A NEW SYNTHESIS OF 3,5-DISUBSTITUTED PYRAZOLES BY REACTION OF α,γ-DIPYROLIDINYLGLUTARONITRILES (MASKED α,γ-DIKETONE EQUIVALENTS) WITH HYDRAZINES

Kazumasa Takahashi*, Akira Suzuki, Katsuyuki Ogura, and Hirotada Iida
Department of Synthetic Chemistry, Faculty of Engineering, Chiba University, Yayoi-cho, Chiba 260, Japan

Abstract ——— An efficient sequence proposed for a new synthetic method of 3,5-disubstituted pyrazoles involves the reaction of α,γ-dipyrrolidinylglutaronitriles (masked α,γ-diketone equivalents) with hydrazines.

The α-aminonitrile synthon is known to be synthetically equivalent to a carbonyl group[1]. However, there is no information about a synthesis of pyrazoles using α-aminonitriles except our previous papers[2]. We report here a new synthetic method for 3-alkyl- and 3,5-dialkyl-pyrazoles (5 and 6) by reaction of α-alkyl- and α,γ-dialkyl-α,γ-dipyrrolidinylglutaronitriles (3 and 4), which are related to masked α,γ-diketone equivalents, with hydrazines.

α,γ-Dipyrrolidinylglutaronitrile (2) was prepared by Strecker synthesis using malonaldehyde bis-(dimethylacetal) (1) and pyrrolidine. Reaction of 2 with alkyl halides was carried out by two methods (methods A and B) to give a mixture of 3 and 4, the formation of which was evidenced by ^{1}H-NMR analysis (see Scheme 1). The unstable products (3 and 4) which decomposed on silica gel were not isolated in pure form. Heating of the crude compounds (3 and 4) with hydrazine in ethanol resulted in cyclocondensation to afford the 3-alkyl- and 3,5-dialkyl-pyrazoles (5 and 6). When mono-methylhydrazine is used in place of hydrazine under similar conditions, the reaction affords two products of N-methylpyrazoles having methyl group on either nitrogen atoms in the pyrazole ring.

By method A, alkylation of 2 using n-propyl and benzyl bromides gave 3-n-propyl-, 3,5-di-n-propyl-, 3-benzyl-, and 3,5-dibenzylpyrazoles (5a, 6a, 5b, and 6b) in

Scheme 1. Preparation of pyrazoles (5, 6, 7b, and 8b)

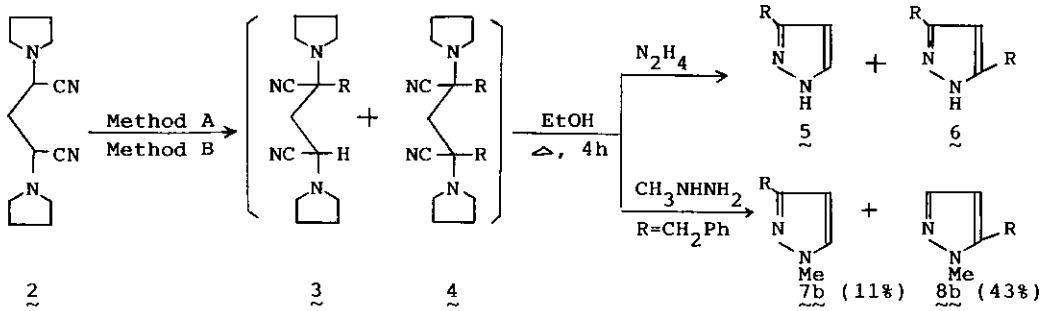

Table 1.

Compound R	Method[c]	Yield (%)[a]		
		5	6	Total
a: R= n-C_3H_7	A	28	40	68
	B	57	32	89
b: R= $PhCH_2$	A	34	15	49
	B	70	0	70
c: R= iso-C_3H_7	B	17	0	42[b]

a) overall yield from 2. b) Pyrazole (R=H) was obtained in 25% yield together with 5c. c) Method A: Alkyl halide was added dropwise to a mixture of 2 and LDA. Method B: A mixture of 2 and alkyl halide was added dropwise to LDA solution.

28%, 40%, 34%, and 15% yields, respectively. On the other hand, by method B, the alkylation predominantly gave mono-alkylated pyrazoles (5a and 5b): The reaction of 2 with benzyl bromide did not give 6b at all, but 5b together with a small amount of stilbene. Furthermore, the reaction using more bulky isopropyl bromide gave 3-isopropylpyrazole (5c) and pyrazole in low yields. A one-pot reaction of 2 with benzyl bromide and methyl iodide gave 3-benzyl-5-methylpyrazole (6d) and 6b in 43% and 6% yields, respectively. Thus, the size of the alkyl group remarkably influences on the alkylation of 2: When a smaller alkyl group such as methyl is used as a second substituent, dialkylation of 2 smoothly takes place. However, when a bulky substituent such as isopropyl is used, even mono-alkylation does not proceed smoothly. Since the method B is a stepwise reaction, the choice of the second substituent is critical. Consequently, it is concluded that steric hindrance between the two clusters of pyrrolidinyl and cyano groups of 2 will strongly contribute to mono- and di-alkylating 2.

Treatment of crude α-benzyl-α,γ-dipyrrolidinylglutaronitrile (3b) with monomethylhydrazine hydrochloride in ethanol heated similarly gave 3-benzyl- and 5-benzyl-1-methylpyrazoles (7b and 8b) in 11% and 43% yields, respectively. The evidence for structural differences between 7b and 8b is provided by means of

Table 2. Physical properties of new pyrazoles[a)]

Compd.	ir(neat) ν_{NH}, cm^{-1}	nmr($CDCl_3$/TMS) δ
5b	3400, 3200	3.95(2H,s), 5.96(1H,b-s), 7.20(5H,s), 7.27 (1H,s), 10.35(1H,b-s)
6b	3500-3150	3.92(4H,s), 5.82(1H,b-s), 7.23(10H,s), 8.87(1H,b-m)
6d	3500-3150	2.21(3H,s), 3.92(2H,s), 5.73(1H,s), 7.19 (5H,s), 10.80(1H,b)
7b		3.69(3H,s), 3.97(2H,s), 5.93(1H,d,J=2 Hz), 7.22(5H,s), 7.60(1H,b)
8b		3.84(3H,s), 3.97(2H,s), 5.97(1H,d,J=2 Hz), 7.22(5H,s), 7.59(1H,b)

a) All new compounds gave satisfactory elemental analyses, and were viscous oil.

^{1}H-NMR spectroscopy: The proton of adjacent N-methyl group to the benzyl group in 8b is more deshielded by the so-called "ring-current effect of aromatic ring" than that of 7b[3]. The each N-CH_3 proton of 7b and 8b gives rise to δ 3.69 and 3.84, respectively.

EXPERIMENTAL

(I) Preparation of α,γ-dipyrrolidinylglutaronitrile (2): A mixture of malonaldehyde *bis-(dimethylacetal)* (1, *1.64 g, 0.01 mol*), *1.2 N sulfuric acid* (30 ml) and pyrrolidine (1.42 g, 0.02 mol) was heated at 50 °C for 15 min, cooled in an ice bath, and then neutralized with sodium carbonate. An aqueous solution (3 ml) of potassium cyanide (1.34 g, 0.021 mol) was added to the mixture at room temperature. The mixture was stirred over 30 min, extracted with dichloromethane (7 x 30 ml), and then the organic layer was dried over anhydrous magnesium sulfate. After removal of the solvent, the residue was chromatographed (Florisil/benzene). Thus, 2 was obtained in 51% yield (1.19 g): Mp 151.5-152 °C; ir (KBr) ν_{CN} 2240 cm^{-1}; ^{1}H nmr ($CDCl_3$)δ 1.82 (8H, m), 2.13 (2H, t, J=7 Hz), 2.65 (8H, m), 4.06 (2H, t, J=7 Hz, C<u>H</u> x 2); Found: C, 67.31; H, 8.62; N, 24.06%. Calcd for $C_{13}H_{20}N_4$: C, 67.21; H, 8.68; N, 24.12%.

(II) Alkylation of α,γ-dipyrrolidinylglutaronitrile (2). Preparation of α-n-propyl- and α,γ-di-n-propyl-α,γ-dipyrrolidinylglutaronitriles (3a and 4a) as a typical example. Method A: Under a nitrogen atmosphere, a solution of 2 (0.303 g, 1.30 mmol) dissolved in a mixture of tetrahydrofuran (THF; 6 ml) and hexa-

methylphosphoramide (HMPA; 2 ml) was added dropwise to a solution of lithium diisopropylamide (LDA; 2.86 mmol) in dry THF (5 ml) cooled at -78 °C. After the solution was stirred for 10 min, n-propyl bromide (0.415 g, 3.37 mmol) was added at -78 °C to the solution. The solution was stirred at -78 °C over 1 h, poured into water (25 ml), and extracted with diethyl ether (3 x 30 ml). The organic layer was washed with brine, and dried over anhydrous magnesium sulfate. After removal of magnesium sulfate and ether, a viscous oil was obtained, and used in the next preparation of pyrazoles. The formation of α-n-propyl- and α,γ-di-n-propyl-α,γ-dipyrrolidinylglutaronitriles (3a and 4a) was confirmed by ^{1}H-NMR of the viscous oil.

Method B: Under a nitrogen atmosphere, a mixture of 2 (0.383 g, 1.65 mmol) and n-propyl bromide (0.569 g, 4.63 mmol) dissolved in a mixture of THF (10 ml) and HMPA (3 ml) was added dropwise to a solution of LDA (4.12 mmol) in dry THF (4 ml) cooled at -78 °C. The mixture was stirred for 1 h under nitrogen at -78 °C. The subsequent procedure is the same with that of method A.

(III) Preparation of pyrazoles (5, 6, 7, and 8). Typical procedure as follows: To a solution of the viscous oil containing 3a and 4a dissolved in ethanol (30 ml) was added dropwise hydrazine hydrate (0.32 ml, 6.6 mmol) and water (0.5 ml). After the ethanolic solution was heated at 75 °C for 5 h, the ethanol and the water were evaporated by means of a rotary evaporator. The residue was chromatographed (Florisil/benzene-ethyl acetate). Thus, 5a and 6a were obtained. By the similar procedure, 5b, 6b, 5c, 6d, 7b, and 8b were obtained. Within them, physical properties of 5a, 6a and 5c agreed with those reported in the literature[4,5]. Physical properties of new compounds, 5b, 6b, 6d, 7b, and 8b are summarized in Table 2.

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