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Synthesis of Pyrazolo[3,4-c]isoquinoline and Pyrazolo[3,4-b]pyridine Derivatives from Azomethines and CH-Acidic Compounds

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Summary. Donor substituted arylidene aminopyrazoles **1a–c** and CH-acidic 1,3-dicarbonyl compounds **2a–e** give in ethanol in an addition/cyclization reaction pyrazolo[3,4-c]isoquinolines **4a–i** and pyrazolo[3,4-b]pyridine derivatives **5a, b**, respectively. Using ethyl cyanoacetate as CH-acidic component, cinnamate **6** and the cyano substituted pyrazolo[3,4-b]pyridine **7** are formed.

Keywords. Azomethine; CH-Acidic compound; Addition/cyclization reaction.

Synthese von Pyrazolo[3,4-c]isochinolin- und Pyrazolo[3,4-b]pyridin-Derivaten aus Azomethinen und CH-aciden Verbindungen

Zusammenfassung. Die Reaktion der donorsubstituierten Aryliden-aminopyrazole **1a–c** mit den CH-aciden 1,3-Dicarbonylverbindungen **2a–e** führt in einer Additions/Cyclisierungsreaktion zu den Pyrazolo[3,4-c]isochinolin- **4a–i** bzw. Pyrazolo[3,4-b]pyridin-Derivaten **5a, b**. Verwendet man Cyanessigester als CH-acide Komponente, werden der Zimtsäureester **6** und das cyanosubstituierte Pyrazolo[3,4-b]pyridin **7** gebildet.

Introduction

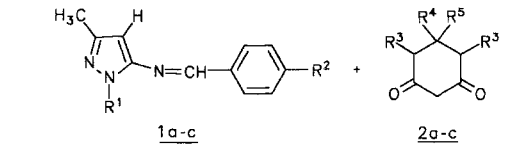
The reaction of azomethines and CH-acidic compounds gives addition products in the first step [1]. Frequently these compounds are not stable and subsequent reactions can proceed. In many cases a deamination from the addition compounds with formation of carbon carbon double bond containing products has been observed [2]. Sometimes these products are stable, but more consecutive reactions are possible.

Results and Discussion

We investigated the reaction of the donor substituted arylidene aminopyrazoles **1a–c** with the CH-acidic compounds cyclohexane-1,3-dione (**2a**), 5,5-dimethyl-cyclohexane-1,3-dione (**2b**), 5-phenyl-4,6-diethoxycarbonyl-cyclohexane-1,3-dione (**2c**), pentane-2,4-dione (**2d**), ethyl acetoacetate (**2e**), and ethyl cyanoacetate (**2f**). The donor substituted azomethines **1a–c** were synthesized by condensation reaction of

the corresponding 5-amino-pyrazoles and 4-dimethylaminobenzaldehyde and 4-methoxybenzaldehyde (anisidine), respectively [3].

First of all, the expected addition products **3** were formed in the reaction of equal amounts of **1a–c** and the cyclic dicarbonyl compounds **2a–c** in ethanol. However, these products could not be isolated and a spontaneously cyclization to the hexahydro-pyrazolo[3,4-c]isoquinoline-6-one derivatives **4a–i** took place by elimination of water.

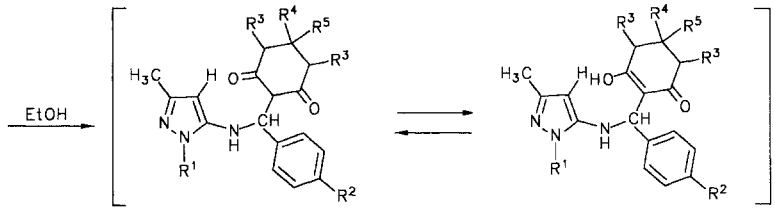


1a-c

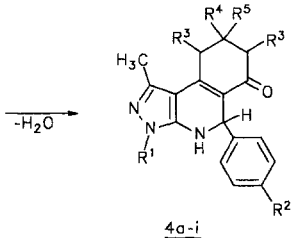
2a-c

	R^1	R^2
1a	H	$N(CH_3)_2$
1b	H	OCH_3
1c	C_6H_5	$N(CH_3)_2$

	R^3	R^4	R^5
2a	H	H	H
2b	H	CH_3	CH_3
2c	$COOC_2H_5$	C_6H_5	H



3



4a-i

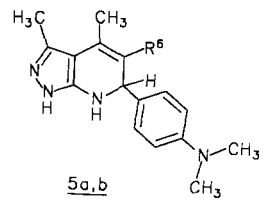
R^1	R^2	R^3	R^4	R^5
H	$N(CH_3)_2$	H	H	H
H	$N(CH_3)_2$	H	CH_3	CH_3
H	$N(CH_3)_2$	$COOC_2H_5$	C_6H_5	H
H	OCH_3	H	H	H
H	OCH_3	H	CH_3	CH_3
H	OCH_3	$COOC_2H_5$	C_6H_5	H
C_6H_5	$N(CH_3)_2$	H	H	H
C_6H_5	$N(CH_3)_2$	H	CH_3	CH_3
C_6H_5	$N(CH_3)_2$	$COOC_2H_5$	C_6H_5	H

An elimination of amine from **3** was not found in contrast to addition products, which have been formed from benzalanilines and the same CH-acidic compounds [2]. The reason is probably the minor tendency for elimination of the 5-amino-pyrazole compared to the aniline molecule.

There are two possibilities for ring closure if the N1-position is unsubstituted like in **1a** and **1b**, either to the N1 or to the C4-atom. Both cyclizations have been found in the reaction of 5-amino-pyrazoles with 1,3-dicarbonyl compounds [4], but we observed only cyclization to the C4-atom. Thus, in the ^{1}H-NMR spectrum the pyrazole ring =CH-signal above 6 ppm disappeared. Additionally, for the R^1 unsubstituted compounds **4a–f** two and for the R^1 phenylsubstituted compounds **4g–i** one NH-signal were found. The resulting condensed heterocycles are fluorescent in organic solvents.

The reaction of azomethine **1a** with pentane-2,4-dione (**2d**) and ethyl acetoacetate (**2e**) was analogous and gave the dihydropyrazolopyridines **5a** and **5b** in good yields.

In contrast to this, an elimination of 5-amino-pyrazole can be observed after the addition step, if ethyl cyanoacetate (**2f**) is used as CH-acidic component. In this case one can isolate a considerable amount (nearly 75%) of ethyl *p*-dimethylamino-α-cyano cinnamate (**6**). This compound already has been synthesized by Lazzareschi

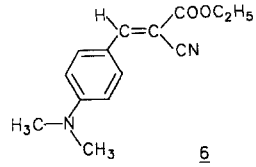


5a,b

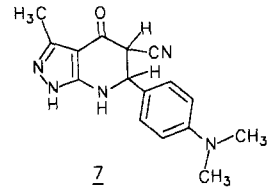
5a $R^6 = COCH_3$

5b $R^6 = COOC_2H_5$

by treatment of ethyl cyanoacetate with the corresponding benzylidene aniline in benzene [5]. However, a small amount of the tetrahydropyrazolo[3,4-b]pyridine-4-one (**7**) as a cyclization product was obtained from the remaining solution after standing for some hours. The unsubstituted 4,7-dihydro-4-oxo-1*H*-pyrazolo[3,4-b]-pyridine as parent compound for this heterocyclic system already has been reported by Dorn et al. in 1982 [6].



6



7

By reason of the low "carbonyl activity" of the cyano group in **2f** in comparison to the keto function of the acyl residue in **2d** and **2e**, a reaction at the ester group with elimination of ethanol took place. By means of the vicinal H,H-coupling constant was proved, that **7** exists as a mixture of *cis/trans* isomers. The isomeric compound with cyano and dimethylaminophenyl group in *trans* position ($^3J_{HH} = 13$ Hz) is the major product (59%), the *cis* isomer ($^3J_{HH} = 8$ Hz) is minor (41%). Compound **7** is already fluorescent in solid state by UV irradiation.

Experimental Part

Melting points were determined using a Boetius melting point apparatus. Elemental analyses were carried out with a "CHN-O-Rapid" (Heraeus) apparatus. NME spectra were determined using a Tesla BS 587 C (80 MHz) and a Varian Unity 400 (400 MHz), respectively, with *DMSO-d_6* or $CDCl_3$ as solvent (chemical shifts in δ, ppm). Mass spectra (70 eV) were recorded with a VG 12-250 spectrometer, IR-spectra (KBr) with a UR-20 (Carl Zeiss Jena), and Vis-spectra with a Specord (Carl Zeiss Jena).

General Procedure for Pyrazolo[3,4-c]isoquinolines **4a–i** *and Pyrazolo[3,4-b]pyridine Derivatives* **5a, b**

0.01 mol of azomethines **1** and 0.01 mol of the corresponding CH-acidic compound **2** were refluxed with stirring in 75 ml ethanol. The reaction was monitored by thin layer chromatography. After cooling, the products crystallize directly from the reaction mixture or were obtained by evaporation of the solvent. The crude products were purified by recrystallization from ethanol.

5-(4-Dimethylamino-phenyl)-1-methyl-4,5,6,7,8,9-hexahydro-pyrazolo[3,4-c]isoquinoline-6-one (**4a**)

$C_{19}H_{22}N_4O$ (322.44); m.p. 177–178 °C; yield: 86%. Anal.: calc. C 70.78, H 6.89, N 17.38; found C 70.46, H 6.98, N 17.27. ^{1}H-NMR (*DMSO-d_6*): 1.91 (s, 3H, CH_3), 2.16 (m, 6H, CH_2), 2.78 (s, 6H, $N(CH_3)_2$),

4.86 (s, 1H, CH), 6.53 (d, 2H, Aryl), 6.94 (d, 2H, Aryl), 9.53 (s, 1H, NH), 11.61 (s, 1H, NH). MS: $m/e = 322$ (M^+, 18%).

5-(4-Dimethylamino-phenyl)-1,8,8-trimethyl-4,5,6,7,8,9-hexahydro-pyrazolo[3,4-c]-isoquinoline-6-one (**4b**)

$C_{21}H_{26}N_4O$ (350.46); m.p. 189–191 °C; yield: 95%. Anal.: calc. C 71.97, H 7.48, N 15.99; found C 71.52, H 7.69, N 15.43. ^{1}H-NMR (*DMSO-d_6*): 0.95 (s, 3H, $C(CH_3)$), 0.98 (s, 3H, $C(CH_3)$), 1.90 (s, 3H, CH_3), 1.99 (s, 2H, CH_2), 2.04 (s, 2H, CH_2), 2.78 (s, 6H, $N(CH_3)_2$), 4.82 (s, 1H, CH), 6.53 (d, 2H, Aryl), 6.94 (d, 2H, Aryl), 9.53 (s, 1H, NH), 11.62 (s, 1H, NH). MS: $m/e = 350$ (M^+, 100%).

7,9-Bis-ethoxycarbonyl-5-(4-dimethylamino-phenyl)-1-methyl-8-phenyl-4,5,6,7,8,9-hexahydro-pyrazolo[3,4-c]isoquinoline-6-one (**4c**)

$C_{31}H_{34}N_4O_5$ (542.68); m.p. 178–180 °C; yield: 75%. Anal.: calc. C 68.61, H 6.32, N 10.32; found C 68.34, H 6.46, N 10.07. ^{1}H-NMR (*DMSO-d_6*): 0.93 (t, 6H, CH_3), 1.96 (s, 3H, CH_3), 2.81 (s, 6H, $N(CH_3)_2$, 3.86 (q, 4H, CH_2), 3.99 (s, 1H, CH–C_6H_5), 4.06 (s, 2H, CH–COOEt), 4.94 (s, 1H, CH–C_6H_4), 6.74 (d, 2H, Aryl), 7.10 (d, 2H, Aryl), 7.26 (s, 5H, C_6H_5), 10.03 (s, 1H, NH), 11.79 (s, 1H, NH).

5-(4-Methoxy-phenyl)-1-methyl-4,5,6,7,8,9-hexahydro-pyrazolo[3,4-c]isoquinoline-6-one (**4d**)

$C_{18}H_{19}N_3O_2$ (309.39); m.p. 172–173 °C; yield: 63%. Anal.: calc. C 69.88, H 6.20, N 13.58; found C 69.57, H 6.27, N 13.32. ^{1}H-NMR (*DMSO-d_6*): 1.90 (s, 3H, CH_3), 2.15 (m, 6H, CH_2), 3.65 (s, 3H, OCH_3), 4.92 (s, 1H, CH), 6.71 (d, 2H, Aryl), 7.04 (d, 2H, Aryl), 9.61 (s, 1H, NH), 11.66 (s, 1H, NH). MS: $m/e = 309$ (M^+, 20%).

5-(4-Methoxy-phenyl)-1,8,8-trimethyl-4,5,6,7,8,9-hexahydro-pyrazolo[3,4-c]isoquinoline-6-one (**4e**)

$C_{20}H_{23}N_3O_2$ (337.42); m.p. 246–248 °C; yield: 82%. Anal.: calc. C 71.19, H 6.86, N 12.45; found C 71.28, H 6.51, N 12.43. ^{1}H-NMR (*DMSO-d_6*): 0.95 (s, 3H, $C(CH_3)$), 0.98 (s, 3H, $C(CH_3)$), 1.89 (s, 3H, CH_3), 2.05 (s, 2H, CH_2), 2.10 (s, 2H, CH_2), 3.64 (s, 3H, OCH_3), 4.90 (s, 1H, CH), 6.71 (d, 2H, Aryl), 7.04 (d, 2H, Aryl), 9.59 (s, 1H, NH), 11.67 (s, 1H, NH). MS: $m/e = 337$ (M^+, 20%).

7,9-Bis-ethoxycarbonyl-5-(4-methoxy-phenyl)-1-methyl-8-phenyl-4,5,6,7,8,9-hexahydro-pyrazolo[3,4-c]isoquinoline-6-one (**4f**)

$C_{30}H_{31}N_3O_6$ (529.64); m.p. 196–198 °C; yield: 81%. Anal.: calc. C 68.03, H 5.91, N 7.93; found C 67.87, H 6.08, N 7.76. ^{1}H-NMR (*DMSO-d_6*): 0.90 (t, 6H, CH_3), 1.94 (s, 3H, CH_3), 3.67 (s, 3H, OCH_3), 3.85 (q, 4H, CH_2), 3.98 (s, 1H, CH–C_6H_5), 4.06 (s, 2H, CH–COOEt), 4.94 (s, 1H, CH–C_6H_4), 6.74 (d, 2H, Aryl), 7.10 (d, 2H, Aryl), 7.26 (s, 5H, C_6H_5), 10.03 (s, 1H, NH), 11.79 (s, 1H, NH).

5-(4-Dimethylamino-phenyl)-1-methyl-3-phenyl-4,5,6,7,8,9-hexahydro-pyrazolo[3,4-c]isoquinoline-6-one (**4g**)

$C_{25}H_{26}N_4O$ (398.51); m.p. 157–159 °C; yield: 76%. Anal.: calc. C 75.35, H 6.58, N 14.06; found C 75.21, H 6.72, N 13.87. ^{1}H-NMR ($CDCl_3$): 2.02 (s, 3H, CH_3), 2.47 (m, 6H, CH_2), 2.87 (s, 6H, $N(CH_3)_2$), 5.09 (s, 1H, CH), 6.61 (d, 2H, Aryl), 7.15 (d, 2H, Aryl), 7.44 (m, 5H, C_6H_5). MS: $m/e = 398$ (M^+, 15%).

5-(4-Dimethylamino-phenyl)-3-phenyl-1,8,8-trimethyl-4,5,6,7,8,9-hexahydro-pyrazolo[3,4-c]-isoquinoline-6-one (**4h**)

$C_{27}H_{30}N_4O_4$ (426.56); m.p. 183–184 °C; yield: 69%. Anal.: calc. C 76.03, H 7.03, N 13.13; found C 75.88, H 7.13, N 13.06. ^{1}H-NMR (*DMSO-d*$_6$): 0.93 (s, 3H, $C(CH_3)$), 0.99 (s, 3H, $C(CH_3)$), 1.89 (s, 3H, CH_3), 2.03 (s, 2H, CH_2), 2.08 (s, 2H, CH_2), 2.80 (s, 6H, $N(CH_3)_2$), 4.87 (s, 1H, CH), 6.57 (d, 2H, Aryl), 7.01 (d, 2H, Aryl), 7.47 (m, 5H, C_6H_5), 9.23 (s, 1H, NH). MS: *m/e* = 426 (M^+, 83%).

7,9-Bis-ethoxycarbonyl-5-(4-dimethylamino-phenyl)-3,8-diphenyl-1-methyl-4,5,6,7,8,9-hexahydro-pyrazolo[3,4-c]isoquinoline-6-one (**4i**)

$C_{37}H_{38}N_4O_5$ (618.73); m.p. 185–186 °C; yield: 73%. Anal.: calc. C 71.82, H 6.19, N 9.06; found C 71.31, H 5.98, N 8.78. ^{1}H-NMR (*DMSO-d*$_6$): 0.90 (t, 6H, CH_3), 1.96 (s, 3H, CH_3), 2.85 (s, 6H, $N(CH_3)_2$), 3.81 (q, 4H, CH_2), 3.97 (s, 1H, CH–C_6H_5), 4.13 (s, 2H, CH–COOEt), 5.49 (s, 1H, CH), 6.65 (d, 2H, Aryl), 7.12 (d, 2H, Aryl), 7.17–7.68 (m, 10H, Aryl).

5-Acetyl-6-(4-dimethylamino-phenyl)-3,4-dimethyl-6,7-dihydro-pyrazolo[3,4-b]pyridine (**5a**)

$C_{18}H_{22}N_4O$ (310.38); m.p. 259–264 °C; yield: 66%. Anal.: calc. C 69.65, H 7.14, N 18.05; found C 69.47, H 6.96, N 18.31. ^{1}H-NMR (*DMSO-d*$_6$): 1.94 (s, 3H, CH_3), 1.96 (s, 3H, CH_3), 2.31 (s, 3H, CH_3), 2.79 (s, 6H, $N(CH_3)_2$), 4.92 (s, 1H, CH), 6.58 (d, 2H, Aryl), 6.97 (d, 2H, Aryl), 9.22 (s, 1H, NH), 11.54 (s, 1H, NH).

6-(4-Dimethylamino-phenyl)-3,4-dimethyl-5-ethoxycarbonyl-6,7-dihydro[3,4-b]pyridine (**5b**)

$C_{19}H_{24}N_4O_2$ (340.42); m.p. 240–242 °C; yield: 70%. Anal.: calc. C 67.03, H 7.11, N 16.46; found C 66.82, H 7.11, N 16.31. ^{1}H-NMR (*DMSO-d*$_6$): 1.06 (t, 3H, CH_3), 1.89 (s, 3H, CH_3), 2.31 (s, 3H, CH_3), 2.81 (s, 6H, $N(CH_3)_2$), 3.87 (q, 2H, CH_2), 4.86 (s, 1H, CH), 6.56 (d, 2H, Aryl), 6.95 (d, 2H, Aryl), 9.15 (s, 1H, NH), 11.53 (s, 1H, NH). MS: *m/e* = 340 (M^+, 100%).

Preparation of **6** *and* **7**

1.14 g (5 mmol) **1a** and 0.57 g (5 mmol) ethyl cyanoacetate were refluxed in 60 ml ethanol for 4 h. After cooling yellow crystals of **6** separated from the solution. **7** was isolated as a nearly colourless compound from the remaining solution after standing overnight.

Ethyl p-dimethylamino-α-cyano Cinnamate (**6**)

$C_{14}H_{16}N_2O_2$ (244.28); m.p. 124–125 °C; yield: 74%. ^{1}H-NMR ($CDCl_3$): 1.36 (t, 3H, CH_3), 3.10 (s, 6H, $N(CH_3)_2$), 4.33 (q, 2H, CH_2), 6.68 (d, 2H, Aryl), 7.92 (d, 2H Aryl), 8.60 (s, 1H, CH). Vis ($CHCl_3$): 424 nm ($\lg \varepsilon = 4.59$).

5-Cyano-6-(4-dimethylamino-phenyl)-4,5,6,7-tetrahydro-pyrazolo[3,4-b]pyridine-4-one (**7**)

$C_{16}H_{17}N_5O$ (295.33); m.p. 294–295 °C; yield: 12%. ^{1}H-NMR (*DMSO-d*$_6$): *trans* (59%): 1.50 (s, CH_3), 2.89 (s, $N(CH_3)_2$), 4.25 (d, CH) 4.53 (d, CH), 6.71 (d, Aryl), 7.16 (d, Aryl), 10.88 (s, NH), 11.99 (s, NH). *cis* (41%): 1.99 (s, CH_3), 2.85 (s, $N(CH_3)_2$), 4.34 (d, CH), 4.76 (d, CH), 6.64 (d, Aryl), 6.93 (d, Aryl), 10.86 (s, NH), 11.91 (s, NH). MS: *m/e* = 295 (M^+, 100%). IR: $\nu = 2370\,cm^{-1}$ (CN), $1695\,cm^{-1}$ (CO).

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