Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

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Published online: 23 Sep 2006.

To cite this article: A. Echevarría & J. Elguero (1993) Synthesis of 4-Benzylpyrazoles from Monobenzylmalononitrile, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 23:7, 925-930, DOI: 10.1080/00397919308013289

To link to this article: http://dx.doi.org/10.1080/00397919308013289

SYNTHETIC COMMUNICATIONS, 23(7), 925-930 (1993)

SYNTHESIS OF 4-BENZYLPYRAZOLES FROM MONOBENZYLMALONONITRILE

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Abstract: The hitherto unknown 4-benzylpyrazoles can be prepared in three steps by monobenzylation of malononitrile, reaction with hydrazines to form 3,5-diamino-4-benzylpyrazoles, followed by double deamination.

Introduction

Pyrazoles monosubstituted at position 4 are inhibitors and deactivators of liver alcohol dehydrogenase[1a] and one of them, namely 4-methylpyrazole has been developed into a drug for the treatment of alcoholism. However, they are difficult to prepare.[1b] Actually, only two general procedures have been described and both are rather laborious. Reichardt's method[2] uses C-mono-substituted malonaldehydes, but these compounds in turn are tedious to prepare.[3] Tolf's method[4] uses 4-R-5-pyrazolinones and 4-R-5-chloropyrazoles as intermediates.

Results and Discussion

We describe in this communication a different approach. It is based in two recent reports, one about the easy preparation of C-monoalkyl

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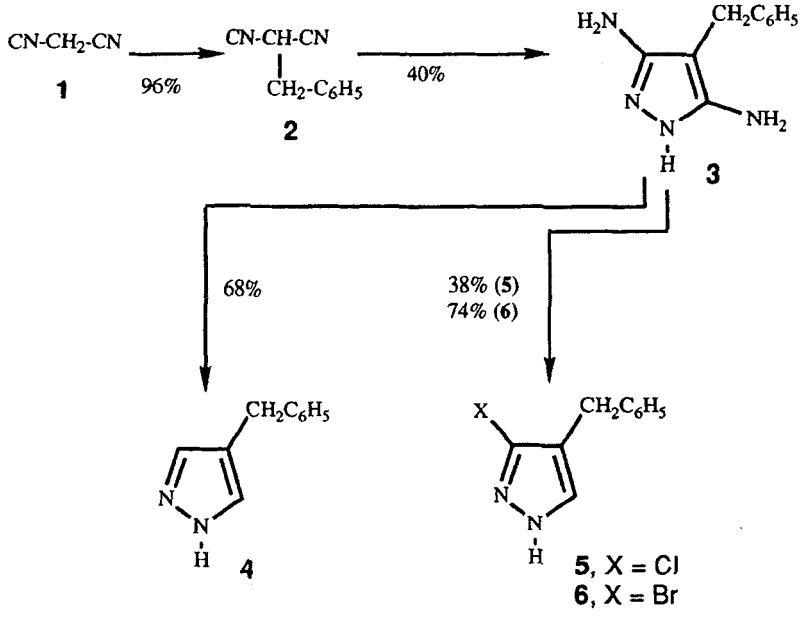
malononitriles[5] and the other concerning the transformation of benzylmalononitriles[5] and the other concerning the transformation of benzylmalononitriles into 3,5-diamino-4-benzyl-pyrazoles[6] (note that malononitrile itself does not yield 3,5-diamino pyrazole when reacting with hydrazine).[7]

Malononitrile **1** is first transformed into benzylmalonotrile **2**,[5] and then into 3,5-diamino-4-benzylpyrazole **3**.[6] Deamination of 3(5)-aminopyrazoles to the corresponding pyrazoles has been reported,[8,9] but nobody attempted the double deamination of 3,5-diaminopyrazoles. In normal conditions (sodium nitrite and hydrochloric acid) compound **3** yields a mixture of the wanted product, 4-benzylpyrazole **4** and 3(5)-chloro-4-benzylpyrazole **5**. The formation of **5** is unusual, since normally the Sandmeyer reaction requires the presence of cuprous chloride (although sulfur dioxide is a useful alternative).[9] If hydrochloric acid is replaced by hydrobromic acid, then 3(5)-bromo-4-benzylpyrazole **6** is obtained together with compound **4**. To synthesize this last compound without any halogenated derivative, the deamination reaction was carried out using only nitrous acid. The yield of unreported 4-benzylpyrazole **4** was 68 %.



Reaction of methylhydrazine with **2** yields 1-methyl-3,5-diamino-4-benzylpyrazole **7**. This compound can be deaminated using nitrous acid to yield 1-methyl-4-benzylpyrazole **8**. This last compound was also prepared by methylation of benzylpyrazole **4**. In conclusion, the described method gives access to new pyrazoles difficult to prepare ortherwise. The possible extension to other C-substituted malononitriles and to other hydrazines is under study.

Experimental Section

All reagents were of commercial quality (Aldrich) from freshly opened containers. Silical gel MN-60 230-400 mesh (from Macherey-Nagel, Germany) was used for chromatography. Reagent quality solvents were used without further purification. Melting points were measured with a Reichert-Jung microscope apparatus and are uncorrected. Micro-analyses were obtained at the Instituto de Química Orgánica General, CSIC, Madrid. ^{1}H NMR spectra were registered on a Varian /Gemini 200 MHz spectrometer.

4-Benzylpyrazole (4); General Procedure: 3,5-Diamino-4-benzylpyrazole (**3**; 565 mg, 3 mmol) prepared following a procedure described in ref 6, was added to a solution of 50% aqueous hypophosphorous acid (9.6 mL, 9 mmol). The resulting solution was diluted with water (5 mL) and then cooled to 5°C. While stirring, a solution of sodium nitrite (460 mg, 6.6 mmol) in water (2 mL) was added dropwise. The reaction mixture was then stirred gently for 30 min at 5°C and finally allowed to come to room temperature and stand for 4h. After neutralization with sodium hydroxide, the product was extracted with ether. The extract was dried (Na_2SO_4), filtered and evaporated under reduced pressure to give product **4**.

4-Benzyl-5-X-pyrazole (5, X=chloro; 6, X=bromo); General Procedure: 3,5-Diamino-4-benzylpyrazole (**3**; 500 mg, 2.7 mmol) was added to appropriate concd. acid (HCl, 35%, 3.6 mL and HBr, 48%, 6 mL). The mixture was cooled (0-5 °C) and sodium nitrite (560 mg, 8.2 mmol) in water (2 mL) was added dropwise. The resulting

Table. 4-Benzylpyrazoles and 4-benzyl-3(5)-X-pyrazoles prepared by double deamination

Product No	Yield %	m.p. (°C)[a]	Molecular Formula[b]	^{1}H NMR ($CDCl_3$)[c] δ (ppm)
3[d]	40	143-144	$C_{10}H_{12}N_4$(188.3)	3.51 (s, 2H, CH_2); 3.98 (br, 4H, NH_2); 7.14 (s, 5H, Harom); 7.43 (br, 1H, NH)[d]
4	68	79-80	$C_{10}H_{10}N_2$ (158.2)	3.82 (s,2H, CH_2); 7.19 (m, 5H, Harom); 7.35 (s, 2H, CH)
5	38[e]	73-75	$C_{10}H_9ClN_2$ (192.5)	3.81 (s,2H, CH_2); 7.26 (m, 5H, Harom); 7.57 (s, 1H, CH); 12.06 (br, 1H, NH)
6	74	78-80	$C_{10}H_9BrN_2$ (237.1)	3.79 (s, 2H, CH_2); 7.26 (m, 5H,Harom) 7.48 (s,1H,CH)
7	12[e]	103-105	$C_{11}H_{14}N_4$ (202.3)	3.21 (br,4H, NH_2); 3.48 (s, 3H, CH_3); 3.59 (s, 2H, CH_2); 7.25 (m, 5H,Harom)
8	76[f]	87-89[f]	$C_{11}H_{12}N_2$ (172.2)	3.81 (s, 2H, CH_2); 3.84 (s, 3H, CH_3); 7.22 (s, 2H, CH); 7.29 (m, 5H, Harom)

[a]Uncorrected; [b]Satisfactory microanalysis obtained: C±0.30, H±0.28, N±0.26; [c]Obtained on a Varian/Gemini 200MHz spectrometer; [d]In DMSO; [e]Yield after purification by column chromatography; [f]Picrate.

solution was stirred and hypophosphorous acid (5.6 mL, 50% aqueous) was added dropwise while the temperature was maintaind at 0°C. The resulting mixture was stirred for an additional 10 min at 0°C, and then placed in refrigerator for 24h. After neutralization with sodium hydroxide, the product was extracted with diethyl ether (3 X 5 mL) and CH_2Cl_2 (3 X 5mL) and the combined organic extracts dried (Na_2SO_4), filtered and evaporated to give a crude solid. Products **5** and **6** were separated by column chromatography on silica gel MN-60 with CH_2Cl_2 and CH_2Cl_2/MeOH (99:1) as eluents.

1-Methyl-3,5-diamino-4-benzylpyrazole (7) : Benzylmalononitrile (**1**; 2 g, 12.8 mmol) was added to a solution of methylhydrazine (1

mL, 19.2 mmol) in ethanol (25 mL) and the mixture was heated at reflux temperature for 10 h. The resultant orange solution was evaporated and the oily residue purified by column chromatography on silica gel MN-60 using CH_2Cl_2/ MeOH (90:10) as eluent to affords pure product **7**.

1-Methyl-4-benzylpyrazole (8) : 1-Methyl-3,5-diamino-4-benzylpyrazole (**7**; 450 mg, 2.2 mmol) was treated by the same procedure as compound **4**. After extraction with diethyl ether and drying (Na_2SO_4), filtration and evaporation, product **8** was obtained as a red-brown oil.

Methylation of 4-benzylpyrazole : Alkylation was carried out using the same procedure of other triazole compounds.[10] 4-Benzylpyrazole (**4**; 315 mg, 2.0 mmol) was introduced in a flask provided with a calcium chloride guard tube with finely ground NaOH (320 mg, 8 mmol), DMF (2 mL) and iodomethane (0.15 mL, 2 mmol). The mixture was stirred 30 min at room temperature. Afterwards, the reaction mixture was poured into water (15 mL) and an oily product separated that was extracted with $CHCl_3$ (4 X 2 mL), washed with water (4 X 2 mL); dried over anhydrous sodium sulphate, filtered and the solvent evaporated under reduced pressure to give an oily product **8**. The picrate derivative was obtained with 76% of yield and a mp. of 87-89°C.

A grant from the CNPQ of Brazil (A.E.) is gratefully acknowledged.

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(Received in UK 8 October 1992)