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Reactivity of 2-Cyano-1,4,5,6-tetrahydro-1-pyridinecarboxylic Acid Esters Towards Various Nucleophiles: Regio- and Stereoselectivity of the Attack

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Summary. The synthesis and reactivity of the title compounds towards nucleophiles are discussed. The regio- and diastereoselectivity of the attack is highly dependent on the carbamic ester and the type of nucleophile applied. Both *Michael* type addition across the activated double bond and S_N2T reaction at the carbamate carbon atom were observed. Structure assignment of the adducts in solution and in the solid state was performed utilizing high temperature NMR techniques as well as single crystal X-ray diffraction.

Keywords. *Michael* type addition; High temperature NMR techniques; Single crystal X-ray diffraction.

Reaktivität von 2-Cyano-1,4,5,6-tetrahydro-1-pyridincarbonsäureestern gegenüber verschiedenen Nucleophilen: Regio- und Diastereoselektivität des Angriffs

Zusammenfassung. Die Synthese und Reaktivität der Titelverbindungen gegenüber Nucleophilen wird diskutiert. Die Regio- und Diastereoselektivität des Angriffs hängt stark vom jeweiligen Carbaminsäureester und vom Nucleophil ab. Sowohl *Michael*-Addition an die aktivierte Doppelbindung als auch S_N2T-Reaktion am Carbamatkohlenstoff wurden beobachtet. Die Strukturaufklärung der Addukte in Lösung und im Festkörper wurde mit Hilfe von Hochtemperatur-NMR-Techniken sowie Einkristallröntgenbeugung durchgeführt.

Introduction

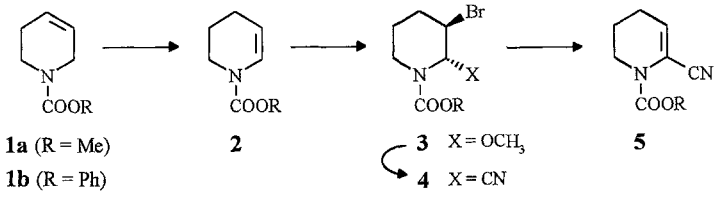
As part of our efforts directed towards the synthesis of perhydro nitrogen heterocycles, our interest focused on some 3-substituted 2-cyanopyridine-1-carboxylates as precursors for potentially antifungal compounds. Our approach for the construction of these structures included a 1,4-addition reaction of various nucleophiles to the title compounds. In the present paper, we would like to report on the regioselectivity of the nucleophilic attack and the diastereoselectivity observed in the course on the *Michael* reaction.

Although 1,4-conjugate nucleophilic additions to activated alkenes are among the important reactions in organic chemistry [1], little has been published regarding their stereochemistry. Both for acyclic and more rigid cyclic *Michael* acceptors in most cases mixtures of *cis*- and *trans*-adducts are reported [2].

The addition reactions in the present heterocyclic series indicate high diastereoselectivity, favoring all-*axial* substituted adducts. Furthermore, the *N*-protecting group plays a significant role for the regioselectivity of the nucleophilic attack.

Results and Discussion

The synthesis of the *Michael* acceptors **5a** and **5b** was carried out starting with the easily accessible compounds **1a** [3] and **1b** [4], respectively (Scheme 1). Isomerization of the double bond into the favored 2-position was achieved by treatment with Pd(0)/C under basic conditions according to *Wanner et al.* [5] in excellent yields. Presumably, this reaction proceeds *via* an oxidative addition of palladium across the double bond followed by subsequent reductive elimination to form the thermodynamically more stable product **2**. The cyano group was then introduced in a modified three step sequence reported by *Shono et al.* [6]. Methoxybromination of the products **2a, b** gave rise to compounds **3a, b**. Treatment with *TMS*CN under *Lewis* acid catalysis afforded the nitriles **4**. This reaction is assumed to proceed *via* an immonium salt formed after elimination of the methoxy group. The stereochemistry of the compounds was established by comparing the NMR spectra with those of the adducts **6–9** whose structure was verified by X-ray crystallography. Finally, elimination of HBr to the desired *Michael* acceptors **5** was accomplished by use of *DBU* as base. Though **3** and **4** were isolable by flash column chromatography, the sequence was usually carried out without purification of the compounds and gave **5** in fair to good overall yield after column chromatography.



Scheme 1

In Table 1, our results obtained in the subsequent reaction of *Michael* acceptors **5a, b** with various nucleophiles are summarized.

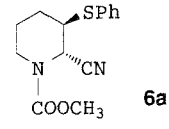
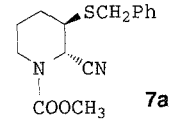
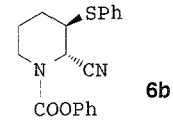
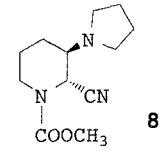
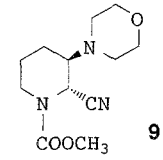
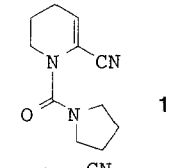
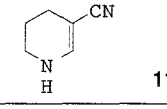
Since thiols are known to be the most reactive nucleophiles for *Michael* type additions, thiophenol (entry 1) and benzylmercaptane (entry 2) were used for the first experiments with compound **5a**. In both reactions, only one diastereoisomer was isolated in high yield (**6a** and **7a**). **5a** gave somewhat lower yields of compound **6b**; however, regio- and stereoselectivity of the reaction was not influenced (entry 3).

As expected, amines proved to be less reactive than thiols; therefore, a large excess of nucleophile was required. Usually the experiments were carried out using the amine as solvent, and conversion of **5a** with pyrrolidine gave compound **8** in good yield (entry 4). A significant decrease in reactivity was observed changing to morpholine as nucleophile (entry 5). Both adducts (**8** and **9**) showed *trans*-axial configuration.

The phenyl carbamate **5b** exhibited a different regioselectivity of the reaction and was attacked at the C=O bond of the carbamate to form urea **10** exclusively in excellent yield (entry 6).

Sodium phenolate as nucleophile reacted only under rather vigorous conditions with **5a** and did not produce any 1,4-adduct. Compound **11** was the only product that could be isolated from the resulting mixture, consisting predominantly of polymeric substances (entry 7). The protecting group $COOCH_3$ was cleaved under

Table 1. Reaction of *Michael* acceptors **5a, b** with various nucleophiles

Entry	Acceptor	Nucleophile	Product	Yield (%)
1	**5a**	PhSH	 **6a**	82
2	**5a**	$PhCH_2SH$	 **7a**	79
3	**5b**	PhSH	 **6b**	61
4	**5a**	pyrrolidine	 **8**	64
5	**5a**	morpholine	 **9**	13
6	**5b**	pyrrolidine	 **10**	96
7	**5a**	PhONa	 **11**	11

the reaction conditions and, moreover, a migration of the cyano functionality was observed. Although **11** is known in the literature, no spectroscopic data have been reported up to now [7]. Therefore, identification of the compound could be accomplished by comparing its ^{13}C NMR shift values with those of the published N-CH_3 compound [8]. The mechanism of this reaction is still unknown and subject to further investigations in our laboratory.

Structural elucidation of the 1,4-adducts

Structural assignment of all 1,4-adducts is based on NMR studies in solution and an X-ray single crystal analysis of compound **6a**. Both ^1H and ^{13}C NMR spectra of the product showed a significant broadening of the signals at position 2, 3, and 6 in $CDCl_3$ obviously caused by the carbamate structure. Resolution of the spin systems of interest (H-2 and H-3) could be improved by changing the solvent to *DMSO*-d_6 and increasing the observation temperature during the NMR experiment. Figure 1 shows the temperature gradient experiments performed with **6a** in *DMSO-d_6* in the range of 26 to 95°C.

Due to the migration of the water peak with increasing temperature to higher field into the spin system of H-6_{ax}, interpretation of the ^1H NMR spectrum of **6a** was based on the trace obtained at 73°C.

Proton H-2 showed a *pseudo*-quintet with an area ratio of 1:2:2:2:1 (Fig. 2). The value of its coupling constant with H-3 of approx. 2.2 Hz is in good correlation with a *gauche* configuration according to the *Karplus-Conroy* equation [9].

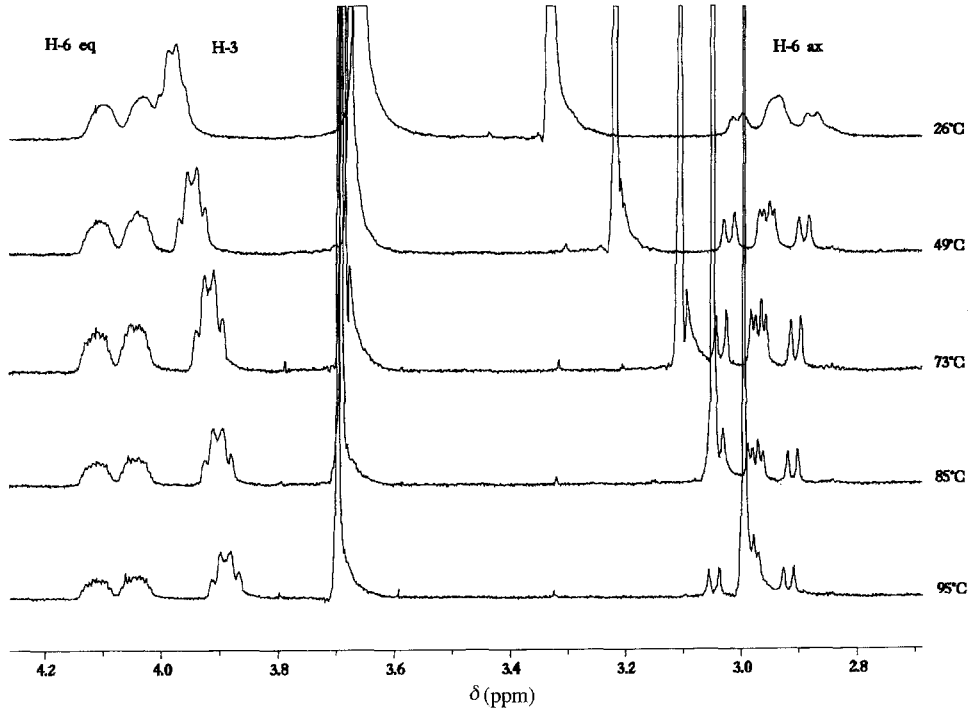


Fig. 1. High temperature ^1H NMR experiments with **6a**

Furthermore, two ^4J_W- coupling constants of approx. 1.1 Hz with H-4_{eq} and H-6_{eq} could be observed. The fact that such long range interactions can be transferred only in planar configurations suggests an equatorial position of H-2 [10], therefore indicating a *trans*-axial relationship of the two substituents at positions 2 and 3.

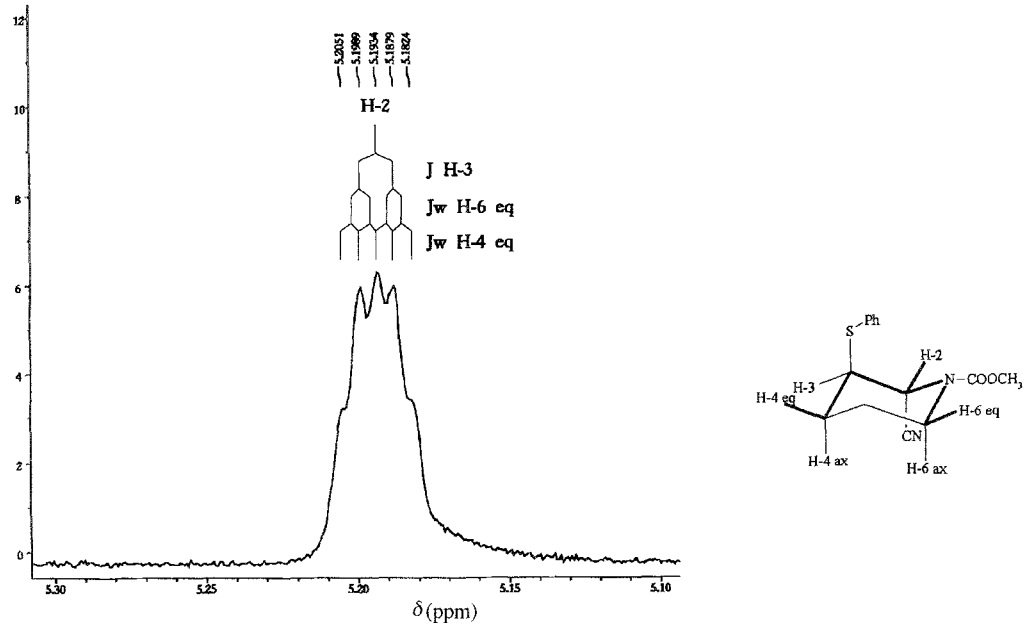


Fig. 2. Spin system H-2 of compound **6a**

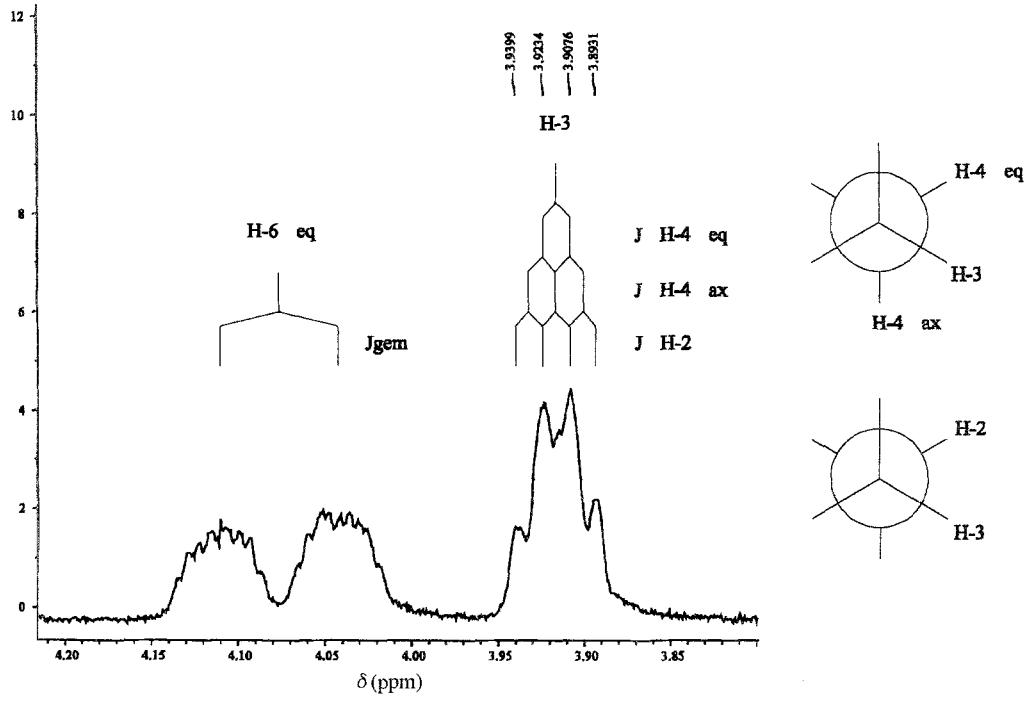


Fig. 3. Spin systems H-3 and H-6_{eq} of compound **6a**

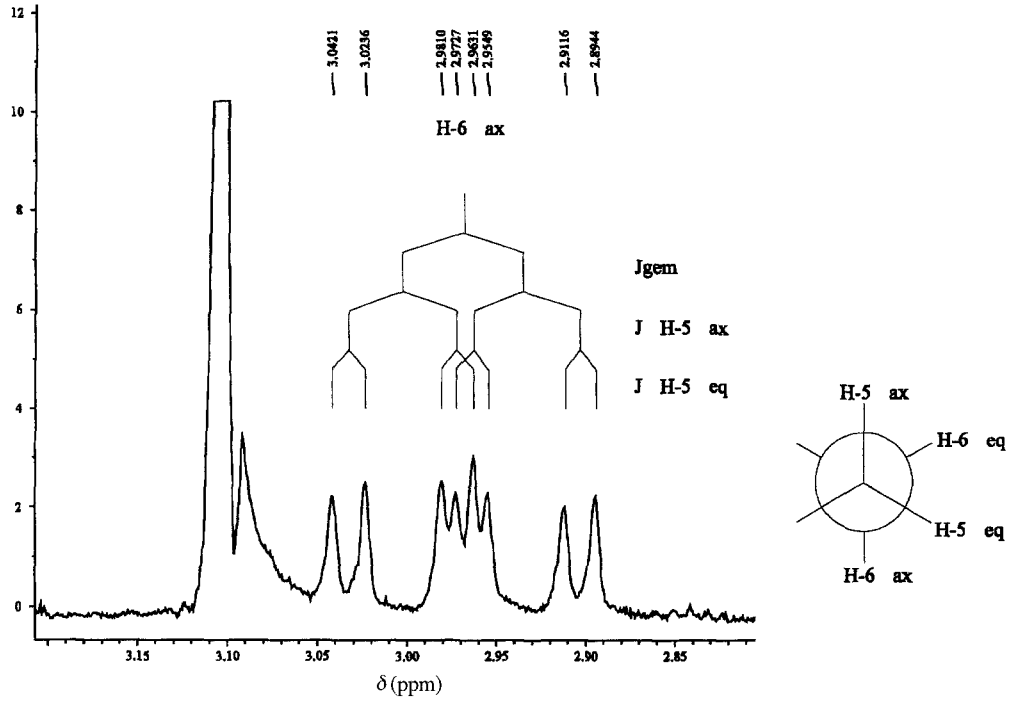


Fig. 4. Spin system H-6_{ax} of compound **6a**

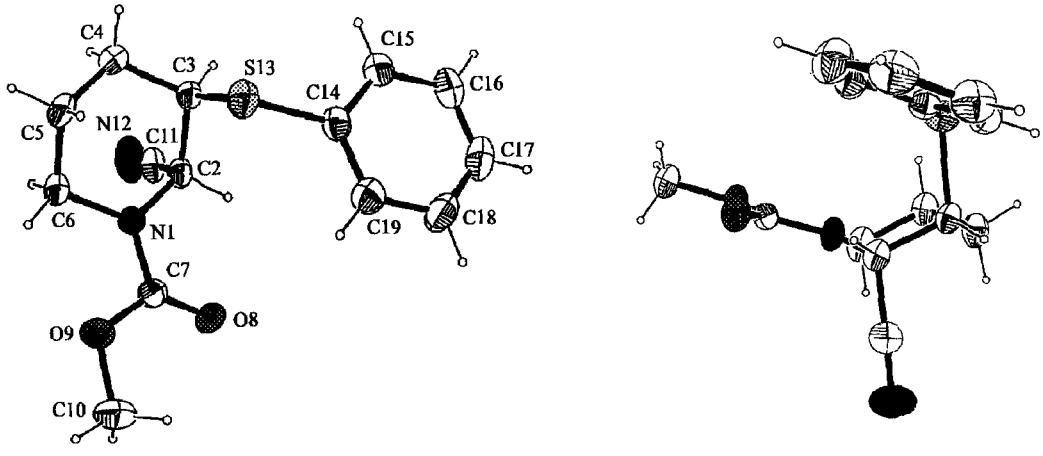


Fig. 5. X-Ray diffraction of compound **6a**

The signal of H-3 represents a quartet with $^3J_{vic} = 2.2$ Hz, caused by 3 *gauche* relationships with H-2, H-4_{eq}, and H-4_{ax} and thus supporting the structural assignment derived from H-2 (Fig. 3).

The assignment of H-6_{eq} (Fig. 3) and H-6_{ax} (Fig. 4) was unambiguous. The axial proton showed a large geminal coupling ($^2J_{gem} = 14$ Hz) with H-6_{ax}, a large vicinal coupling ($^3J_{trans} = 12$ Hz) and a small vicinal coupling ($^3J_{gauche} = 3$ Hz) with H-5_{eq}/H-5_{ax}. In the case of the equatorial hydrogen, only the geminal

interaction is resolved, the remaining small *gauche* coupling constants with H-5_{eq}/H-5_{ax} and J_W with H-2 leading to a complex multiplet.

From the high temperature NMR study, an all-*trans*-axial substitution pattern for **6a** was deduced in solution which could be confirmed in the solid state by a single crystal X-ray diffraction experiment [11]. The piperidine ring adopts a chair conformation with the sp^2-nitrogen atom in plane with the carboxylic acid ester functionality and the substituents at opposite sides of the ring (Fig. 5).

Experimental

General

All solvents were distilled prior to use. Dry *THF* was prepared by distillation from sodium benzophenone, dry CH_2Cl_2 and dioxane by distillation from P_2O_5, and dry MeOH by distillation from Mg. Commerically available dry *DMF* was treated with molecular sieves (4 Å). TLC was performed on Merck precoated silica gel plates (5554), flash column chromatography on silica gel 60 from Merck (40–63 μm, 9385). Melting points were determined using a Reichert micro hot stage apparatus and are uncorrected. Elemental analyses were performed in the Microanalytical Laboratory of the University of Vienna. The NMR spectra were recorded in $CDCl_3$ or *DMSO*-d_6 solutions with a Bruker AC 200 (200 MHz) spectrometer; chemical shifts are reported in ppm relative to Me_4Si as internal standard.

Isomerization of the double bond using Pd(0)

An approx. 20% solution of **1** in a mixture of dry *THF* : dry NEt_3 = 4 : 1 was heated at 130°C for 48 h in a Miniclave® (Büchi Glas Uster) in the presence of 5% (w/w) Pd/C (10%; Pd on charcoal; external temperature of the oil bath). Filtration over Celite® and evaporation of the volatiles gave compounds **2a**, **b**.

1,2,3,4-Tetrahydro-1-pyridinecarboxylic acid methylester (**2a**)

Compound **1a** (10.00 g, 70.84 mmol) gave 9.30 g (93%) of pure **2a** as yellow oil without further purification. ^{1}H NMR ($CDCl_3$): δ = 1.70–1.90 (m, 2H, H-3), 1.90–2.10 (m, 2H, H-4), 3.44–3.66 (m, 2H, H-2), 3.72 (s, 3H, OCH_3), 4.73–4.99 (m, 1H, H-5), 6.63–6.92 (m, 1H, H-6); ^{13}C NMR ($CDCl_3$, spectrum showed *E/Z* isomers): δ = 21.2, 21.3 and 21.6 (3s, C-3 and C-4, *E/Z*), 42.1 and 42.2 (2s, C-2, *E/Z*), 52.7 (q, OCH_3), 106.1 and 106.4 (2d, C-5, *E/Z*), 124.8 and 125.3 (2d, C-6, *E/Z*), 153.7 and 154.1 (2s, CO, *E/Z*).

1,2,3,4-Tetrahydro-1-pyridinecarboxylic acid phenylester (**2b**)

Product **1b** (10.00 g, 49.20 mmol) gave 9.42 g (94%) of pure **2b** as colorless crystals after recrystallization from light petroleum. Mp.: 61–62°C; ^{1}H NMR ($CDCl_3$): δ = 1.83–2.00 (m, 2H, H-3), 2.03–2.18 (m, 2H, H-4), 3.65–3.86 (m, 2H, H-2), 4.95–5.13 (m, 1H, H-5), 6.86–7.03 (m, 1H, H-6), 7.08–7.45 (m, 5H, arom. H); ^{13}C NMR ($CDCl_3$, spectrum showed *E/Z* isomers): δ = 21.1, 21.3, 21.4 and 21.6 (4t, C-3, C-4, *E/Z*), 42.3 and 42.8 (2t, C-2, *E/Z*), 107.4 and 107.8 (2d, C-5, *E/Z*), 121.5 (d, C-2′), 124.7 and 125.1 (2d, C-6, *E/Z*), 125.3 (d, C-4′), 129.2 (d, C-3′), 151.0 and 151.1 (2s, C-1′ and CO); $C_{12}H_{13}NO_2$; calc.: C 70.92, H 6.45, N 6.89; found: C 70.97, H 6.38, N 6.79.

Methoxybromination of **2**

To a mixture of **2** (1 equiv.) and sodium methoxide (1.1 equiv.) in dry methanol (approx. 10% solution), 1.1 equiv. of Br_2 dissolved in a few ml of methanol were added maintaining the temperature below 20°C. The reaction mixture was stirred until completion (TLC control), hydrolyzed with satd. $NaHCO_3$ solution, and extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*.

trans-3-Bromo-2-methoxy-1-piperidinecarboxylic acid methylester (**3a**)

2a (9.17 g, 64.96 mmol) gave 16.03 g (98%) of pure **3a** as a yellow oil without further purification. ^{1}H NMR ($CDCl_3$) $\delta = 1.32$–2.39 (m, 4H, H-4 and H-5), 2.80–3.09 (m, 1H, H-6_{ax}), 3.15–3.41 (bs, 3H, OCH_3), 3.71 (s, 3H, $COOCH_3$), 3.80–4.10 (m, 1H, H-6^*_{eq}), 4.21–4.36 (m, 1H, H-3*), 5.22–5.59 (m, 1H, H-2); ^{13}C NMR ($CDCl_3$, spectrum showed *E/Z* isomers): $\delta = 19.2$ (t, C-5), 26.7 (t, C-4), 37.9 (bt, C-6), 48.9 (d, C-3), 52.7 (q, $COOCH_3$), 54.9 (q, OCH_3), 85.0 (bd, C-2), 155.6 (s, CO).

trans-3-Bromo-2-methoxy-1-piperidinecarboxylic acid phenylester (**3b**)

2b (7.79 g, 38.33 mmol) gave 12.00 g (100%) of pure **3b** as pale yellow oil. In order to get an analytically pure sample, a small fraction was purified by flash column chromatography (basic cond. silica gel 15:1, light petroleum: ethyl acetate = 20:1). ^{1}H NMR ($CDCl_3$): $\delta = 1.43$–2.48 (m, 4H, H-4 and H-5), 2.93–3.30 (m, 1H, H-6_{ax}), 3.31–3.49 (bs, 3H, OCH_3), 3.98–4.25 (m, 1H, H-6_{eq}), 4.30–4.42 (m, 1H, H-3), 5.50–5.66 (m, 1H, H-2), 7.00–7.45 (m, 5H, arom. H); ^{13}C NMR ($CDCl_3$, spectrum showed *E/Z* isomers): $\delta = 19.3$ and 19.6 (2t, C-5, *E/Z*), 26.8 (t, C-4), 38.2 and 39.0 (2t, C-6, *E/Z*), 48.8 and 49.3 (2d, C-3, *E/Z*), 55.1 (q, OCH_3), 85.0 and 85.7 (2d, C-2, *E/Z*), 121.6 (d, C-2′), 125.4 (d, C-4′), 129.2 (d, C-3′), 151.1 (s, C-1′), 154.2 (s, CO); $C_{13}H_{16}BrNO_3$; calc.: C 49.70, H 5.13, N 4.46; found: C 49.42, H 5.01, N 4.40.

Cyanylation of **3a, b**

A mixture of **3** (1 equiv.) and trimethylsilyl cyanide (2 equiv.) in dry CH_2Cl_2 (approx. 10% solution) was treated with $TiCl_4$ (0.95 equiv., 25% in dry CH_2Cl_2) at −70°C under nitrogen. The reaction was warmed up to 0°C and stirred until TLC indicated complete consumption of the starting material (approx. 2 h). The mixture was hydrolyzed with satd. $NaHCO_3$ solution and extracted with CH_2Cl_2. In case of an emulsion, the mixture was filtered over celite®. The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*.

trans-3-Bromo-2-cyano-1-piperidinecarboxylic acid methylester (**4a**)

Conversion of **3a** (15.85 g, 62.87 mmol) yielded 15.23 g (98%) of pure **4a** as an orange oil without further purification. ^{1}H NMR ($CDCl_3$): $\delta = 1.43$–2.41 (m, 4H, H-4 and H-5), 2.89–3.18 (m, 1H, H-6_{ax}), 3.76 (s, 3H, OCH_3), 4.02–4.35 (m, 1H, H-6_{eq}*), 4.40–4.58 (m, 1H, H-3*), 5.28–5.62 (m, 2H, H-2); ^{13}C NMR ($CDCl_3$, spectrum showed *E/Z* isomers): $\delta = 19.1$ (t, C-5), 28.7 (t, C-4), 41.5 (bt, C-6), 45.6 (bd, C-3*), 49.8 (bd, C-2*), 52.7 (q, OCH_3), 114.6 (s, CN), 153.7 (s, CO).

trans-3-Bromo-2-cyano-1-piperidinecarboxylic acid phenylester (**4b**)

3b (12.00 g, 38.19 mmol) gave 10.13 g (86%) of pure **4b** as pale yellow crystals. To obtain an analytically pure sample, a small fraction was submitted to a flash column chromatography (basic cond. silica gel 30:1, light petroleum : ethyl acetate = 10:1). Mp.: 118–121°C; ^{1}H NMR ($CDCl_3$):

δ = 1.50–2.45 (m, 4H, H-4 and H-5), 3.00–3.40 (m, 1H, H-6_{ax}), 4.28–4.48 (m, 1H, H-6_{eq}), 4.50–4.60 (m, 1H, H-3), 5.51–5.68 (bs, 1H, H-2), 7.05–7.48 (m, 5H, arom. H); ^{13}C NMR ($CDCl_3$, spectrum showed *E/Z* isomers): δ =19.1 (t, C-5), 28.8 (t, C-4), 41.4 (t, C-6), 45.8 (d, C-3*), 49.8 (d, C-2*), 114.6 (s, CN), 121.5 (d, C-2′), 125.9 (d, C-4′), 129.4 (d, C-3′), 150.7 (s, C-1′), 153.7 (s, CO); $C_{13}H_{13}BrN_2O_2$; calc.: C 50.51, H 4.24, N 9.06; found: C 50.36, H 4.05, N 8.81.

Elimination of HBr from compounds **4a**, **b**

To a 10% solution of **4** (1 equiv.) in dry *DMF*, *DBU* (2 equiv.) was slowly added and the resulting mixture was heated to 80°C for 2.5 h (TLC-control). The reaction solution was hydrolyzed with water and extracted with diethyl ether. The combined organic layers were washed with water, dried over Na_2SO_4, and evaporated to dryness.

2-Cyano-1,4,5,6-tetrahydro-1-pyridinecarboxylic acid methylester (**5a**)

Treatment of **4a** (15.17 g, 61.39 mmol) with *DBU* gave 9.19 g (90%) of **5a** as pale yellow crystals after purification by flash column chromatography (basic cond. silica gel 10:1, light petroleum:ethyl acetate = 5 : 1). Mp.: 53–57°C; ^{1}H NMR ($CDCl_3$): δ = 1.76–1.92 (m, 2H, H-5), 2.18–2.32 (m, 2H, H-4), 3.56–3.69 (m, 2H, H-6), 3.80 (s, 3H, OCH_3), 6.01 (t, J = 4 Hz, 1H, H-3); ^{13}C NMR ($CDCl_3$): δ = 21.2 (t, C-5), 23.1 (t, C-4), 42.9 (t, C-6), 53.1 (q, OCH_3), 113.6 (s, C-2*), 114.8 (s, CN*), 129.3 (d, C-3), 152.9 (s, CO).

2-Cyano-1,4,5,6-tetrahydro-1-pyridinecarboxylic acid phenylester (**5b**)

4b (8.05 g, 26.04 mmol) gave 3.91 g (66%) of **5b** as colorless crystals after purification by flash column chromatography (basic cond. silica gel 10:1, light petroleum : ethyl acetate = 5:1) Mp.: 66–68°C; ^{1}H NMR ($CDCl_3$): δ = 1.80–1.99 (m, 2H, H-5), 2.17–2.35 (m, 2H, H-4), 3.65–3.85 (m, 2H, H-6), 6.10 (t, J = 5 Hz, 1H, H-3), 7.10–7.28 (m, 3H, H-2′ and H-4′), 7.28–7.45 (m, 2H, H-3′); ^{13}C NMR ($CDCl_3$): δ = 21.4 (t, C-5) , 23.3 (t, C-4), 43.5 (t, C-6), 113.6 (s, C-2*), 114.7 (s, CN*), 121.2 (d, C-2′), 125.7 (d, C-4′), 129.2 (d, C-3′), 130.6 (d, C-3), 150.4 and 150.9 (2s, C-1′ and CO); $C_{13}H_{12}N_2O_2$; calc.: C 68.41, H 5.30, N 12.27; found: C 68.52, H 5.13, N 12.30.

Michael addition with sulfur nucleophiles

Precursor **5** (1 equiv.) and the nucleophile (5 equiv.) were dissolved in dry dioxane (approx. 5% solution) under nitrogen. After addition of piperidine as catalyst, the reaction mixture was heated to 60°C until TLC indicated complete conversion (approx. 20 h). After cooling, the solution was hydrolyzed with water and extracted with CH_2Cl_2. The combined organic layers were washed with 2 *N* NaOH, 2 *N* HCl, and satd. NaCl solution, dried over Na_2SO_4, and concentrated. Purification of the crude compound was performed by flash column chromatography.

trans-2-Cyano-3-phenylthio-1-piperidinecarboxylic acid methylester (**6a**)

Treatment of **5a** (1.00 g, 6.02 mmol) with thiophenol and 0.5 ml of piperidine as catalyst gave 1.36 g (82%) of **6a** as colorless crystals (basic cond. silica gel 25:1, light petroleum:ethyl acetate = 10:1). Mp.: 70–73°C; ^{1}H NMR ($CDCl_3$): δ = 1.46–2.37 (m, 4H, H-4 and H-5), 2.92–3.19 (m, 1H, H-6_{ax}), 3.50–3.62 (m, 1H, H-3), 3.78 (s, 3H, OCH_3), 4.09–4.32 (m, 1H, H-6_{eq}), 5.00–5.38 (m, 1H, H-2), 7.29–7.59 (m, 5H, arom. H); ^{1}H NMR (*DMSO*-d_6): δ = 1.50–2.21 (m, 4H, H-4 and H-5), 2.82–3.05 (m, 1H, H-6_{ax}), 3.68 (s, 3H, OCH_3), 3.95–4.15 (m, 2H, H-3 and H-6_{eq}), 5.13–5.21 (m, 1H, H-2),

7.28–7.54 (m, 5H, arom. H); ^{13}C NMR ($CDCl_3$): δ = 19.6 (t, C-5), 25.6 (t, C-4), 41.0 (t, C-6), 46.8 (d, C-2), 47.9 (d, C-3), 53.2 (q, OCH_3), 116.2 (s, CN), 128.4 (d, C-4′), 129.2 (d, C-2′*), 132.5 (s, C-1′), 133.4 (d, C-3′*), 155.6 (s, CO); $C_{14}H_{16}N_2O_2S$; calc.: C 60.85, H 5.84, N 10.14; found: C 61.14, H 5.95, N 10.10.

trans-2-Cyano-3-phenylthio-1-piperidinecarboxylic acid phenylester (**6b**)

Treatment of **5b** (0.320 g, 1.402 mmol) with thiophenol and 0.1 ml of piperidine as catalyst gave 0.290 g (61%) of **6b** as colorless oil (basic cond. silica gel 25:1, light petroleum:ethyl acetate = 10:1). ^{1}H NMR ($CDCl_3$): δ = 1.56–2.40 (m, 4H, H-4 and H-5), 3.02–3.40 (m, 1H, H-6_{ax}, 3.51–3.70 (m, 1H, H-3), 4.27–4.48 (m, 1H, H-6_{eq}), 5.30–5.40 (m, 1H, H-2), 7.00–7.61 (m, 10H, arom. H); ^{13}C NMR ($CDCl_3$, spectrum showed *E/Z* isomers): δ = 19.9 (t, C-5), 25.8 (t, C-4), 41.6 and 41.9 (2t, C-6, *E/Z*), 47.0 and 48.4 (2d, C-2 and C-3), 116.1 (s, CN), 121.3 (d, C-2′), 125.6 (d, C-4′), 128.6 (d, C-4″), 129.3 and 129.4 (2d, C-3′ and C-2″*), 132.9 and 134.1 (2d, C-3″*, *E/Z*), 135.6 (s, C-1″), 150.7 (s, C-1′), 153.3 (s, CO); $C_{19}H_{19}N_2O_2S$; calc.: C 67.23, H 5.64, N 8.25; found: C 67.70, H 5.14, N 8.39.

trans-2-Cyano-3-(phenylmethyl)thio-1-piperidinecarboxylic acid methylester (**7a**)

Reaction of **5a** (0.80 g, 4.81 mmol) with benzylmercaptane and 0.5 ml of piperidine as catalyst gave 1.10 g (79%) of **6a** as colorless oil (basic cond. silica gel 25:1, light petroleum:ethyl acetate = 10:1). ^{1}H NMR ($CDCl_3$): δ = 1.40–2.23 (m, 4H, H-4 and H-5), 2.84–3.12 (m, 2H, H-3 and H-6_{ax}), 3.77 (s, 5H, OCH_3 and SCH_2), 4.01–4.25 (m, 1H, H-6_{eq}), 4.88–5.49 (m, 1H, H-2), 7.19–7.41 (m, 5H, arom. H); ^{13}C NMR ($CDCl_3$): δ = 19.8 (t, C-5), 26.0 (t, C-4), 36.1 (t, SCH_2), 41.0 (t, C-6), 42.6 (d, C-3), 47.0 (d, C-2), 53.3 (q, OCH_3), 116.2 (s, CN), 127.4 (d, C-4′), 128.6 (d, C-3′*), 128.7 (d, C-2′*), 136.8 (s, C-1′), 155.6 (s, CO); $C_{15}H_{18}N_2O_2S$; calc.: C 62.04, H 6.25, N 9.65; found: C 61.98, H 6.03, N 9.58.

Addition of nitrogen nucleophiles to precursors **5a, b**

A 10% solution of **5** in the corresponding amine was stirred for 3 days at room temperature. After evaporation of the volatiles, purification of the crude product was performed by flash column chromatography.

trans-2-Cyano-3-pyrrolidino-1-piperidinecarboxylic acid methylester (**8a**)

Reaction of **5a** (1.00 g, 6.02 mmol) with pyrrolidine gave 0.92 g (64%) of adduct **8a** as yellow oil (basic cond. silica gel 15:1, light petroleum:ethyl acetate = 2:1). ^{1}H NMR ($CDCl_3$): δ = 1.31–2.08 (m, 8H, H-4, H-5 and H-3′), 2.39–2.70 (m, 5H, H-3 and H-2′), 2.89–3.17 (m, 1H, H-6_{ax}), 3.71 (s, 3H, OCH_3), 3.98–4.26 (m, 1H, H-6_{eq}), 5.21–5.63 (m, 1H, H-2); ^{13}C NMR ($CDCl_3$): δ = 18.8 (t, C-5), 23.5 (t, C-3′), 25.1 (t, C-4), 41.2 (t, C-6), 47.0 (d, C-2), 51.7 (t, C-2′), 53.1 (q, OCH_3), 61.1 (d, C-3), 116.9 (s, CN), 155.6 (s, CO); $C_{12}H_{19}N_3O_2$; calc.: C 60.73, H 8.07, N 17.71; found: C 60.83, H 8.01, N 17.64.

trans-2-Cyano-3-(4-morpholinyl)-1-piperidinecarboxylic acid methylester (**9a**)

Treatment of **5a** (0.300 g, 1.805 mmol) with morpholine at 60°C gave 0.057 g (13%) of **9a** as colorless oil (basic cond. silica gel 30:1, light petroleum:ethyl acetate = 5:1). ^{1}H NMR ($CDCl_3$): δ = 1.38–2.16 (m, 4H, H-4 and H-5), 2.40–2.63 (m, 5H, H-3 and NCH_2), 3.03–3.20 (m, H-6_{ax}), 3.69 (t, J = 5 Hz, 4H, OCH_2), 3.76 (s, 3H, OCH_3), 4.03–4.19 (m, 1H, H-6_{eq}), 5.43–5.57 (m, 1H, H-2);

^{13}C NMR ($CDCl_3$): δ = 19.1 (t, C-5), 22.5 (t, C-4), 41.3 (t, C-6), 45.3 (d, C-2), 50.5 (t, NCH_2), 53.3 (q, OCH_3), 60.8 (d, C-3), 66.9 (t, OCH_2), 117.1 (s, CN), 155.5 (bs, CO); $C_{12}H_{19}N_3O_3$; calc.: C 56.90, H 7.56, N 16.59; found: C 57.13, H 7.83, N 16.29.

1,4,5,6-Tetrahydro-1-((1-pyrrolidino)carbonyl)-pyridine-2-carbonitrile (**10**)

Reaction of **5b** (0.200 g, 0.876 mmol) with pyrrolidine gave 0.173 g (96%) of **10** as colorless oil (basic cond. silica gel 30:1, light petroleum:ethyl acetate = 5:1) that crystallized upon treatment with diisopropyl ether. Mp.: 67–69°C; ^{1}H NMR ($CDCl_3$): δ =1.70–2.01 (m, 6H, H-5 and H-3′), 2.19–2.35 (m, 2H, H-4), 3.30–3.55 (m, 6H, H-6 and H-2′), 5.93 (t, J = 4 Hz, 1H, H-3); ^{13}C NMR ($CDCl_3$): δ = 21.6 (t, C-5), 23.0 (t, C-4), 25.3 (t, C-3′), 45.3 (t, C-6), 47.9 (t, C-2′), 115.4 and 116.1 (2 s, C-2 and CN), 125.4 (d, C-3), 157.8 (s, CO); $C_{11}H_{15}N_3O$: calc.: C 64.37, H 7.37, N 20.47; found: C 64.23, H 7.77, N 20.57.

1,4,5,6-Tetrahydropyridine-3-carbonitrile (**11**)

To a solution of phenolate, generated by treatment of phenol (1.1 equiv.) with NaH (1.1 equiv.) in dry dioxane, a solution of **5a** (1.00 g, 6.02 mmol) in dry dioxane was added, and the resulting mixture was heated under reflux for 6 days. The cooled reaction solution was hydrolyzed with 2 *N* NaOH, extracted with diethyl ether, dried over Na_2SO_4, and concentrated. Purification of the crude product by flash column chromatography (basic cond. silica gel 20:1, light petroleum:ethyl acetate = 10:1) gave 0.07 g (11%) of **11** as colorless liquid. ^{1}H NMR ($CDCl_3$): δ = 1.84 (quintet, J = 6 Hz, 2H, H-5), 2.26 (t, J = 6 Hz, 2H, H-4), 3.12–3.27 (m, 2H, H-6), 4.58 (bs, 1H, NH), 6.91 (d, J = 6 Hz, 1H, H-2); ^{13}C NMR ($CDCl_3$): δ = 20.3 (t, C-5), 22.3 (t, C-4), 39.9 (t, C-6), 72.8 (s, C-3), 123.6 (s, CN), 144.7 (d, C-2); IR (film in nujol): 1625 (C=C), 2180 (CN), 3359 (NH) cm^{-1}.

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