 126.4, 128.4, 139.3 (arom. C); 128.6 (arom. *C*, C(2)); 151.1 (C(4)). EI-MS (104°): 202 (100, M^+), 174 (34, $M - C_2H_4]^+$), 91 (46, $[C_7H_7]^+$). HR-MS ($C_{12}H_{14}N_2O$): 202.1106 (calc. 202.1106).

5-Ethyl-4-methoxyimidazole (**5d**): tert-*Butyl 2-cyano-2-isocyanobutanoate* (**2b**; 194 mg, 1 mmol) in MeOH yielded 101 mg (80%) of **5d**. M.p. 98–100° (C_6H_{12}). IR (KBr): 3123*m*, 3026*m*, 2970*s*, 2934*s*, 2833*s*, 2677*m*, 1617*s*, 1499*m*, 1473*s*, 1382*m*, 1369*m*, 1300*m*, 1132*m*, 1044*m*, 1014*m*. ^{1}H-NMR ($CDCl_3$): 1.19 (*t*, ^3J = 7.6, *Me*CH_2); 2.58 (*q*, ^3J = 7.6, MeCH_2); 3.87 (*s*, MeO); 7.18 (*s*, H–C(2)); 8.45 (*s*, NH). ^{13}C-NMR ($CDCl_3$): 13.9 (*Me*CH_2); 16.6 (Me*C*H_2); 58.2 (MeO); 112.2 (C(5)); 127.7 (C(2)); 150.8 (C(4)). EI-MS (49°): 126 (55, M^+), 111 (100, $[M - Me]^+$). HR-MS ($C_6H_{10}N_2O$): 126.0793 (calc. 126.0793).

*Alkyl 4-Alkyl-5-(alkylthio)-4*H*-imidazole-4-carboxylates* **7** *and α-Cyano-α-{[(alkylthio)methylidene]imino}-alkanoates* **6**. *General Procedure.* α-Cyano-α-isocyanoalkanoate **2** (1 mmol) was dissolved in CH_2Cl_2 (15 ml), and the soln. was cooled to 0°. Then, EtSH (69 mg, 0.082 ml, 1.1 mmol) and Et_3N (203 mg, 0.28 ml, 2 mmol) were added under stirring during 10 min. The mixture was allowed to warm to r.t., stirred for additional 72 h, and adsorbed on silica (3 g). CC (silica gel; 20 × 3 cm) of the crude products first with CH_2Cl_2 gave **6** as pure yellow oil after evaporation of the solvent. Further elution with Et_2O yielded the crude product **7** as colorless oil. Purification of **7** was accomplished by CC (silica gel; 20 × 3 cm, Et_2O).

tert-*Butyl 5-(Ethylthio)-4-methyl-4*H*-imidazole-4-carboxylate* (**7a**) *and* tert-*Butyl 2-cyano-2-{[(ethylthio)-methyliden]amino}propanoate* (**6a**). Compound **2a** (180 mg, 1 mmol) yielded **6a** (pale yellow oil; 60 mg (24%); R_f (CH_2Cl_2) 0.60) and **7a** (colorless oil; 121 mg; (50%); R_f (Et_2O) 0.55).

Data of **7a**: IR (film): 3061*w*, 2979*m*, 2934*m*, 2875*w*, 1738*s* (CO), 1567*m*, 1466*s*, 1370*s*, 1257*s*, 1253*m*, 1129*s*, 1065*m*, 1036*s*, 914*w*, 843*m*. ^{1}H-NMR ($CDCl_3$): 1.41 (*t*, ^3J = 8.8, *Me*CH_2S); 1.42 (*s*, *t*-Bu); 1.53 (*s*, Me); 1.67 (*m*, ^3J = 8.8, MeCH_2S); 8.00 (*s*, H–C(2)). ^{13}C-NMR ($CDCl_3$): 13.9 (*Me*CH_2S); 21.6 (Me); 26.9 (Me*C*H_2S); 27.7 (*Me*$_3$C); 82.9 (Me$_3$*C*); 88.6 (C(4)); 165.1 (C(2)); 165.6 (CO); 199.9 (C(5)). EI-MS (55°): 242 (0.2, M^+), 227 (2, $[M - CH_3]^+$), 141 (10, $[M - CO_2C_4H_9]^+$), 57 (100, $[C_4H_9]^+$). HR-MS ($C_{11}H_{18}N_2O_2S$): 242.1089 (calc. 242.1089).

Data of **6a**: IR (film): 2980*s*, 2933*m*, 2872*m*, 2250*m* (CN), 1741*s* (CO), 1592*s*, 1458*m*, 1370*m*, 1258*s*, 1157*s*, 1128*s*, 1123*s*, 840*s*. ^{1}H-NMR ($CDCl_3$): 1.32 (*t*, ^3J = 7.1, *Me*CH_2S); 1.49 (*s*, *t*-Bu); 1.75 (*s*, Me); 2.99 (*m*, ^3J = 7.1, MeCH_2S); 8.12 (*s*, H–C(2)). ^{13}C-NMR ($CDCl_3$): 15.3 (*Me*CH_2S); 23.5 (Me*C*H_2S); 25.3 (Me); 27.7 (*Me*$_3$C); 66.8 (C(2)); 83.9 (Me$_3$*C*); 117.2 (CN); 162.1 (CH); 164.8 (CO). EI-MS (57°): 242 (0.1, M^+), 227 (3, $[M - Me]^+$), 142 (23, $[M - CO_2C_4H_8]^+$), 141 (21, $[M - CO_2C_4H_9]^+$), 57 (100, $[C_4H_9]^+$). HR-MS ($C_{11}H_{18}N_2O_2S$): 242.1089 (calc. 242.1089).

tert-*Butyl 4-Ethyl-5-ethylthio-4*H*-imidazole-4-carboxylate* (**7b**) *and* tert-*Butyl 2-cyano-2-{[(ethylthio)-methylidene]amino}butanoate* (**6b**). Compound **2b** (194 mg, 1 mmol) yielded **6b** (pale-yellow oil; 54 mg (21%); R_f (CH_2Cl_2) 0.61) and **7b** (colorless oil; 159 mg (62%); R_f (Et_2O) 0.56).

Data of **7b**: IR (film): 3063*w*, 2977*s*, 2934*m*, 2879*w*, 1738*s* (CO), 1567*m*, 1468*s*, 1458*s*, 1370*m*, 1255*s*, 1153*s*, 1066*m*, 1039*m*, 970*w*, 842*m*. ^{1}H-NMR ($CDCl_3$): 0.68 (*t*, ^3J = 7.3, *Me*CH_2); 1.40 (*t*, ^3J = 7.4, *Me*CH_2S); 1.49 (*s*, *t*-Bu); 1.82 (*m*, ^3J = 7.4, 1 H, MeCH_2); 2.35 (*m*, ^3J = 7.4, 1 H, MeCH_2); 3.21 (*q*, ^3J = 7.4, MeCH_2S); 8.04 (*s*, H–C(2)). ^{13}C-NMR ($CDCl_3$): 7.5 (*Me*CH_2); 13.8 (*Me*CH_2S); 26.9 (MeCH_2S); 27.8 (*Me*$_3$C); 29.4 (Me*C*H_2); 82.6 (Me$_3$*C*); 92.2 (C(4)); 165.0 (C(2)); 165.5 (CO); 197.9 (C(5)). EI-MS (67°): 256 (0.3, M^+), 241 (3, $[M - Me]^+$), 156 (16, $[M - CO_2C_4H_8]^+$), 155 (13, $[M - CO_2C_4H_9]^+$), 57 (100, $[C_4H_9]^+$). HR-MS ($C_{12}H_{20}N_2O_2S$): 256.1245 (calc. 256.1246).

Data of **6b**: IR (film): 2979*m*, 2935*m*, 2882*w*, 2247*w* (CN), 1742*s* (CO), 1589*m*, 1459*w*, 1371*m*, 1255*m*, 1156*m*, 840*m*. ^{1}H-NMR ($CDCl_3$): 1.00 (*t*, ^3J = 7.4, *Me*CH_2); 1.33 (*t*, ^3J = 7.1, *Me*CH_2S); 1.50 (*s*, *t*-Bu); 2.13 (*m*, ^3J = 7.4, MeCH_2); 3.01 (*m*, ^3J = 7.1, MeCH_2S); 8.60 (*s*, CH). ^{13}C-NMR ($CDCl_3$): 8.5 (*Me*CH_2); 11.12 (*Me*CH_2S); 23.6 (MeCH_2S); 27.8 (*Me*$_3$C); 31.6 (Me*C*H_2); 63.3 (C(2)); 84.3 (Me$_3$*C*); 116.1 (CN); 162.0 (*C*H);

165.1 (CO). EI-MS (57°): 256 (0.1, M^+), 241 (2, $[M-Me]^+$), 156 (23, $[M-CO_2C_4H_8]^+$), 155 (21, $[M-CO_2C_4H_9]^+$), 57 (100, $[C_4H_9]^+$). HR-MS ($C_{12}H_{20}N_2O_2S$): 256.1245 (calc. 256.1246).

tert-*Butyl 4-Benzyl-5-(ethylthio)-4*H-*imidazole-4-carboxylate* (**7c**) *and* tert-*Butyl 2-cyano-α-[[(ethylthio)-methylidene]amino]-3-phenylpropanoate* (**6c**). Compound **2c** (256 mg, 1 mmol) yielded **6c** (pale-yellow oil; 80 mg (25%); R_f (CH_2Cl_2) 0.72) and **7c** (colorless oil; 162 mg (51%); R_f (Et_2O) 0.50).

Data of **7c**: IR (film): 3087*w*, 3062*w*, 3032*w*, 2979*m*, 2932*m*, 2879*w*, 1738*s* (CO), 1567*m*, 1467*s*, 1370*m*, 1256*s*, 1257*s*, 1066*m*, 989*w*, 840*m*, 701*m*. ^{1}H-NMR ($CDCl_3$): 1.35 (*t*, $^3J=7.3$, *Me*CH_2S); 1.42 (*s*, *t*-Bu); 3.10–3.20 (*d*, $^2J=13.5$, 1 H, PhCH_2; *m*, $^3J=7.3$, MeCH_2S); 3.63 (*d*, $^2J=13.5$, 1 H, PhCH_2); 7.16–7.2 (*m*, 5 arom. *H*); 7.83 (*s*, H–C(2)). ^{13}C-NMR ($CDCl_3$): 13.8 (*Me*CH_2S); 27.0 (Me*C*H_2S); 27.7 (*Me*$_3$C); 42.1 (Ph*C*H_2); 83.4 (Me$_3$*C*); 92.3 (C(4)); 127.2; 127.7, 130.4, 134.0 (arom. C); 165.1 (C(2)); 165.2 (CO); 197.6 (C(5)). EI-MS (101°): 318 (0.4, M^+), 227 (5, $[M-C_7H_7]^+$), 217 (10, $[M-CO_2C_4H_9]^+$), 91 (100, $[C_7H_7]^+$), 57 (76, $[C_4H_9]^+$). HR-MS ($C_{17}H_{22}N_2O_2S$): 318.1404 (calc. 318.1402).

Data of **6c**: IR (film): 3062*w*, 3031*w*, 2976*m*, 2930*m*, 2238*w* (CN), 1743*s* (CO), 1580*m*, 1455*m*, 1371*m*, 1155*m*, 1032*m*, 841*m*. ^{1}H-NMR ($CDCl_3$): 1.32 (*t*, $^3J=7.1$, *Me*CH_2S); 1.50 (*s*, *Me*$_3$C); 2.90–3.20 (*m*, MeCH_2); 3.39 (*d*, $^2J=13.5$, 1 H, PhCH_2); 3.69 (*d*, $^2J=13.5$, 1 H, PhCH_2); 7.20–7.40 (*m*, 5 arom. *H*); 8.25 (*s*, CH). ^{13}C-NMR ($CDCl_3$): 13.8 (*Me*CH_2S); 27.0 (Me*C*H_2S); 27.9 (*Me*$_3$C); 35.8 (Ph*C*H_2); 67.4 (C(2)); 84.3 (Me$_3$*C*); 116.6 (CN); 127.7, 128.9, 130.2, 135.5 (arom. *C*); 159.8 (CH); 165.2 (CO). EI-MS (105°): 318 (0.1, M^+), 91 (87, $[C_7H_7]^+$), 57 (100, $[C_4H_9]^+$). HR-MS ($C_{17}H_{22}N_2O_2S$): 318.1404 (calc. 318.1403).

*Alkyl 4-alkyl-5-(alkylamino)-4*H-*imidazole-4-carboxylate* **10a–c**. *General Procedure.* A soln. of α-cyano-α-isocyanoalkanoate (**2**, 1 mmol) in CH_2Cl_2 (10 ml) was cooled to 0°, followed by dropwise addition of dry $PrNH_2$ (590 mg, 0.82 ml, 10 mmol) under stirring. The mixture was allowed to warm to r.t. and stirred for 120 h. After evaporation of the solvent, the remaining yellow oil was diluted with Et_2O (3 ml). Crystals of **10** formed, which were separated and recrystallized from cyclohexane. Evaporation of the mother liquor and CC (silica gel, 10 × 1 cm, Et_2O) of the residue led to the pure by-product **9**.

tert-*Butyl 4-Methyl-5-(propylamino)-4*H-*imidazole-4-carboxylate* (**10a**). Compound **2a** (180 mg, 1 mmol) yielded **10a** (colorless crystals; 103 mg (43%); m.p. 156–158° (C_6H_{12})) and tert-*butyl* N-*propylcarbamate* (**9**; colorless oil; 59 mg (37%)).

Data of **10a**: IR (KBr): 3432*m* (NH), 3256*s* (NH), 2982*m*, 2935*m*, 2878*w*, 1730*s* (CO), 1623*s*, 1499*s*, 1368*s*, 1278*m*, 1251*m*, 1157*s*, 1124*s*, 934*w*, 841*m*, 606*w*. ^{1}H-NMR ($CDCl_3$): 0.98 (*t*, $^3J=7.4$, *Me*CH_2CH_2); 1.47 (*s*, *t*-Bu); 1.54 (*s*, Me); 1.67 (*q*, $^3J=7.4$, MeCH_2CH$_2$); 3.43 (*q*, $^3J=4.1$, MeCH$_2$CH_2); 6.29 (*s*, NH); 7.72 (*s*, H–C(2)). ^{13}C-NMR ($CDCl_3$): 11.0 (*Me*CH_2CH_2); 22.3 (Me*C*H_2CH$_2$); 24.3 (Me); 27.7 (*Me*$_3$C); 45.5 (MeCH$_2$*C*H$_2$); 79.2 (C(4)); 83.1 (Me$_3$*C*); 166.9 (C(2)); 169.3 (CO); 184.1 (C(5)). EI-MS (20°): 239 (6, M^+), 180 (6, $[M-NHC_3H_7]^+$), 139 (22, $[M-CO_2C_4H_9]^+$), 110 (33, $[M-CO_2C_4H_9-C_2H_4]^+$), 57 (100, $[C_4H_9]^+$). HR-MS ($C_{12}H_{21}N_3O_2$): 239.1634 (calc. 239.1634).

tert-*Butyl 4-Ethyl-5-(propylamino)-4*H-*imidazole-4-carboxylate* (**10b**). Compound **2b** (194 mg, 1 mmol) yielded **10b** (colorless crystals; 57 mg (22%); m.p. 155–156° (C_6H_{12})) and **9** (colorless oil; 56 mg (35%)).

Data of **10b**: IR (KBr): 3433*m* (NH), 3246*s* (NH), 2971*s*, 2935*m*, 2877*m*, 1729*s* (CO), 1617*s*, 1502*m*, 1437*w*, 1371*w*, 1322*w*, 1258*m*, 1155*s*, 1101*m*, 992*w*, 840*w*. ^{1}H-NMR ($CDCl_3$): 0.81 (*t*, $^3J=7.3$, *Me*CH_2); 0.97 (*t*, $^3J=7.5$, *Me*CH_2CH_2NH); 1.48 (*s*, *t*-Bu); 1.61–1.82 (*m*, 1 H of MeCH_2 and MeCH_2CH$_2$NH); 2.09–2.29 (*m*, 1 H, MeCH_2); 3.42 (*q*, $^3J=6.3$, MeCH$_2$CH_2NH); 6.15 (*s*, NH); 7.77 (*s*, H–C(2)). ^{13}C-NMR ($CDCl_3$): 7.7 (*Me*CH_2); 11.0 (MeCH_2CH$_2$NH); 22.3 (MeCH$_2$*C*H$_2$NH); 27.8 (*Me*$_3$C); 32.0 (MeCH_2); 45.4 (MeCH$_2$*C*H$_2$NH); 78.4 (C(4)); 83.2 (Me$_3$*C*); 167.0 (C(2)); 169.5 (CO); 182.5 (C(5)). EI-MS (20°): 253 (4, M^+), 194 (3, $[M-NHC_3H_7]^+$), 153 (14, $[M-CO_2C_4H_9]^+$), 124 (13, $[M-CO_2C_4H_9-C_2H_4]^+$), 57 (100, $[C_4H_9]^+$). HR-MS ($C_{13}H_{23}N_3O_2$): 253.1791 (calc. 253.1790).

tert-*Butyl 4-Benzyl-5-(propylamino)-4*H-*imidazole-4-carboxylate* (**10c**). Compound **2c** (256 mg, 1 mmol) yielded **9** (94 mg, 59%) as only product. Colorless oil. *α-Cyano-α-[[(dialkylamino)methylidene]amino]alkanoic acid esters* **11a–d** – *General Procedure:* α-Cyano-α-isocyanoalkanoic acid ester (**2**, 2 mmol) was dissolved in 15 ml of the cooled (0°) corresponding secondary amine. After stirring for 1 h at 0° and for 20 h at r.t., the amine was removed in vacuo. The crude products remained as pale yellow oils. CC (silica 10 × 3 cm, diethyl ether) gave the pure compounds **11** as colorless oils after evaporation of the solvent.

tert-*Butyl 2-Cyano-2-[[(diethylamino)methylidene]amino]propanoate* (**11a**): Compound **2a** (360 mg, 2 mmol) and Et_2NH yielded 455 mg (90%) of **11a**. Colorless oil. R_f (Et_2O) 0.75. IR (film): 2978*s*, 2937*m*, 2875*m*, 2228*w* (CN), 1744*s* (CO), 1636*s*, 1457*m*, 1370*m*, 1270*s*, 1221*m*, 1161*s*, 1121*s*, 845*s*. ^{1}H-NMR ($CDCl_3$): 1.14 (*t*, $^3J=7.1$, 2 *Me*CH_2); 1.48 (*s*, *t*-Bu); 1.70 (*s*, 3 H–C(3)); 3.28 (*m*, $^3J=7.1$, 2 MeCH_2); 7.62 (*s*, CH). ^{13}C-NMR ($CDCl_3$): 26.5 (Me); 27.8 (*Me*$_3$C); 62.6 (C(2)); 83.1 (Me$_3$*C*); 119.2 (CN); 154.5 (CH); 167.9 (CO). EI-MS

(97°): 253 (1.1, M^+), 152 (100, $[M-CO_2C_4H_9]^+$), 57 (22, $[C_4H_9]^+$). HR-MS ($C_{13}H_{23}N_3O_2$): 253.1791 (calc. 253.1790).

tert-*Butyl 2-Cyano-2-{[(diethylamino)methylidene]amino}butanoate* (**11b**). Compound **2b** (388 mg, 2 mmol) and Et_2NH yielded 422 mg (79%) of **11b**. Colorless-to-pale-yellow oil. R_f (Et_2O) 0.78. IR (film): 2977*m*, 2936*m*, 2880*w*, 2228*w* (CN), 1745*s* (CO), 1636*s*, 1460*m*, 1390*m*, 1370*m*, 1250*m*, 1156*m*, 999*w*, 968*w*, 840*m*. ^{1}H-NMR ($CDCl_3$): 1.00 (*t*, ^3J = 7.4, 3 H–C(4)); 1.14 (*t*, ^3J = 7.1, 2 *Me*CH_2); 1.48 (*s*, *t*-Bu); 2.06 (*m*, ^3J = 7.4, 2 H–C(3)); 3.29 (*m*, ^3J = 7.1, 2 MeCH_2); 7.59 (*s*, CH). ^{13}C-NMR ($CDCl_3$): 8.5 (C(4)); 27.8 (*Me*$_3$C); 32.3 (C(3)); 68.3 (C(2)); 83.0 (Me$_3$*C*); 118.2 (CN); 154.4 (CH); 167.1 (CO). EI-MS (74°): 267 (1, M^+), 166 (100, $[M-CO_2C_4H_9]^+$)57 (17, $[C_4H_9]^+$). HR-MS ($C_{14}H_{25}N_3O_2$): 267.1947 (calc. 267.1947).

tert-*Butyl 2-Cyano-2-{[(diethylamino)methylidene]amino}-3-phenylpropanoate* (**11c**). Compound **2c** (512 mg, 2 mmol) and Et_2NH yielded 546 mg (83%) of **11c**. Pale-yellow oil. R_f (Et_2O) 0.70. IR (film): 3064*w*, 3032*w*, 2976*m*, 2934*m*, 2872*w*, 2238*w* (CN), 1743*s* (CO), 1636*s*, 1455*m*, 1370*m*, 1268*m*, 1155*m*, 1082*m*, 1032*m*, 841*m*, 701*s*. ^{1}H-NMR ($CDCl_3$): 1.08 (*t*, ^3J = 7.1, 2 *Me*CH_2); 1.47 (*s*, *t*-Bu); 3.1–3.4 (*m*, PhCH_2, 2 MeCH_2); 7.19–7.42 (*m*, 6 arom. *H*, CH). ^{13}C-NMR ($CDCl_3$): 27.7 (*Me*$_3$C); 44.5 (Ph*C*H$_2$); 68.5 (C(2)); 83.3 (Me$_3$*C*); 117.6 (CN); 127.2, 127.9, 131.0, 134.5 (arom. *C*); 154.4 (CH); 166.7 (CO). EI-MS (121°): 329 (1, M^+), 238 (25, $[M-C_7H_7]^+$), 228 (100, $[M-CO_2C_4H_9]^+$), 91 (7, $[C_7H_7]^+$), 57 (25, $[C_4H_9]^+$). HR-MS ($C_{19}H_{27}N_3O_2$): 329.2102 (calc. 329.2103).

tert-*Butyl 2-cyano-2-{[(diisopropylamino)methylidene]amino}butanoate* (**11d**). From **2b** (388 mg, 2 mmol) (i-Pr)$_2$NH, and Cu_2O (200 mg) as catalyst. In contrast to the *General Procedure*, the mixture was stirred for 72 h and the catalyst was filtered off: 490 mg (83%) of **11d**. Colorless-to-pale-yellow oil. R_f (Et_2O) 0.75. IR (film): 2976*s*, 2936*m*, 2880*m*, 2202*w* (CN), 1745*s* (CO), 1632*s*, 1461*m*, 1440*m*, 1369*s*, 1294*m*, 1250*m*, 1161*s*, 1132*s*, 997*m*, 971*m*, 843*m*. ^{1}H-NMR ($CDCl_3$): 1.00 (*t*, ^3J = 7.4, 3 H–C(4)); 1.22 (*d*, ^3J = 6.9, 2 *Me*$_2$CH); 1.47 (*s*, *t*-Bu); 2.06 (*m*, ^3J = 7.4, 2 H–C(3)); 3.5–4.4 (*m*, 2 Me$_2$C*H*); 7.74 (*s*, CH). ^{13}C-NMR ($CDCl_3$): 8.5 (C(4)); 27.8 (*Me*$_3$C); 32.0 (C(3)); 68.7 (C(2)); 82.8 (Me$_3$*C*); 118.3 (CN); 152.5 (CH); 167.2 (CO). EI-MS (20°): 295 (6, M^+), 194 (100, $[M-CO_2C_4H_9]^+$), 57 (24, $[C_4H_9]^+$). HR-MS ($C_{16}H_{29}N_3O_2$): 295.2259 (calc. 295.2260).

Alkyl 2-(2-Arenamido-2-oxoacetamido)-2-cyano-3-phenylpropanoates **13a–d**. *General Procedure*. A soln. of α-cyano-α-isocyanoalkanoate **2** in CH_2Cl_2 (10 ml) was dried for several days over activated molecular sieve (4 Å) at −25° and evaporated at max. 15°. Compound **2** (1 mmol) was dissolved in dry Et_2O (4 ml), and a soln. of the corresponding acyl isocyanate (1 mmol) in dry Et_2O (3 ml) was added dropwise during 10 min under stirring at 0°. After stirring for 3 h, H_2O-saturated Et_2O (5 ml) was added. Stirring for additional 15 min, evaporation of the solvent *in vacuo*, and recrystallization of the resulting solids from EtOH gave the pure compounds **13** as colorless crystals.

Ethyl 2-(2-Benzamido-2-oxoacetamido)-2-cyano-3-phenylpropanoate (**13a**). Compound **2d** (228 mg, 1 mmol) and benzoyl isocyanate (147 mg, 1 mmol) yielded 162 mg (41%) of **13a**. M.p. 151–153° (EtOH). IR (KBr): 3351*s* (NH), 3315*s* (NH), 3170*m*, 3064*m*, 2980*w*, 2254*w* (CN), 1758*s* (CO), 1748*s* (CO), 1696*s* (CO), 1683*s* (CO), 1465*s*, 1172*m*, 700*s*, 608*m*. ^{1}H-NMR ($CDCl_3$): 1.28 (*t*, ^3J = 7.1, *Me*CH_2); 3.53 (*d*, ^2J = 13.6, 1 H, PhCH_2); 3.63 (*d*, ^2J = 13.6, 1 H, PhCH_2); 4.30 (*m*, ^3J = 7.1, MeCH_2); 7.2–7.9 (*m*, 10 arom. *H*); 8.24 (*s*, PhCON*H*); 10.34 (*s*, NH–C(2)). ^{13}C-NMR ($CDCl_3$): 13.3 (*Me*CH$_2$); 41.3 (PhCH$_2$); 57.0 (C(2)); 63.8 (MeCH$_2$); 114.1 (CN); 127.2, 127.3, 128.3, 128.7, 129.3, 130.1, 131.2, 133.2 (arom. *C*); 155.5 (*C*ONH–C(2)); 157.6 (PhCONH*C*O); 163.2 (C(1)); 163.7 (Ph*C*O). EI-MS (169°): 393 (8, M^+), 201 (13, $[M-CO_2C_4H_8-C_7H_7]^+$), 105 (100, $[Ph-CO]^+$), 91 (100, $[C_7H_7]^+$). HR-MS ($C_{21}H_{19}N_3O_5$): 393.1325 (calc. 393.1325).

Ethyl 2-[2-(4-Chlorobenzamido)-2-oxoacetamido]-2-cyano-3-phenylpropanoate (**13b**). Compound **2d** (228 mg, 1 mmol) and 4-chlorobenzoyl isocyanate (181 mg, 1 mmol) yielded 231 mg (54%) of **13b**. M.p. 158–160° (EtOH). IR (KBr): 3354*s* (NH), 3319*s* (NH), 3090*w*, 3034*w*, 2992*w*, 2254*w* (CN), 1767*s* (CO), 1746*s* (CO), 1695*s* (CO), 1681*s* (CO), 1592*m*, 1465*s*, 1257*m*, 1221*m*, 1171*m*, 1094*m*, 1011*m*, 703*m*. ^{1}H-NMR ($CDCl_3$): 1.28 (*t*, ^3J = 7.2, *Me*CH_2); 3.52 (*d*, ^2J = 13.6, 1 H, PhCH_2); 3.62 (*d*, ^2J = 13.6, 1 H, PhCH_2); 4.30 (*m*, ^3J = 7.2, MeCH_2); 7.2–7.4 (*m*, 5 arom. *H*); 7.49 (*d*, ^3J = 8.7, 2 arom. *H*); 7.85 (*d*, ^3J = 8.7, 2 arom. *H*); 8.18 (*s*, NH–C(2)); 10.31 (*s*, 4-ClC$_6$H$_4$CON*H*). ^{13}C-NMR ($CDCl_3$): 13.8 (*Me*CH$_2$); 41.7 (PhCH$_2$); 57.4 (C(2)); 64.4 (MeCH$_2$); 114.5 (CN); 128.8, 129.1, 129.2, 129.3, 129.7, 130.0, 130.5, 140.3 (arom. *C*); 155.9 (CONH–C(2)); 157.9 (*C*O–CO–NH–C(2)); 162.8 (C(1)); 164.1 (4-ClC$_6$H$_4$*C*O). EI-MS (189°): 429 (4, $[M(^{37}Cl)]^+$), 427 (11, $[M(^{35}Cl)]^+$), 141 (29, $[^{37}ClC_6H_4CO]^+$), 139 (94, $[^{35}ClC_6H_4CO]^+$), 91 (100, $[C_7H_7]^+$). HR-MS ($C_{21}H_{18}{}^{35}ClN_3O_5$): 427.0935 (calc. 427.0935).

tert-*Butyl 2-(2-Benzamido-2-oxoacetamido)-2-cyano-3-phenylpropanoate* (**13c**). Compound **2c** (256 mg, 1 mmol) and benzoyl isocyanate (147 mg, 1 mmol), yielded 200 mg (47%) of **13c**. M.p. 147–149° (EtOH). IR (KBr): 3366*s* (NH), 3316*s* (NH), 2984*m*, 2254*w* (CN), 1764*s* (CO), 1748*s* (CO), 1695*s* (CO), 1599*m*, 1464*s*, 1155*s*, 702*s*. ^{1}H-NMR ($CDCl_3$): 1.49 (*s*, *t*-Bu); 3.47 (*d*, ^2J = 13.8, 1 H, PhCH_2); 3.63 (*d*, ^2J = 13.8, 1 H, PhCH_2);

7.21-7.92 (*m*, 10 arom. *H*); 8.12 (*s*, NH–C(2)); 10.39 (*s*, PhCON*H*). ^{13}C-NMR ($CDCl_3$): 27.6 (*Me*$_3$C); 41.4 (Ph*C*H$_2$); 57.6 (C(2)); 86.6 (Me$_3$*C*); 114.9 (CN); 127.7, 128.6, 128.9, 129.9, 130.8, 131.7, 133.6 (arom. *C*); 156.0 (*C*O–NH–C(2)); 157.9 (*C*O–CO–NH–C(2)); 162.6 (C(1)); 163.6 (Ph*C*O). EI-MS (155°): 421 (1, M^+), 365 (9, $[M-C_4H_8]^+$), 321 (8, $[M-C_4H_8-CO_2]^+$), 105 (100, $[PhCO]^+$), 91 (100, $[C_7H_7]^+$). HR-MS ($C_{23}H_{23}N_3O_5$): 421.1639 (calc. 421.1638).

tert-*Butyl 2-[2-(4-Chlorobenzamido)-2-oxoacetamido]-2-cyano-3-phenylpropanoate* (**13d**). Compound **2c** (256 mg, 1 mmol) and 4-chlorobenzoyl isocyanate (181 mg, 1 mmol) yielded 302 mg (66%) of **13d**. M.p. 148–150° (EtOH). IR (KBr): 3347*s* (NH), 3324*s* (NH), 3065*w*, 2997*w*, 2988*w*, 2934*w*, 2243*w* (CN), 1770*s* (CO), 1751*s* (CO), 1696*s* (CO), 1592*m*, 1457*s*, 1260*m*, 1158*m*, 1091*m*, 1011*m*, 788*m*, 703*m*. ^{1}H-NMR ($CDCl_3$): 1.48 (*s*, *t*-Bu); 3.47 (*d*, ^2J = 13.8, 1 H, PhC*H*$_2$); 3.62 (*d*, ^2J = 13.8, 1 H, PhC*H*$_2$); 7.22–7.41 (*m*, 5 arom. *H*); 7.50 (*d*, ^3J = 8.7, 2 arom. *H*); 7.86 (*d*, ^3J = 8.7, 2 arom. *H*); 8.11 (*s*, NH–C(2)); 10.32 (*s*, 4-Cl*C*$_6$H$_4$CO–N*H*). ^{13}C-NMR ($CDCl_3$): 27.6 (*Me*$_3$C); 41.4 (Ph*C*H$_2$); 57.5 (C(2)); 86.8 (Me$_3$*C*); 114.9 (CN); 128.7, 129.0, 129.2, 129.9, 130.1, 130.8, 140.3 (arom. *C*); 156.0 (*C*O–NH–C(2)); 157.8 (*C*O–CO–NH–C(2)); 162.6 (C(1)); 162.8 (4-Cl*C*$_6$H$_4$*C*O). EI-MS (152°): 457 (1, $[M(^{37}Cl)]^+$), 455 (3, $[M(^{35}Cl)]^+$), 141 (12, $[^{37}ClC_6H_4CO]^+$), 139 (35, $[^{35}ClC_6H_4CO]^+$), 91 (26, $[C_7H_7]^+$). HR-MS ($C_{23}H_{22}ClN_3O_5$): 455.1250 (calc. 455.1248).

tert-*Butyl 2-[2-(2-Chloroacetoxy)-3-methylbutanamido]-2-cyanoalkanoates* **14**/**15**. *General Procedure.* To a soln. of **2** (2 mmol) in AcOEt (3 ml) were added, under stirring at 0°, 2-methylpropanal (216 mg, 0.27 ml, 3 mmol) and a soln. of $ClCH_2COOH$ (284 mg, 3 mmol) in AcOEt (3 ml). After stirring for 15 min, the mixture was allowed to warm to r.t. and stirred for another 72 h. AcOEt was removed *in vacuo*, and CH_2Cl_2 (15 ml) and H_2O (25 ml) were added. The org. layer was separated, washed twice with H_2O (25 ml), and dried ($MgSO_4$). Evaporation of the solvent gave colorless oils which were dissolved in Et_2O (10 ml). After 30 min. in an ice bath, diastereoisomer **14** crystallized from the Et_2O soln. The crystals were separated and washed with a small amount of Et_2O. The mother liquor was evaporated, dissolved in CH_2Cl_2, and filtered over silica gel (5 × 1 cm). Removal of the solvent *in vacuo* gave the other diastereoisomer **15** as a pale-yellow oil, which crystallized very slowly. The crystals were washed with pentane, separated, and dried on air.

tert-*Butyl 2-[2-(2-chloroacetoxy)-3-methylbutanamido]-2-cyanopropanoate* (**14a**/**15a**): From **2a** (360 mg, 2 mmol): **14a** (356 mg (50%); m.p. 113–115° (Et_2O)), and colorless crystals of **15a** (121 mg (17%); m.p. 78–80° (Et_2O)).

Data of **14a**: IR (KBr): 3286*s* (NH), 2977*m*, 2936*m*, 2255*w* (CN), 1769*s* (CO), 1750*s* (CO), 1740*s* (CO), 1669*s* (CO), 1534*s*, 1457*m*, 1372*m*, 1291*m*, 1180*m*, 1134*s*, 1022*m*, 844*w*. ^{1}H-NMR ($CDCl_3$): 0.99 (*d*, ^3J = 7.0, *Me*$_2$CH); 1.53 (*s*, *t*-Bu); 1.87 (*s*, 3 H–C(3)); 2.30–2.45 (*m*, Me$_2$C*H*); 4.14 (*d*, ^2J = 13.9, 1 H, C*H*$_2$Cl); 4.21 (*d*, ^2J = 13.9, 1 H, CH$_2$Cl); 5.19 (*d*, ^3J = 3.9, 1 H, Me$_2$CHC*H*); 6.86 (*s*, NH). ^{13}C-NMR ($CDCl_3$): 16.9 (1 C, *Me*$_2$CH); 18.4 (1 C, *Me*$_2$CH); 23.5 (C(3)); 27.6 (*Me*$_3$C); 31.0 (Me$_2$*C*H); 40.6 (CH$_2$Cl); 52.8 (C(2)); 78.9 (Me$_2$CH*C*H); 86.0 (Me$_3$*C*); 116.4 (CN); 165.1 (CO); 165.9 (CO); 168.1 (CO). EI-MS (89°): 346 (0.2, M^+), 246 (3 $[M-CO_2C_4H_9]^+$), 57 (100, $[C_4H_9]^+$). HR-MS ($C_{15}H_{23}{}^{35}ClN_2O_5$): 346.1295 (calc. 346.1296).

Data of **15a**: ^{1}H-NMR ($CDCl_3$): 1.01 (*d*, ^3J = 6.8, *Me*$_2$CH); 1.52 (*s*, *t*-Bu); 1.85 (*s*, 3 H–C(3)); 2.30–2.45 (*m*, Me$_2$C*H*); 4.20 (*d*, ^2J = 15.0, 1 H, CH$_2$Cl); 4.29 (*d*, ^2J = 15.0, 1 H, CH$_2$Cl); 5.14 (*d*, ^3J = 4.1, Me$_2$CHC*H*); 7.35 (*s*, NH). ^{13}C-NMR ($CDCl_3$): 16.7 (1 C, *Me*$_2$CH); 18.2 (1 C, *Me*$_2$CH); 23.0 (C(3)); 27.6 (*Me*$_3$C); 30.7 (Me$_2$*C*H); 40.5 (CH$_2$Cl); 53.0 (C(2)); 78.5 (Me$_2$*C*HCH); 85.3 (Me$_3$*C*); 116.7 (CN); 164.9 (CO); 166.2 (CO); 168.4 (CO).

tert-*Butyl 2-[2-(2-chloroacetoxy)-3-methylbutanamido]-2-cyanobutanoate* (**14b**/**15b**). From **2b** (388 mg, 2 mmol): **14b** (322 mg (34%); m.p. 136–137° (Et_2O)), and colorless crystals of **15b** (118 mg (23%); m.p. 83–85° (Et_2O)).

Data for **14b**: IR (KBr): 3282*s* (NH), 2973*m*, 2939*m*, 2881*w*, 2244*w* (CN), 1775*s* (CO), 1764*s* (CO), 1732*s* (CO), 1689*s* (CO), 1517*s*, 1457*m*, 1373*m*, 1261*m*, 1167*s*, 1017*w*, 979*w*, 856*w*, 795*w*). ^{1}H-NMR ($CDCl_3$): 1.00 (*d*, ^3J = 7.0, *Me*$_2$CH); 1.07 (*t*, ^3J = 7.4, 3 H–C(4)); 1.53 (*s*, *t*-Bu); 2.05–2.18 (*m*, ^3J = 7.4, 1 H–C(3)); 2.28–2.45 (*m*, Me$_2$C*H*, 1 H–C(3)); 4.15 (*d*, ^2J = 13.7, 1 H, CH$_2$Cl); 4.22 (*d*, ^2J = 13.7, 1 H, CH$_2$Cl); 5.15 (*d*, ^3J = 3.9, Me$_2$CHC*H*); 6.35 (*s*, NH). ^{13}C-NMR ($CDCl_3$): 7.9 (C(4)); 16.8 (1 C, *Me*$_2$CH); 18.3 (1 C, Me$_2$CH); 27.6 (*Me*$_3$C); 29.7 (C(3)); 30.9 (Me$_2$*C*H); 40.5 (CH$_2$Cl); 57.6 (C(2)); 78.8 (Me$_2$CH*C*H); 85.6 (Me$_3$*C*); 115.9 (CN); 164.3 (CO); 165.9 (CO); 168.1 (CO). EI-MS (100°): 360 (0.2, M^+), 304 (4.3, $[M-C_4H_8]^+$), 260 (3, $[M-CO_2C_4H_9]^+$), 57 (100, $[C_4H_9]^+$). HR-MS ($C_{16}H_{25}{}^{35}ClN_2O_5$): 360.1452 (calc. 360.1452).

Data of **15b**: ^{1}H-NMR ($CDCl_3$): 1.01 (*d*, ^3J = 7.0, *Me*$_2$CH); 1.05 (*t*, ^3J = 7.4, 3 H–C(4)); 1.54 (*s*, *Me*$_3$C); 2.05–2.20 (*m*, ^3J = 7.4, 1 H–C(3)); 2.25–2.40 (*m*, Me$_2$C*H*, 1 H–C(3)); 4.16 (*d*, ^2J = 14.4, 1 H, CH$_2$Cl); 4.23 (*d*, ^2J = 14.4, 1 H, CH$_2$Cl); 5.18 (*d*, ^3J = 4.4, Me$_2$CHC*H*); 6.83 (*s*, NH). ^{13}C-NMR ($CDCl_3$): 8.0 (C(4)); 16.8 (1 C, *Me*$_2$CH); 18.5 (1 C, Me$_2$CH); 27.7 (*Me*$_3$C); 29.6 (C(3)); 31.0 (Me$_2$*C*H); 40.6 (CH$_2$Cl); 57.6 (C(2)); 79.0 (Me$_2$CH*C*H); 85.8 (Me$_3$*C*); 116.0 (CN); 164.6 (CO); 166.1 (CO); 168.2 (CO).

tert-*Butyl 2-[2-(2-chloroacetoxy)-3-methylbutanamido]-2-cyano-3-phenylpropanoate* (**14c**/**15c**). From **2c** (512 mg, 2 mmol): **14c** (350 mg (33%); m.p.: 128–129° (Et_2O)) and a pale-yellow oil of **15c** (318 mg (30%)).

Data of **14c**: IR (KBr): 3311*s* (NH), 3061*m*, 3034*m*, 2971*m*, 2938*m*, 2882*w*, 2245*w* (CN), 1772*s* (CO), 1720*s* (CO), 1690*s* (CO), 1517*s*, 1457*m*, 1372*m*, 1322*m*, 1234*m*, 1178*m*, 1156*m*, 1140*s*, 1018*m*, 849*w*, 699*s*. ^{1}H-NMR ($CDCl_3$): 0.98 (*d*, ^3J = 7.0, 3 H, Me_2CH); 1.00 (*d*, ^3J = 7.0, 3 H, Me_2CH); 1.50 (*s*, *t*-Bu); 2.25–2.45 (*m*, Me_2CH); 3.33 (*d*, ^2J = 13.7, 1 H, $PhCH_2$); 3.65 (*d*, ^2J = 13.7, 1 H, $PhCH_2$); 3.93 (*s*, CH_2Cl); 5.21 (*d*, ^3J = 4.4, Me_2CHCH); 6.77 (*s*, NH); 7.19–7.34 (*m*, 5 arom. *H*). ^{13}C-NMR ($CDCl_3$): 16.8 (1 C, Me_2CH); 18.4 (1 C, Me_2CH); 27.7 (Me_3C); 31.0 (Me_2CH); 40.4 (CH_2Cl); 41.1 ($PhCH_2$); 57.1 (C(2)); 79.0 (Me_2CHCH); 86.4 (Me_3C); 115.9 (CN); 128.5; 128.9; 130.2; 131.8 (arom. C); 164.0 (CO); 165.8 (CO); 168.1 (CO). EI-MS (96°): 422 (0.5, M^+), 322 (1.5, $[M - CO_2C_4H_9]^+$), 91 (100, $[C_7H_7]^+$), 57 (96, $[C_4H_9]^+$). HR-MS ($C_{21}H_{27}{}^{35}ClN_2O_5$): 422.1608 (calc. 422.1607).

Data of **15c**: ^{1}H-NMR ($CDCl_3$): 0.93 (*d*, ^3J = 7.0, 3 H, Me_2CH); 0.94 (*d*, ^3J = 7.0, 3 H, Me_2CH); 1.46 (*s*, *t*-Bu); 2.20–2.40 (*m*, Me_2CH); 3.37 (*d*, ^2J = 13.7, 1 H, $PhCH_2$); 3.52 (*d*, ^2J = 13.7, 1 H, $PhCH_2$); 4.12 (*s*, CH_2Cl); 5.12 (*d*, ^3J = 4.4, Me_2CHCH); 6.76 (*s*, NH); 7.20–7.37 (*m*, 5 arom. *H*). ^{13}C-NMR ($CDCl_3$): 16.8 (1 C, Me_2CH); 18.4 (1 C, Me_2CH); 27.7 (Me_3C); 30.8 (Me_2CH); 40.5 (CH_2Cl); 41.5 ($PhCH_2$); 57.4 (C(2)); 78.8 (Me_2CHCH); 86.0 (Me_3C); 116.1 (CN); 128.6, 129.0, 130.4, 131.7 (arom. C); 163.9 (CO); 166.0 (CO); 168.2 (CO).

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