SYNTHESES WITH NITRILES LXX[1]:

CONDENSATION PRODUCTS OF DIMERIC MALONONITRILE DERIVATIVES WITH 2,4-DIKETONES AND THEIR APPLICATION FOR THE SYNTHESIS OF SUBSTITUTED 1,6-NAPHTYRIDINES

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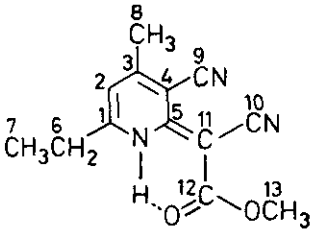
Abstract - Reaction of 2-amino-1,1,3-tricyanopropene 1a and methyl 3-amino-2,4-dicyanocrotonate 1b with 2,4-diketones 2a-c leads to the substituted 1,2-dihydropyridines 3a-d in good yields. The cyclisation of the resulting 1,3-dicarbonitrile system 3a in basic od acidic medium is explored. Structure proof of the resulting isomeric substituted 1,6-naphtyridines 4, 5a,b is provided by spectroscopical means.

We showed that the condensation of malononitrile dimer, 2-amino-1,1,3-tricyano-propene 1a (R=CN) and 2,4-diketones of type 2 in basic medium leads to the corresponding 1,2-dihydropyridines 3 (R^3=CN)[2]. This reaction has been recently investigated again and the assumed structures were confirmed[3]. We now report the reaction of methyl 3-amino-2,4-dicyanocrotonate 1b (R=CO_2CH_3)[4] with 2a-c forming the 1,2-dihydropyridines 3b-d (R^3=CO_2CH_3) under similar conditions. Thus, 3-cyano-2-cyano(methoxycarbonyl)-methylene-4,6-dimethyl-1,2-dihydropyridine 3b (R^1,R^2=CH_3, R^3=CO_2CH_3) is obtained by refluxing 1b (6.67 mmol), pentane-2,4-dione 2a (10 mmol) and sodium (0.1g) in ethanol (15 ml) for 3 min. The solution is acidified with diluted HCl, the precipitate is collected and recrystallised from glacial acetic acid. $C_{12}H_{11}N_3O_2$, yield 92%, mp 237°C, IR (KBr): 3080-2910 (NH), 2220, 2200 (CN), 1655 (CO) cm^{-1}, ^{1}H-NMR (d^6-DMSO): 2.52 (s,3H), 2.58(s,3H), 3.73(s,3H), 6.68 (s,1H) ppm.

Similarly 3-cyano-2-cyano(methoxycarbonyl)-methylene-4,6-diethyl-1,2-dihydropyridine 3c (R^1,R^2=C_2H_5, R^3=CO_2CH_3) is prepared by heating the previously described molar amounts of 1b and heptane-3,5-dione 2b in methanol for 2 min. $C_{14}H_{15}N_3O_2$, yield 87%, mp 227°C (AcOH), IR (KBr): 3100-2950 (NH), 2210,2195 (CN), 1650 (CO) cm^{-1}, ^{1}H-NMR (d^6-DMSO): 1.31 (t,6H), 2.83 (m,4H), 3.71 (s,3H), 6.82 (s,1H) ppm. For the preparation of 3-cyano-2-cyano(methoxycarbonyl)-methylene-6-ethyl-4-methyl-1,2-dihydropyridine 3d (R^1=CH_3, R^2=C_2H_5, R^3=CO_2CH_3), 1b (6.67 mmol), hexane-2,4-dione 2c (10 mmol) and sodium (0.1g) in methanol (15 ml) are heated for 2 min. $C_{13}H_{13}N_3O_2$, yield 99%, mp 230°C (AcOH), IR (KBr): 3080-2950 (NH), 2215, 2195 (CN), 1650 (CO) cm^{-1}, ^{1}H-NMR (d^6-DMSO): 1.34 (t,3H), 2.50 (s,3H), 2.83 (q,2H), 3.73 (s,3H), 6.83 (s,1H) ppm. Structure proof for the positions of R^1 and R^2 was provided by interpretation of the C,H-coupling of the ring carbons 1 and 3. The ^{13}C-spectrum of 3d is listed in table 1. The low carbonyl absorption bands of compounds 3b-d indicate the existence of a hydrogen bond confirming the Z-isomers. All formulae were supported by satisfactory C,H,N-analyses.



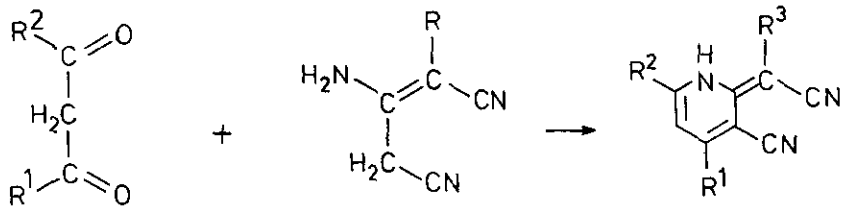
3d

Table 1. ^{13}C-data of 3d (d^6-DMSO), δ (ppm)

C 1	161.4	C 5	151.6	C 9, C 10	116.0, 112.8
C 2	114.0	C 6	26.0	C 11	60.5
C 3	155.0	C 7	10.0	C 12	170.0
C 4	97.6	C 8	20.0	C 13	50.8

coupling constants: CH_3(8), C 3 (q) J = 5 Hz
CH_2(6), C 1 (t) J = 6 Hz

The 1,3-dicarbonitriles 3a-d were supposed to be promising starting materials for the synthesis of 1,6-naphtyridines. The cyclisation of 1,3-dicarbonitriles has been investigated repeatedly. The hydrogen bromide induced cyclisation of 1a was described in 1957[5]. The structure of the formed product has been proved recently[6]. There are reported some more examples for the use of these 1,3-dicarbonitriles for the synthesis of halogenated heterocyclic compounds[7,8] as well as the addition of alcohols in basic medium[9-13] leading to alkoxy-substituted

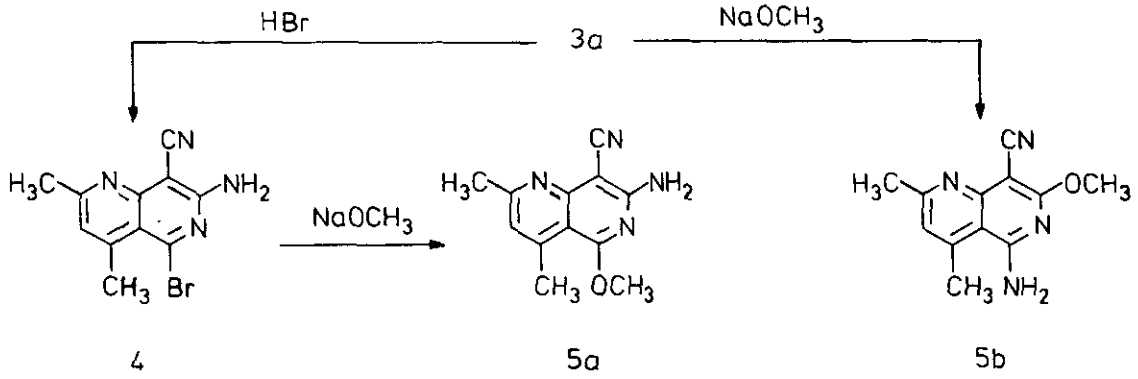


2a-c 1ab 3a-d

	R^1	R^2
2a	CH_3	CH_3
b	C_2H_5	C_2H_5
c	CH_3	C_2H_5

1a	R = CN
b	R = CO_2CH_3

	R^1	R^2	R^3
3a	CH_3	CH_3	CN
b	CH_3	CH_3	CO_2CH_3
c	C_2H_5	C_2H_5	CO_2CH_3
d	CH_3	C_2H_5	CO_2CH_3



4 5a 5b

heterocyclic compounds. In extension of our work on the basic cyclisation of 1a[1] we investigated the cyclisation of 3a[2] in some detail.

To a suspension of 3a (2.0g, 10.2 mmol) in glacial acetic acid (50 ml) warmed up to 60°C, HBr-gas is bubbled through for 80 min. Then the reaction mixture is allowed to stand for 2 h at room temperature. The precipitate is collected, washed with water, dried and recrystallised from DMF. Yield 1.1g (39%), light yellow needles, *7-amino-5-bromo-8-cyano-2,4-dimethyl-1,6-naphtyridine* (4), $C_{11}H_9N_4Br$, mp 300°C, ^{1}H-NMR (200 MHz, d^6-DMSO): 2.56 (s,3H), 2.76 (s,3H), 7.31 (s,1H), 7.91 (2H, broad) ppm, IR (KBr): 3480, 3300, 3200 (NH_2), 2220 (CN),

1630, 1590 cm^{-1}, MS: 278 (50), 276 (50), 197 (100), 170 (25) m/e (%).

5-Amino-8-cyano-2,4-dimethyl-7-methoxy-1,6-naphtyridine (5b) is prepared by refluxing a solution of 3a (2.0g, 10 mmol) and sodium (0.7g, 30 mmol) in methanol (30 ml) for 48 h. Then the solution is kept in a refrigerator overnight. The formed precipitate is collected by suction (0.16g) and by evaporating the filtrate additional 0.2g can be isolated (total yield 16%). Light yellow needles from methanol, $C_{12}H_{12}N_4O$, mp 250°C, ^{1}H-NMR (d^6-DMSO): 2.48 (s,3H), 2.57 (s,3H), 3.99 (s,3H), 6.88 (s,1H), 7.07 (s,2H) ppm, IR (KBr): 3440, 3330, 3220 (NH_2), 2220 (CN), 1640, 1580 cm^{-1}, MS: 228 (100), 213 (19), 199 (50), 132 (16) m/e (%). Analytical and spectroscopical data indicated that cyclisation occurred accompanied by the addition of hydrogen bromide or methanol, respectively, and the infrared spectra of 4 and 5b showed in contrast to that of 3a (CN 2190-2220 cm^{-1}) only one sharp signal due to a nitrile group in accordance with the assumed cyclic structure. Then, in order to explore whether different nitrile groups are involved for cyclisation in alkaline or acidic medium, 7-amino-8-cyano-2,4-dimethyl-5-methoxy-1,6-naphtyridine (5a) was prepared by treatment of 4 (0.55g, 2 mmol) with sodium (0.46g, 20 mmol) in methanol (300 ml) under reflux for 20 h. The hot mixture is filtered, the filtrate is concentrated in vacuo to 100 ml and kept in a refrigerator overnight. The precipitate is collected, the filtrate is concentrated again and cooled. Total yield 0.24g (53%). Colourless needles from methanol, mp 258°C. $C_{12}H_{12}N_4O$, ^{1}H-NMR (d^6-DMSO): 2.55 (s), 2.68 (s,3H), 3.99 (s,3H), 6.98 (s,1H), 7.54 (s,2H) ppm, IR (KBr): 3500, 3330, 3240 (NH_2), 2220 (CN), 1625 cm^{-1}.

While 5a and 5b were analytically identical and the melting points of the pure substances were not significantly different, a 1 : 1 mixture of the two compounds showed considerable depression of the melting point and the infrared spectra were not identical. Apparently, 5a and 5b are isomeric products. The suggested structures of 5a and 5b were confirmed by spectroscopic data. By applying a perturbance field on the signal of the 4-methyl group of compound 5b at 2.57 ppm a Nuclear-Overhauser-Effect was observed for the aromatic proton at 6.88 ppm (almost 50%) as well as for the signal of the amino group at 7.07 ppm (17%). The same experiment carried out with 5a led to an increase of intensity of the aromatic proton signal at 6.98 ppm and of the methoxyprotons at 3.99 ppm. Effect on the

methoxyprotons is about 60% of the effect on the aromatic proton. The absolute percentage of intensity increase could hardly be measured due to the broad signal of the amino group.

So it could be proved that methanol in alkaline solution is added specifically to the nitrile group in position 3 of the pyridine ring. These results are in accordance with related systems[6,9]. No reaction of this type could be observed under these conditions with compounds 3b-d.

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Received, 25th July, 1983