Reactions of α-cyanochalcones with phenylhydrazine

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Abstract

α-Cyanochalcones react with phenylhydrazine in acetic acid, forming 5-cyano-1-phenyl-3,4,6-triaryl-1*H*-pyrazolo[3,4-*b*]pyridines, while retroaldol condensation takes place in ethanol under acidic catalysis. The structures of the compounds obtained were determined by elemental analysis, IR-, ^{1}H NMR-spectroscopy and X-ray study.

Keywords: α-Cyanochalcones, pyrazolo[3,4-*b*]pyridines, phenylhydrazine, binucleophiles

Introduction

1,3-Diarylpropenones (chalcones) and their derivatives are known to be suitable reagents for synthesis of various heterocyclic systems, building-blocks and biologically active compounds.[1] For instance, a number of heterocyclic derivatives were obtained starting from chalcones.[2]

Generally, the presence of a CN-group in an α-position to a CO-group in the molecule of α-cyanochalcone should extend it's activity towards 1,2-binucleophiles because of extra-polarization of C=C double bond. After preliminary Michael addition by C=C-bond, bi-nucleophile can alternatively attack CN-group or CO-group; furthermore, the first step of interaction may occur by CO-group, which is also highly polarized. Hence, this issue remains open.

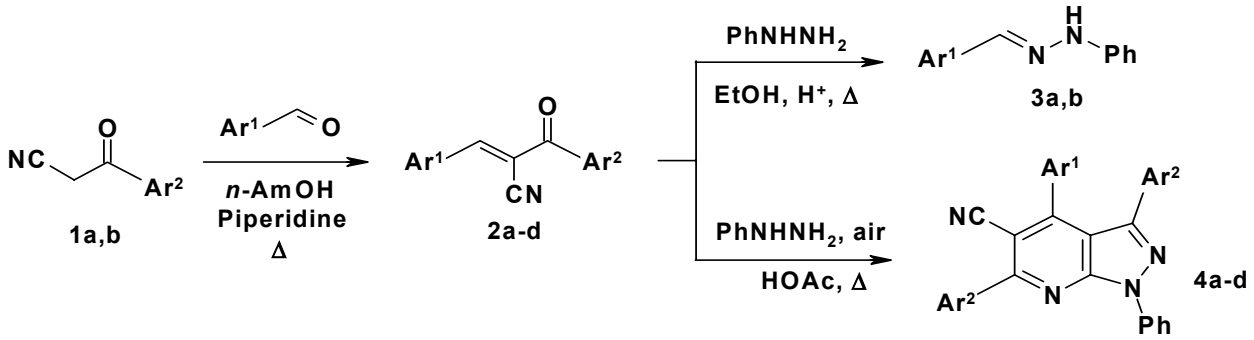
In the present paper we discuss the reactivity of α-cyanochalcones towards phenylhydrazine, and we propose a new efficient one-step procedure for 5-cyano-1-phenyl-3,4,6-triaryl-1*H*-pyrazolo[3,4-*b*]pyridines synthesis.

Results and Discussion

The reaction of α-cyanochalcones with phenylhydrazine was realized by two ways: 1) in refluxing ethanol using catalytic amounts of H_2SO_4; 2) in refluxing glacial acetic acid.

It was found that in ethanol in the presence of catalytic amounts of H_2SO_4 α-cyanochalcones **2a–d** underwent retroaldol condensation, resulting in formation of the corresponding phenylhydrazones **3a** and **3b**, in accordance with data [3] (Scheme 1).

If the reaction was carried out in glacial acetic acid, its pathway changed. Thus, the corresponding pyrazolo[3,4-*b*]pyridines **4a–d** formed, as was shown by ^{1}H NMR- and IR-spectra of substances obtained (Scheme 1).



Ar^1 = 4-$Me_2NC_6H_4$ (a, b), 4-$MeOC_6H_4$ (c,d), Ar^2 = Ph (a, c), 4-MeC_6H_4 (b, d)

Scheme 1

IR-spectra of compounds **4a-d** did not contain C=O-group signals, but, in contrast, the signal of CN-group (2200 cm^{-1}) was present. The signal of the vinyl proton disappeared in ^{1}H NMR-spectra of the compounds **4a-d** (comparing with starting chalcones **2a-d**), besides, the signals of two nonequivalent Ar^2-substituents and Ar^1-substituent were present.

Interestingly, compounds **4a-d** possessed intensive luminescence both in the solid state and in solutions in ethanol, acetonitrile or ethyl acetate. Luminescence weakened in the presence of acids.

The structure of compound **4a** was finally determined by X-ray diffraction analysis (Figure 1).

Benzene rings are turned relative to the dihydroazolopyrimidine cycle (the torsion angles are: C(2)-C(3)-C(7)-C(8) 55.4(5)°, C(4)-C(6)-C(13)-C(14) 39.8(6)°, C(5)-N(3)-C(19)-C(24) 31.5(6)° and C(2)-C(1)-C(25)-C(30) -52.1(5)°). The bulky substituents cause a considerable steric strain. It is confirmed by the presence of the short intramolecular contacts C(30)…C(31) 3.05 Å, C(8)…C(31) 3.00 Å, C(12)…C(14) 3.17 Å (Van der Waals radii sum is 3.42 Å [4]), H(30)…C(31) 2.77 Å, H(8)…C(31) 2.76 Å, H(14)…C(7) 2.72 Å and H(24)…C(5) 2.82 Å (2.87 Å). Thus, the pyridine ring is rather non-planar. The maximum amplitude of the torsion angles is: C(2)-C(3)-C(4)-C(5) 4.2(4)°, and C(3)-C(4)-C(5)-N(1) -5.2(5)°. Such deformation of the aromatic rings is

quite common in crystals and does not lead either to the loss of aromaticity or to significant increase of the total energy of the molecule.[4, 5]

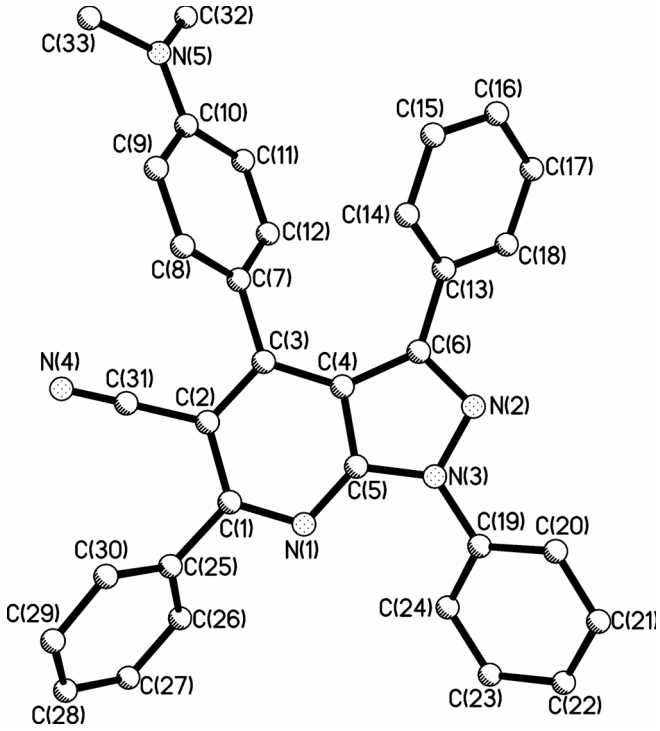
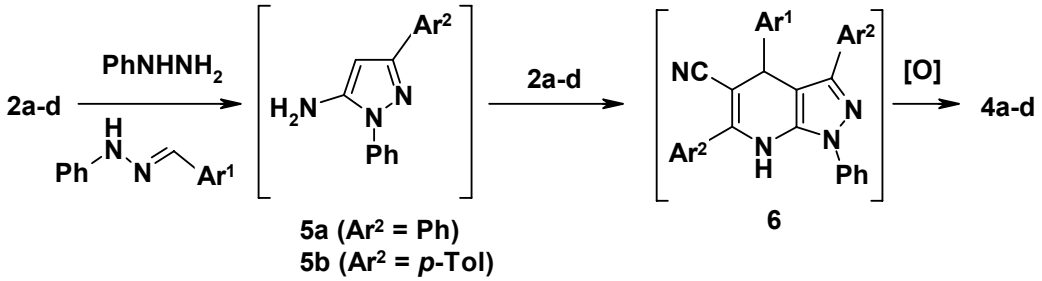


Figure 1

We proposed the following scheme of the compounds **4** formation. At the first step the retro-aldol condensation of cyanochalcone takes place and formation of the corresponding 5-aminopyrazole **5** occurs, which interacts with another molecule of α-cyanochalcone, giving cyclic compound **6**, which at the next step easily undergoes an oxidizing aromatization to the compound type **4** (Scheme 2).

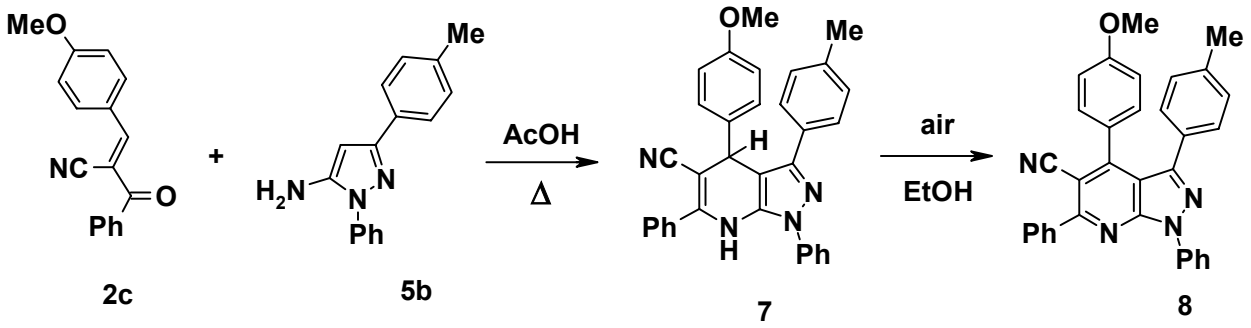


Scheme 2

Signals at 5.1 ppm and 9.6 ppm were observed in the ^{1}H NMR-spectra of crude product **4b**. We associated them with CH- and NH-protons of the intermediate like **6**. After crystallization from ethanol only pure compounds **4a-d** were obtained, so this fact pointed on the slight aromatization of the compounds like **6** even under action of air. Besides, we confirmed the proposed scheme by alternative synthesis of compound **8** starting from the α-cyanochalcone **2c** and the aminopyrazole **5b** (Scheme 3). This way is close to what has been reported [6] that led to formation of 5-cyano-1,3,4,6-tetraaryl-1*H*-pyrazolo[3,4-*b*]pyridines with non-equivalent substituents in positions (3) and (6) of pyrazolo[3,4-*b*]pyridine cycle. The regioselectivity of interaction of 5-amino-3-arylpyrazoles to chalcones, as well to α-cyanochalcones, was shown earlier.[6, 7]

Refluxing of compounds **2c** and **5b** in glacial acetic acid resulted in the formation of the 1,4-dihydroderivative **7**. There were the singlets of 1,4-dihydroform CH- and NH- protons in ^{1}H NMR-spectra of compound **7**, which were similar to those for non-purified product **4b**.

The compound **7** (its suspension in ethanol, in the presence of piperidine) was easily oxidized by air bubbling (the conditions of recrystallization of crude products **4a–d**), forming the fully aromatic system **8** (Scheme 3).



Scheme 3

Yields, melting points and spectroscopic data of compounds obtained are given below (see Table 1).

Table 1. Yields, melting points, elemental analysis and spectroscopic data of compounds **1–8**

№	M.p., °C / lit.	Yield, %	Elemental analysis (found / calc. %), N	IR, ν, cm^{-1}	^{1}H NMR, δ (ppm), ^3J (Hz)
2a	157-9	30	9.89 10.14	1610 1650 2195	3.08 (6H, s, $N(CH_3)_2$); 6.83 (2H, d, J = 6 Hz, CH); 7.49-7.57 (2H, m, CH); 7.63 (1H, t, J = 4.8 Hz, CH); 7.70-7.76 (2H, m, CH); 7.93 (1H, s, C=CH); 7.98 (2H, d, J = 6 Hz, CH)
2b	136-8	46	9.51 9.65	1610 1650 2200	2.43 (3H, s, CH_3); 3.13 (6H, s, $N(CH_3)_2$); 6.71 (2H, d, J = 9.2 Hz, CH); 7.29 (2H, d, J = 8.4 Hz, CH); 7.78 (2H, d, J = 8 Hz, CH); 7.99 (2H, d, J = 8.8 Hz, CH), 8.016 (1H, s, C=CH)
2c	95-6 98-9[8] 95-7[9]	40	5.25 5.32	1585 1650 2200	3.87 (3H, s, CH_3O); 7.14 (2H, d, J = 8.8 Hz, CH); 7.50-7.61 (2H, m, CH); 7.62-7.73 (1H, m, CH); 7.77-7.86 (2H, m, CH); 8.08 (2H, d, J = 8.8 Hz, CH) 8.10 (1H, s, C=CH)
2d	85-6 94-6[10]	34	4.93 5.05	1590 1650 2200	2.40 (3H, s, CH_3); 3.87 (3H, s, CH_3O); 7.14 (2H, d, J = 8.8 Hz, CH); 7.37 (2H, d, J = 8 Hz, CH); 7.73 (2H, d, J = 8 Hz, CH); 8.07 (3H, d, J = 8.8 Hz, CH), 8.09 (1H, s, C=CH)
4a	263-5	67	14.07 14.25	1524 1610 2215 2920	2.9 (6H, s, $N(CH_3)_2$); 6.52 (2H, d, J = 8.8 Hz, CH); 7.07-7.34 (7H, m); 7.40 (1H, t, J = 7.4 Hz, CH); 7.52-7.69 (5H, m); 7.92-8.05 (2H, m); 8.28 (2H, d, J = 7.4 Hz, CH)
4b	230-2	49	13.30 13.48	1524 1606 2217 2921	2.26 (3H, s, CH_3); 2.42 (3H, s, CH_3); 2.91 (6H, s, $N(CH_3)_2$); 6.51 (2H, d, J = 9 Hz, CH); 6.92 (2H, d, J = 8.2 Hz, CH), 7.01 (2H, d, J = 8 Hz, CH); 7.14 (2H, d, J = 9 Hz, CH); 7.38 (1H, t, J = 8 Hz, CH), 7.40 (2H, d, J = 8.2 Hz, CH); 7.60 (2H, t, J = 8 Hz, CH); 7.88 (2H, d, J = 8.2 Hz, CH); 8.27 (2H, d, J = 8 Hz, CH)

4c	192-4	18	11.53 11.71	1248 1610 2215 2920	3.75 (3H, s, CH_3O); 6.79 (2H, d, J = 8.8 Hz, CH); 7.13 (4H, d, J = 4.2 Hz, CH); 7.22-7.35 (1H, m); 7.30 (2H, d, J = 8.8 Hz, CH); 7.42 (2H, t, J = 7.2 Hz, CH); 7.54-7.71 (5H, m); 7.91-8.05 (2H, m); 8.28 (2H, d, J = 7.8 Hz, CH)
4d	230-2	11	10.89 11.06	1252 1606 2215 2916	2.26 (3H, s, CH_3); 2.42 (3H, s, CH_3); 3.75 (3H, s, CH_3O); 6.79 (2H, d, J = 8.6 Hz, CH); 6.92 (2H, d, J = 8.2 Hz, CH); 7.00 (2H, d, J = 8.2 Hz, CH); 7.27 (2H, d, J = 8.6 Hz, CH); 7.40 (1H, t, J = 8.2 Hz, CH); 7.41 (2H, d, J = 8.2 Hz, CH); 7.60 (2H, t, J = 8.2 Hz, CH); 7.88 (2H, d, J = 8.2 Hz, CH); 8.27 (2H, d, J = 8.2 Hz, CH)
7	127-8	93	11.35 11.33	1535 2200 2923 3430	2.26 (3H, s, CH_3); 3.68 (3H, s, CH_3O); 5.32 (1H, s, CH); 6.79 (2H, d, J = 9 Hz, CH); 7.09 (2H, d, J = 8 Hz, CH); 7.20 (2H, d, J = 9 Hz, CH); 7.35-7.65 (10H, m); 7.71 (2H, d, J = 8 Hz, CH); 9.95 (1H, s, NH)
8	218-20	55	11.32 11.37	1255 1509 1610 2323	2.25 (3H, s, CH_3); 3.75 (3H, s, CH_3O); 6.79 (2H, d, J = 8.6 Hz, CH); 6.85-7.05 (4H, m); 7.27 (2H, d, J = 9 Hz, CH); 7.39 (1H, t, J = 8 Hz, CH); 7.52-7.67 (5H, m); 7.92-8.04 (2H, m); 8.26 (2H, d, J = 8 Hz, CH)

Experimental Section

General Procedures. TLC was performed on Silufol UV-254 plates using acetonitrile–toluene (1:1) mixture as eluent. IR spectra (wave numbers, cm^{-1}) were obtained with a Specord-75 IR spectrometer in KBr pellets. ^{1}H NMR spectra were measured with a Varian Mercury-200 VX (200 MHz) spectrometer in DMSO-d_6 solutions using TMS as internal standard.

X-ray diffraction analysis of **4a** was carried out at room temperature with a "Siemens P3/PC" diffractometer (graphite monochromated Mo-Kα) radiation, 2θ/θ-scans, $2\theta_{max}$=50°). Crystal data: triclinic, $\boldsymbol{a}$ = 9.510(2), $\boldsymbol{b}$ = 12.268(3), $\boldsymbol{c}$ = 13.448(4) Å, $\boldsymbol{\alpha}$ = 116.30(2)°, $\boldsymbol{\beta}$ = 94.60(2)°, $\boldsymbol{\gamma}$ = 104.20(2)°, V = 1330.9(6) Å^3, M_r = 491.58, Z = 2, space group $P\bar{1}$, d_c= 1.227 g/cm^3, μ(MoK_α) = 0.074 mm^{-1}, F(000) = 516. 4958 reflections measured (4653 of which were unique), R_{int} = 0.092. The structure of **4a** was solved by direct methods and refined by full matrix least squares on F^2 using SHELXTL suite of programs.[11] H-atoms were placed in calculated positions and refined in

riding model approximation with U_{iso}=nU_{eq} of the carrier atom (n=1.5 for methyl groups and n=1.2 for the remaining H-atoms). The final refinement converged to wR_2 = 0.196 for 4599 reflections and R_1 = 0.066 for 1962 reflections with F>4σ(F), S = 0.865. Crystallographic data (excluding structure factors) have been deposited with the Cambridge Crystallographic Data Center, deposition number is CCDC 614076. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 1223 336033, or by e-mail: deposit@ccdc.cam.ac.uk).
Starting 3-aryl-3-oxopropanenitriles, aromatic aldehydes, phenylhydrazine and 5-amino-3-aryl-1-phenylpyrazoles are commercially available.

α-Cyanochalcones (2a-d). The solution of the corresponding 3-aryl-3-oxopropane-nitrile **1** (0.01 mol), appropriate aromatic aldehyde (0.012 mol) and 3 drops of piperidine in 6 ml of *n*-AmOH was refluxed for 15 minutes. After cooling the precipitate formed was filtered off, washed with *n*-AmOH, hexane and air-dried.
5-Cyano-1,3,4,6-triaryl-1*H*-pyrazolo[3,4-*b*]pyridines (4a-d). The solution of appropriate compound **2** (1 mmol) and phenylhydrazine (1.2 mmol) in 10 ml of HOAc was refluxed for 15 minutes, cooled and diluted with 100 ml of brine. The aqueous solution was removed, the organic phase was dried and recrystallized from EtOH.
5-Cyano-1,6-diphenyl-4-(4-methoxyphenyl)-3-(4-methylphenyl)-4,7-dihydro-1*H*-pyrazolo-[3,4-*b*]pyridine (7). The solution of the compounds **2c** (0.26 g, 1 mmol) and **5b** (0.30 g, 1.2 mmol) in 3 ml of HOAc was refluxed for 1 hour. After cooling the precipitate was filtered off, washed by 3 ml of HOAc and by water, then dried, giving 93% of **7**.
5-Cyano-1,6-diphenyl-4-(4-methoxyphenyl)-3-(4-methylphenyl)-1*H*-pyrazolo[3,4-*b*]pyridine (8). The air was bubbled during 8 h through the suspension of the compound **7** (0.2 g, 0.4 mmol), N-methylmorpholine (1 ml) and 30 ml of EtOH at r.t. During the bubbling dissolution of compound **7** occurred. The solvent was removed under reduced pressure, the residue was cooled to give the precipitate of compound **8,** which was filtered off, washed by EtOH and dried.

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