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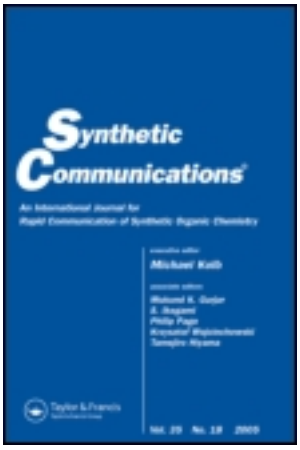

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β-Chlorocinnamonitriles in a New Synthesis of 3-Functionally Substituted 6-amino-1,2-Dihydropyridin-2-ones

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β-Chlorocinnamonitriles in a New Synthesis of 3-Functionally Substituted 6-Amino-1,2-dihydropyridin-2-ones

Sergii A. Trofymchuk,[1] Andrij O. Tolmachov,[1] Kostàntyn M. Kondratyuk,[1] Yulian M. Volovenko,[1] Pavlo S. Lebed,[2] and Mykhaylo V. Vovk[2]

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Abstract: β-Chlorocinnamonitriles react with methylene-active compounds containing N-substituted carboxamide group in DMSO solution in the presence of potassium hydroxide, forming 3-functionally substituted 1,2-dihydropyridin-2-ones.

Keywords: Anilides of malonic and acetoacetic acids; β-chlorocinnamonitriles; 3-functionally substituted 1,2-dihydropyridin-2-ones; N-monosubstituted cyanoacetamides

β-Chlorocinnamonitriles, easily available by a one-pot procedure starting from acetophenones,[1,2] are convenient electrophilic reagents for obtaining various five-membered heterocyclic systems. In particular, their cyclocondensations with esters of α-mercaptoacetic acid are widely used for the effective synthesis of 3-amino-2-thiophenecarboxylic acid derivatives,[3–7] reactions with hydrazine afford 3-aminopyrazoles,[8] and interaction with sodium hydrosulfite gives 3-aminoisothiazoles.[9] At the same time, utilization of mentioned reagents for obtaining six-membered heterocycles (for instance, highly functionalized aminopyridines) remains unexplored. Meanwhile, compounds of 6-amino-1,2-dihydropyrimidin-2-one series

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exhibit high pharmacological activity[10] and are valuable precursors for azo-dyes synthesis.[11]

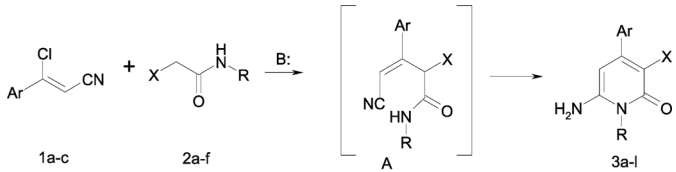
It is also important to note that the presence of an enamine fragment in their structure (absence of a substituent in the C-5 position within the pyridine ring together with an amino group in the C-6 position) gives a chance to use them for obtaining annulated heterocyclic systems.

In the literature, there is only one method of direct formation of a 1,2-dihydropyridin-2-one cycle containing an amino group at the 6-position and electron-withdrawing C≡N group at the 3-position, based on condensation of S,N-ketene acetals with cyanoacetate.[12] Other methods for synthesis of such types of compounds are multistep and include amination of primarily formed 6-chloropyridin-2-ones[10,13,14] or scission of 6-cyano-1,8-naphthyridin-7-ones upon action of secondary amines.[15]

The approach proposed by us profitably differs from that described previously, and we propose a new synthetic methodology based on cyclocondensation of *β*-chlorocinnamonitriles **1a–c** with methylene-active compounds containing an N-substituted carboxamide group, that is, N-monosubstituted cyanoacetamides **2a–c**, anilide ester **2d** and dianilide **2e** of malonic acid, and acetoacetic acid anilide **2f**. It is demonstrated that in the presence of potassium hydroxide the reaction between **1a–c** and **2a–f** proceeds in dimethyl sulfoxide (DMSO) solution at room temperature and leads to the formation of target 3-functionally substituted 1,2-dihydropyridin-2-ones **3a–l** in 50–76% yields (Scheme 1).

Taking into consideration the experimental conditions found, it may be assumed that interaction of reagents **1a–c** and **2a–f** is realized via the stage of formation of primary C-alkenylation products **A**, which then undergo intramolecular cyclization into the products **3a–l**.

The structure of synthesized compounds is confirmed by results of chromatography mass analysis, ^{1}H NMR, and IR spectra. It should be



1a: Ar = 4-ClC_6H_4; 1b: Ar = 4-MeOC_6H_4; 1c: Ar = 4-PhC_6H_4.

2a: X = CN, R = Me; 2b: X = CN, R = Ph; 2c: X = CN, R = 2-MeOC_6H_4; 2d: X = EtOC(O), R = Ph; 2e: X = PhNHC(O), R = Ph; 2f: X = MeC(O), R = 4-ClC_6H_4.

Scheme 1. Reaction between *β*-chlorocin namonitriles 1a-c and methylene-active compounds containing an N-substituted carboxamide group 2a-f.

Table 1. Physical properties of 3-functionally substituted 1,2-dihydropyridin-2-ones **3a-l** prepared

Entry	R	Ar	X	Yield (%)	Mp (°C)
a	Me	4-ClC_6H_4	CN	65	221–222
b	Me	4-$MeOC_6H_4$	CN	62	270–272
c	Me	4-PhC_6H_4	CN	61	310–311
d	Ph	4-ClC_6H_4	CN	60	>310
e	Ph	4-$MeOC_6H_4$	CN	51	>310
f	Ph	4-PhC_6H_4	CN	66	>310
g	2-$MeOC_6H_4$	4-ClC_6H_4	CN	67	>310
h	2-$MeOC_6H_4$	4-$MeOC_6H_4$	CN	56	>310
i	2-$MeOC_6H_4$	4-PhC_6H_4	CN	66	>310
j	4-ClC_6H_4	4-ClC_6H_4	MeC(O)	59	282–284
k	Ph	4-ClC_6H_4	EtOC(O)	72	281–283
l	Ph	4-ClC_6H_4	PhNHC(O)	75	>310

noted that in ^{1}H NMR spectra, singlets of C^5-H pyridine cycle protons observed in the range of 5.43–5.7 ppm are distinctive. Yields and melting points of synthesized compounds are shown in Table 1.

In conclusion, we showed a possibility of using β-chlorocinnamonitriles for the convenient preparative synthesis of 3-functionally substituted 1,2-dihydropyridin-2-ones.

EXPERIMENTAL

Melting points were measured with Tomas Hoover apparatus and are uncorrected. IR spectra were recorded on a Nexus-470 spectrophotometer in KBr tablets. ^{1}H NMR spectra were registered in D_6-DMSO on a Brucker-400 instrument with TMS as an internal standard.

Starting compounds were synthesized according to reported procedures: **1a–c**,[2] **2a**,[16] **2b**,[17] **2c**,[18] **2d**,[19] **2e**,[20] and **2f**[21].

6-Amino-3-R-1,2-dihydropyridin-2-ones 3a–l: General Procedure

To a mixture of β-chlorocinnamonitrile **1** (0.02 mol) and amide **2** (0.02 mol) in 15 mL of freshly distilled DMSO, the solution of KOH (2.3 g, 0.041 mol) in 5 mL of water was added dropwise with intensive stirring and cooling with ice water. The reaction mixture was stirred for 1 h, left for 24 h, and then poured onto water (100 mL). The precipitate formed was filtered, washed with water (50×3 mL), dried, and

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recrystallized from acetic acid (compounds **3a–c, f–i, k**), DMF (compounds **3d, e, l**), or MeOH (compound **3j**).

Data

Compound **3a**. IR: 1713 (C=O), 2220 (C≡N), 3450 (NH_2). ^{1}H NMR δ 3.39 (s, 3H, CH_3), 5.61 (s, 1H, C^5–H), 7.63 (d, 2H_{Ar}, $J = 7.6$ Hz), 7.78 (d, 2H_{Ar}, $J = 7.8$ Hz), 7.84 (s, 2H, NH_2). Anal. calculated for $C_{13}H_{10}ClN_3O$: C, 60.13; H, 3.88; N, 16.18. Found: C, 60.25; H, 3.80; N, 16.02.

Compound **3b**. IR: 1715 (C=O), 2200 (C≡N), 3430 (NH_2). ^{1}H NMR δ 3.42 (s, 3H, CH_3), 3.81 (s, 3H, CH_3O), 5.60 (s, 1H, C^5–H), 7.08 (d, 2H_{Ar}, $J = 7.6$ Hz), 7.38 (d, 2H_{Ar}, $J = 7.7$ Hz), 7.45 (s, 2H, NH_2). Anal. calculated for $C_{14}H_{13}N_3O_2$: C, 65.87; H, 5.13; N, 16.46. Found: C, 66.05; H, 5.08; N, 16.32.

Compound **3c**. IR: 1675 (C=O), 2200 (C≡N), 3460 (NH_2). ^{1}H NMR δ 3.40 (s, 3H, CH_3), 5.69 (s, 1H, C^5–H), 7.43 (t, 1H_{Ar}, $J = 8.0$ Hz), 7.52 (t, 2H_{Ar}, $J = 7.9$ Hz), 7.64 (d, 2H_{Ar}, $J = 7.9$ Hz), 7.70 (s, 2H, NH_2), 7.76 (d, 2H_{Ar}, $J = 7.8$ Hz), 7.85 (d, 2H_{Ar}, $J = 7.9$ Hz). Anal. calculated for $C_{19}H_{15}N_3O$: C, 75.73; H, 5.02; N, 13.94. Found: C, 75.97; H, 4.99; N, 13.96.

Compound **3d.** IR: 1670 (C=O), 2200 (C≡N), 3460 (NH_2). ^{1}H NMR δ 5.67 (s, 1H, C^5–H), 7.35 (d, 2H_{Ar}, $J = 8.0$ Hz), 7.57–7.66 (m, 9H_{Ar} + NH_2). Anal. calculated for $C_{18}H_{12}ClN_3O$: C, 67.19; H, 3.76; N, 13.06. Found: C, 67.15; H, 3.88; N, 12.99.

Compound **3e.** IR: 1670 (C=O), 2200 (C≡N), 3480 (NH_2). ^{1}H NMR, δ 3.82 (s, 3H, CH_3O), 5.70 (s, 1H, C^5–H), 6.72 (s, 2H, NH_2), 6.99 (d, 2H_{Ar}, $J = 7.8$ Hz), 7.34 (d, 2H_{Ar}, $J = 7.8$ Hz), 7.58–7.66 (m, 5H_{Ar}). Anal. calculated for $C_{19}H_{15}N_3O_2$: C, 71.91; H, 4.76; N, 13.24. Found: C, 71.97; H, 4.65; N, 13.35.

Compound **3f**. IR: 1655 (C=O), 2200 (C≡N), 3455 (NH_2). ^{1}H NMR δ 5.61 (s, 1H, C^5–H), 7.34–7.75 (m, 16H_{Ar} + NH_2). Anal. calculated for $C_{24}H_{17}N_3O$: C, 79.32; H, 4.72; N, 11.56. Found: C, 79.28; H, 4.67; N, 11.50.

Compound **3g**. IR: 1665 (C=O), 2210 (C≡N), 3465 (NH_2). ^{1}H NMR δ 3.84 (s, 3H, CH_3O), 5.6 (s, 1H, C^5–H), 6.83 (s, 2H, NH_2), 7.22–7.65 (m, 8H_{Ar}). Anal. calculated for $C_{19}H_{14}ClN_3O_2$: C, 64.87; H, 4.01; N, 11.94. Found: C, 65.07; H, 3.95; N, 11.87.

Compound **3h**. IR: 1665 (C=O), 2210 (C≡N), 3460 (NH_2). ^{1}H NMR δ 3.80 (s, 3H, CH_3O), 3.85 (s, 3H, CH_3O), 5.60 (s, 1H, C^5–H), 6.75 (s, 2H, NH_2), 7.10 (d, 2H_{Ar}, $J = 7.6$ Hz), 7.14–2.20 (m, 3H_{Ar}), 7.49 (t, 1H, $J = 7.2$ Hz), 7.55 (d, 2H_{Ar}, $J = 7.7$ Hz). Anal. calculated for $C_{20}H_{17}N_3O_3$: C, 69.15; H, 4.93; N, 12.10. Found: C, 69.01; H, 5.00; N, 12.21.

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Compound **3i**. IR: 1665 (C=O), 2205 (C≡N), 3470 (NH_2). ^1H NMR δ 3.80 (s, 3H, CH_3O), 5.70 (s, 1H, C^5-H), 7.12–7.66 (m, $13H_{Ar} + NH_2$), 7.82 (d, 2H, $J = 8.0$ Hz). Anal. calculated for $C_{25}H_{19}N_3O_2$: C, 76.32; H, 4.87; N, 10.68. Found: C, 76.19; H, 4.99; N, 10.60.

Compound **3j**. IR: 1680 (C=O), 3480 NH_2. ^1H NMR δ 2.34 (s, 3H, CH_3), 5.43 (s, 1H, C^5-H), 6.85 (s, 2H, NH_2), 7.20 (d, $2H_{Ar}$, $J = 7.8$ Hz), 7.32 (d, $2H_{Ar}$, $J = 7.4$ Hz), 7.40 (d, $2H_{Ar}$, $J = 7.3$ Hz), 7.61 (d, $2H_{Ar}$, $J = 7.8$ Hz). Anal. calculated for $C_{19}H_{14}Cl_2N_2O_2$: C, 61.14; H, 3.78; N, 7.51. Found: C, 61.02; H, 3.85; N, 7.44.

Compound **3k**. IR: 1705 (C=O), 3470 (NH_2). ^1H NMR, δ 1.26 (t, 3H, CH_3), 3.82 (q, 2H, CH_2), 5.54 (s, 1H, C^5-H), 6.52 (s, 2H, NH_2), 7.31 (d, $2H_{Ar}$, $J = 7.4$ Hz), 7.40 (d, $2H_{Ar}$, $J = 7.3$ Hz), 7.6 (m, 5H). Anal. calculated for $C_{20}H_{17}ClN_2O_3$: C, 65.13; H, 4.65; N, 7.60. Found: C, 65.34; H, 4.59; N, 7.45.

Compound **3l**. IR: 1650 (C=O), 3400 (NH_2). ^1H NMR, δ 5.62 (s, 1H, C^5-H), 6.96–7.61 (m, $16H_{Ar} + NH_2$), 11.47 (s, 1H, NH). Anal. calculated for $C_{24}H_{18}ClN_3O_2$: C, 69.31; H, 4.36; N, 10.10. Found: C, 69.52; H, 4.44; N, 10.02.

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