Synthesis and Transformations of Methyl (*E*)-2-(Acetylamino)-3-cyanoprop-2-enoate und Methyl (*E*)-2-(Benzoylamino)-3-cyanoprop-2-enoate, Versatile Reagents for the Preparation of Polyfunctional Heterocyclic Systems

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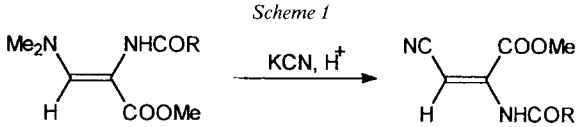
Methyl (*E*)-2-(acetylamino)-3-cyanoprop-2-enoate (**2a**) and its 2-benzoyl analog **2b** were prepared from the corresponding methyl (*Z*)-2-(acylamino)-3-(dimethylamino)propenoates **1**. Multifunctional compounds **2** are versatile synthons for preparation of polysubstituted heterocyclic systems such as pyrroles **4**, pyrimidines **5** and **6**, pyridazines **7**, pyrazoles **8**, **9**, and **11**, and isoxazoles **10**.

Introduction. – Derivatives of 2-amino-3-cyanoprop-2-enoates have been prepared from dichloromaleic anhydride [1] and by condensation of alkyl cyanoformates and analogous compounds with active methylene compounds [2–4]. Inspite of the fact that these compounds have been described as precursors for the synthesis of α,β-didehydro-α-amino acids, reactions involving either CN or ester group have not been reported.

Results and Discussion. – In our studies on the syntheses and transformations of alkyl 2-(acylamino)-3-(dimethylamino)prop-2-enoates as simple and versatile reagents for the preparation of various cyclic systems [5][6], we observed that the Me_2N group in methyl (*Z*)-2-(acetylamino)-3-(dimethylamino)prop-2-enoate (**1a**) and methyl (*Z*)-2-(benzoylamino)-3-(dimethyamino)prop-2-enoate (**1b**), obtained from *N*-acetylglycine [6] and *N*-benzoylglycine (hippuric acid) [7][8], respectively, can be easily exchanged by a CN group to give methyl (*E*)-2-(acetylamino)-3-cyanoprop-2-enoate (**2a**) and methyl (*E*)-2-(benzoylamino)-3-cyanoprop-2-enoate (**2b**) in 70 and 52% yield, respectively (*Scheme 1*). The configuration around the C=C bond in compounds **2** was established by X-ray analysis[1]).

Since the compounds **2** are multifunctional, they turned out to be useful synthons for the preparation of several polyfunctional substituted five- and six-membered heterocyclic

Scheme 1



1a R= Me
1b R= Ph

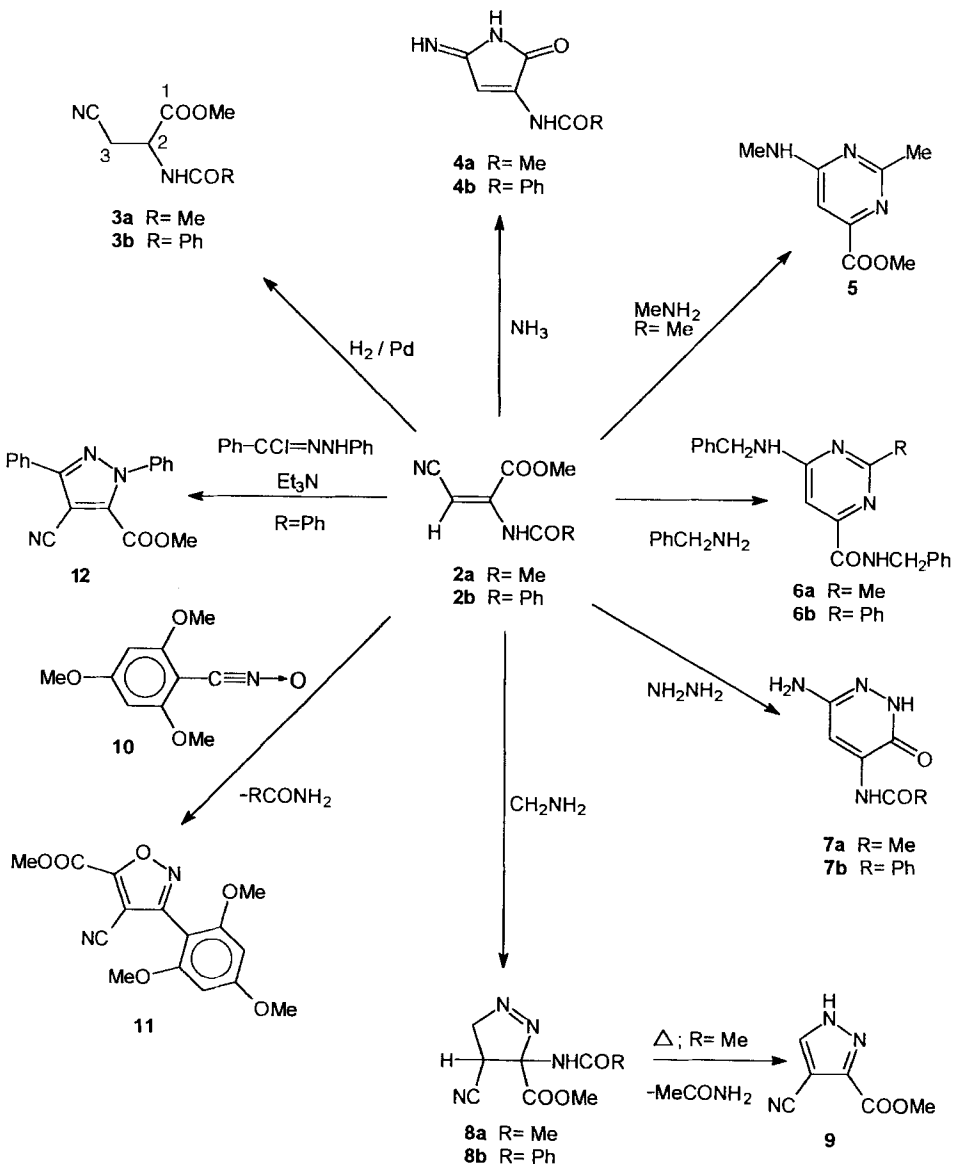
2a R= Me
2b R= Ph

[1]) X-Ray data of structure analyses of the compounds **2a** and **2b** will be published elsewhere.

systems. There are several types of synthetic methods for preparation of pyrroles [9], pyrimidines [10–11], pyridazines [12–14], pyrazoles [15][16], and isoxazoles [17][18]. Especially, systems with an amino, cyano, carboxylic, and/or ester group(s) require tedious, multistep procedures, resulting usually in low overall yields.

In the reaction of **2** with NH_3, CN, and COOMe groups are involved in cyclization to give pyrrole derivative **4**, while in the reaction with primary amines CN and AcNH groups react to give substituted pyrimidine derivatives **5** and **6**. The reaction of hydrazine

Scheme 2



with CN and COOMe groups produced 4,6-diamino-substituted pyridazin-3(2*H*)-ones **7**.

1,3-Dipolar cycloaddition of CH_2N_2 to the activated C=C bond takes place under mild conditions to form methyl 3-(acetylamino)-4-cyano-4,5-dihydro-3*H*-pyrazole-3-carboxylate (**8a**) and its 3-benzoylamino analog **8b**, as the primary cycloadducts (*Scheme 2*). Thermal elimination of acetamide from **8a** leads to the 3,4-disubstituted pyrazole derivative **9**. On the other hand, the 1,3-dipolar cycloaddition of nitrile oxides **10** requires more drastic conditions, under which acetamide or benzamide is eliminated spontaneously to give the corresponding substituted isoxazole derivative **11**. Similarly, 1,3-dipolar cycloaddition of diphenylnitrile imine, generated *in situ* from *N*-phenylbenzohydrazonoyl chloride in the presence of Et_3N, yields methyl 4-cyano-2,5-diphenylpyrazole-3-carboxylate (**12**) by elimination of benzamide from the primary cycloadduct, which was not isolated. The structures of compounds were determined by NMR spectra, elemental analyses, and, in some instances, by X-ray structure analyses.

Experimental Part

General. M.p.: *Kofler* micro hot stage. The ^{1}H-NMR spectra: *Varian EM 360 L* and *Bruker Avance 300 DPX* spectrometers. MS: *Autospeck Q* spectrometer. Elemental analyses: *Perkin-Elmer Analyser 2400. Methyl (Z)-2-(acetylamino)-3-(dimethylamino)prop-2-enoate* (**1a**) [6] and *methyl (Z)-2-(benzoylamino)-3-(dimethylamino)-prop-2-enoate* (**1b**) [7] were prepared according to literature procedures.

Methyl (E)-2-(Acetylamino)-3-cyanoprop-2-enoate (**2a**). To a mixture of **1a** (0.930 g, 5 mmol), KCN (0.358 g, 5.5 mmol), and toluene (15 ml), glacial AcOH (15 ml) was added dropwise. Then, the mixture was heated under reflux for 1.5 h, cooled to r.t., and the solvent was evaporated *in vacuo*. To the oily residue, H_2O (30 ml) was added and the precipitate collected by filtration to give **2a** in 71% yield. M.p. 115–116°. ^{1}H-NMR (300 MHz, $CDCl_3$): 2.23 (*s*, COMe); 4.03 (*s*, MeO); 7.37 (*s*, CH); 8.27 (br. *s*, NH). MS: 168 (29, M^+). Anal. calc. for $C_7H_8N_2O_3$ (168.15): C 50.00, H 4.80, N 16.66; found: C 50.20, H 4.61, N 16.55. X-Ray analysis confirms the (*E*)/configuration.)

Methyl (E)-2-(Benzoylamino)-3-cyanoprop-2-enoate (**2b**). Similarly, **2b** was prepared from **1b** in 52% yield. M.p. 96–98° (PrOH). ^{1}H-NMR (60 MHz, (D_6)DMSO): 3.87 (*s*, MeO); 6.10 (*s*, CH); 7.50–7.80 (*m*, H–C(3'), H–C(4'), H–C(5') of Ph); 7.93–8.10 (*m*, H–C(2'), H–C(6') of Ph); N*H*COPh exchanged. Anal. calc. for $C_{12}H_{10}N_2O_3$ (230.22): C 62.61, H 4.38, N 12.17; found: C 62.30, H 4.35, N 12.11.

Methyl (RS)-2-(Acetylamino)-3-cyanopropanoate (**3a**). To a soln. of **2a** (0.168 g, 1 mmol) in EtOH (10 ml), Pd/C (10%, 0.020 g) was added and the mixture was hydrogenated at normal pressure for 5 h. The filtrate was evaporated *in vacuo*. Et_2O (5 ml) was added to the oily residue, and the precipitate was collected by filtration to give **2a** in 98% yield. M.p. 72–75°. ^{1}H-NMR (300 MHz, $CDCl_3$): 2.09 (*s*, COMe); 2.95 (*dd*, J = 4.3, 17, H–C(3)); 3.09 (*dd*, J = 5.3, 17, H–C(3)); 3.87 (*s*, MeO); 4.73–4.78 (br. *ddd*, J = 4.3, 5.3, 17, H–C(2)); 6.43 (br. *s*, NH). Anal. calc. for $C_7H_{10}N_2O_3$ (170.17): C 49.41, H 5.92, N 16.46; found: C 49.16, H 5.71, N 16.42.

Methyl (RS)-2-(Benzoylamino)-3-cyanopropanoate (**3b**). Similarly, **3b** was prepared from **2b** in 99% yield. M.p. 135–138° (from AcOEt/MeOH). ^{1}H-NMR (300 MHz, $CDCl_3$): 3.06 (*dd*, J = 4.4, 17, H–C(3)); 3.23 (*dd*, J = 5.5, 17, H–C(3)); 3.80 (*s*, MeO); 4.93–4.98 (*m*, J = 4.4, 5.5, 5.6, 17, H–C(2)); 7.17 (*d*, J = 5.6, NH); 7.45–7.56 (*m*, H–C(3'), H–C(4'), H–C(5') of Ph); 7.82–8.85 (*m*, H–C(2'), H–C(6') of Ph). Anal. calc. for $C_{12}H_{12}N_2O_3$ (232.24): C 62.06, H 5.21 N, 12.06; found: C 61.74, H 5.13, N 12.03.

*3-(Acetylamino)-5-imino-1,5-dihydro-2*H*-pyrrol-2-one* (**4a**). A soln. of **2a** (0.168 g, 1 mmol) in EtOH (5 ml) was treated with NH_3 for 10 min. The soln. was cooled on ice, and the precipitate was collected by filtration to give **4a** in 53% yield. M.p. > 350°. ^{1}H-NMR (300 MHz, (D_6)DMSO): 2.12 (*s*, COMe); 6.60 (*s*, CH); 9.11 (br. *s*, N*H*COMe); 9.87 (br. *s*, NH); 10.22 (br. *s*, NH). Anal. calc. for $C_6H_7N_3O_2$ (153.14): C 47.06, H 4.61, N 27.44; found: C 47.10, H 4.55, N 27.45.

*3-(Benzoylamino)-5-imino-1,5-dihydro-2*H*-pyrrol-2-one* (**4b**). Similarly, **4b** was prepared from **2b** in 45% yield. M.p. > 230° (dec.). ^{1}H-NMR (60 MHz, (D_6)DMSO): 6.83 (*s*, H–C(4)); 7.47–7.67 (*m*, H–C(3'), H–C(4'), H–C(5') of Ph); 7.90–8.10 (*m*, H–C(2'), H–C(6') of Ph); 8.70–9.80 (br. *s*, N*H*COPh, N*H*); 10.23 (br. *s*, NH). Anal. calc. for $C_{11}H_9N_3O_2$ (215.21): C 61.39, H 4.22 N, 19.53; found: C 61.18, H 4.20, N 19.82.

Methyl 2-Methyl-6-(methylamino)pyrimidine-4-carboxylate (**5**). A soln. of **2a** (0.168 g, 1 mmol) and $MeNH_2$ (40%, 0.0775 g) in MeOH (3 ml) was heated under reflux for 3 h. The solvent was evaporated *in vacuo*, and the solid residue was purified by radial chromatography using *Chromatotron* ($CHCl_3$/AcOEt 3:2) to give **5** in 19% yield. M.p. 195–198°. ^{1}H-NMR (300 MHz, $CDCl_3$): 2.24 (*s*, Me); 3.11 (*s*, NH*Me*); 3.41 (*s*, MeO); 7.04 (*s*, CH); 7.92 (br. *s*, NH). MS: 181 (54, M^+). Anal. calc. for $C_8H_{11}N_3O_2$ (181.19): C 53.03, H 6.12, N 23.19; found: C 53.33, H 6.18, N 23.17.

N-*Benzyl-6-(benzylamino)-2-methylpyrimidine-4-carboxamide* (**6a**). A soln. of **2a** (0.168 g, 1 mmol) and $PhCH_2NH_2$ (0.5 ml, 5 mmol) in EtOH (3 ml) was heated under reflux for 4 h. The soln. was left overnight at r.t., and the precipitate was collected by filtration to give **6a** in 38% yield. M.p. 155–156°. ^{1}H-NMR (300 MHz, $CDCl_3$): 2.48 (*s*, Me); 4.57, 4.59 (2*s*, 2 CH_2); 5.63 (br. *t*, NH); 7.11 (*s*, H–C(5)); 7.25–7.36 (*m*, 2 Ph); 8.36 (br. *t*, CONH). Anal. calc. for $C_{20}H_{20}N_4O$ (332.40): C 72.27, H 6.06, N 16.85; found: C 72.10, H 6.12, N 16.79.

N-*Benzyl-6-(benzylamino)-2-phenylpyrimidine-4-carboxamide* (**6b**). Similarly, **6b** was prepared from **2b** and $PhCH_2NH_2$ in 47% yield. M.p. 208–210° (EtOH). ^{1}H-NMR (60 MHz, (D_6)DMSO): 4.63 (*d*, J = 7, CH_2NH); 4.80 (*d*, J = 6, CH_2NHCO); 7.17 (*s*, H–C(5)); 7.30–7.57 (*m*, H–C(3′), H–C(4′), H–C(5′) of $CONHCH_2Ph$, 2 $PhCH_2$); 8.40 (*t*, J = 7, $NHCH_2$); 8.47–8.67 (*m*, H–C(2′), H–C(6′) of Ph–C(2)); 9.47 (*t*, J = 6, $CONHCH_2$). Anal. calc. for $C_{25}H_{22}N_4O$ (394.48): C 76.12, H 5.62, N 14.20; found: C 75.83, H 5.56, N 14.03.

4-(Acetylamino)-6-amino-2H-pyridazin-3-one (**7a**). A mixture of **2a** (0.168 g, 1 mmol) and hydrazine hydrate (0.1 ml, 2 mmol) in EtOH (3 ml) was stirred at r.t. for 2 h. The precipitate was collected by filtration and recrystallized from EtOH to give **7a** in 62% yield. M.p. 235°. ^{1}H-NMR (300 MHz, (D_6)DMSO): 2.17 (*s*, COMe); 5.54 (*s*, NH_2); 7.69 (*s*, CH); 9.55 (*s*, NHCOMe); 11.88 (br. *s*, NH). MS: 168 (49, M^+). Anal. calc. for $C_6H_8N_4O_2$ (168.16): C 42.86, H 4.80, N 33.32; found: C 42.71, H 4.85, N 32.95.

6-Amino-4-(benzoylamino)-2H-pyridazin-3-one (**7b**). Similarly, **7b** was prepared from **2b** in 81% yield. M.p. 284–286° (MeOH). ^{1}H-NMR (60 MHz, (D_6)DMSO): 5.60 (br. *s*, NH_2); 7.57–7.77 (*m*, H–C(3′), H–C(4′), H–C(5′) of Ph); 7.90 (*s*, CH); 7.90–8.07 (*m*, H–C(2′), H–C(6′) of Ph); 9.57 (*s*, NHCOPh); 12.20 (br. *s*, NH). Anal. calc. for $C_{11}H_{10}N_4O_2$ (230.23): C 57.39, H 4.38, N 24.34; found: C 57.35, H 4.41, N 24.44.

Methyl 3-(Acetylamino)-4-cyano-4,5-dihydro-3H-pyrazole-3-carboxylate (**8a**). To a soln. of **2a** (0.168 g, 1 mmol) in $CHCl_3$ (3 ml), excess of CH_2N_2 (in Et_2O, 10 mmol) was added and left overnight at −20°. The mixture was left for a few hours in the open air. The precipitate was collected by filtration to give **8a** in 58% yield. M.p. 128–132°. ^{1}H-NMR (300 MHz, (D_6)DMSO): 1.98 (*s*, COMe); 3.64 (*dd*, J = 7.4, 9.6, H–C(4)); 3.77 (*s*, MeO); 4.83 (*dd*, J = 7.4, 18, H–C(5)); 5.32 (*dd*, J = 9.6, 18, H–C(5)); 9.38 (*s*, NH). MS: 211 (43, MH^+). Anal. calc. for $C_8H_{10}N_4O_3$ (210.19): C 45.71, H 4.80, N 26.66; found: C 45.93, H 4.84, N 26.54.

Methyl 3-(Benzoylamino)-4-cyano-4,5-dihydro-3H-pyrazole-3-carboxylate (**8b**). Similarly, **8b** was prepared from **2b** in 86% yield. M.p. 98° (CH_2Cl_2/Et_2O). ^{1}H-NMR (60 MHz, (D_6)DMSO, D_2O): 3.80 (deg. *dd* and *s*, J = 7, 10, H–C(4), MeO); 4.83 (*dd*, J = 7, 18, H–C(5)); 5.45 (*dd*, J = 10, 18, H–C(5)); 7.50–7.70 (*m*, H–C(3′), H–C(4′), H–C(5′) of Ph); 7.87–8.07 (*m*, H–C(2′), H–C(6′) of Ph); 9.83 (*s*, NHCOPh, exchanged). Anal. calc. for $C_{13}H_{12}N_4O_3$ (272.26): C 57.35, H 4.44, N 20.58; found: C 57.30, H 4.52, N 20.35.

Methyl 4-Cyanopyrazole-3-carboxylate (**9**). The compound **8a** (0.210 g, 1 mmol) in xylene (3 ml) was heated under reflux for 3 h. The precipitate was collected by filtration to give **9** in 79% yield. M.p. 221–227° ([19]: m.p. 225–228°). ^{1}H-NMR (300 MHz, (D_6)DMSO): 3.88 (*s*, MeO); 8.69 (*s*, CH); 14.40 (*s*, NH). MS: 151 (72, M^+). Anal. calc. for $C_6H_5N_3O_2$ (151.12): C 47.69, H 3.33, N 27.80; found: C 47.33, H 3.15, N 27.89.

Methyl 4-Cyano-3-(2,4,6-trimethoxyphenyl)isoxazole-5-carboxylate (**11**). A mixture of **2a** (0.168 g, 1 mmol) and *2,4,6-trimethoxybenzenecarbonitrile oxide* (**10**; 0.209 g, 1 mmol) in $CHCl_3$ (3 ml) was heated under reflux for 6 h. The solvent was evaporated *in vacuo*, and MeOH (1 ml) was added to the oily residue. The precipitate was collected by filtration to give **10** in 72% yield. M.p. 129–131°. ^{1}H-NMR (300 MHz, $CDCl_3$): 3.82 (*s*, 2′,6′-$(OMe)_2$); 3.88 (*s*, 4′-OMe); 4.07 (*s*, COOMe); 6.21 (*s*, H–C(3′), H–C(5′) of Ar). Anal. calc. for $C_{15}H_{14}N_2O_6$ (318.29): C 56.60, H 4.43, N 8.80; found: C 56.71, H 4.44, N 8.45.

The compound **11** was obtained also from **4b** in 71% yield.

Methyl 4-Cyano-1,3-diphenylpyrazole-5-carboxylate (**12**). To a mixture of **2b** (0.230 g, 1 mmol) and *N*-phenylbenzohydrazonyl chloride (0.230 g, 1 mmol) in CH_2Cl_2 (3 ml), Et_3N (0.2 ml) was added, and the mixture was heated under reflux for 0.5 h. The solvent was evaporated *in vacuo*. The oily residue was dissolved in EtOH (3 ml), H_2O (5 ml) was added and the precipitate was collected by filtration to give **11** in 81% yield. M.p. 172–174°. ^{1}H-NMR (60 MHz, (D_6)DMSO): 3.87 (*s*, MeO); 7.50–7.67 (*m*, Ph–N(1), H–C(3′), H–C(4′), H–C(5′) of Ph–C(3)); 7.93–8.13 (*m*, H–C(2′), H–C(6′) of Ph–C(3)). Anal. calc. for $C_{18}H_{13}N_3O_2$ (303.32): C 71.28, H 4.32, N 13.85; found: C 70.80, H 4.29, N 14.03.

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