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REGIOSELECTIVE ADAMANTYLATION OF N-UNSUBSTITUTED PYRAZOLE DERIVATIVES

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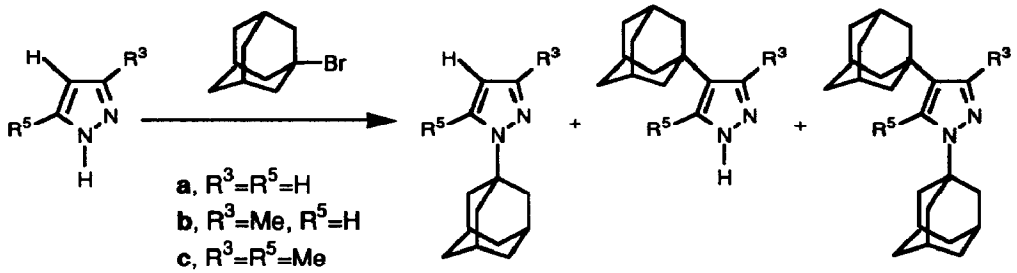
Abstract: Reaction of NH-pyrazoles with 1-bromoadamantane in a high pressure stainless steel autoclave (250 ml, maximum working pressure of 200 atm) gives regioselectively 1-adamantyl or 4-adamantylpyrazoles depending on the temperature.

The physico-chemical and biological properties of 1-(1-adamantyl)pyrazoles **2** have been extensively studied by us.[1-8] We achieved the syntheses of such derivatives first, by treating 1-adamantylhydrazine with the suitable β-dicarbonyl compound,[1,2] and secondly by heating an homogeneous mixture of one mole of 1-bromoadamantane (BrAd) with two moles of the NH-pyrazole derivatives **1** at 190-200°C.[3] However their corresponding isomers 4-(1-adamantyl)pyrazoles **3** have been scarcely mentioned in the literature.[9,10] We report here the direct adamantylation of NH-pyrazoles with BrAd in a high pressure stainless steel autoclave in 1-, 4- or 1,4-positions, depending on the reaction conditions.



1a-c **2a-c** **3a-c** **4a-c**

To our knowledge the only related results are those of Trofimenko[11] on the reaction of pyrazole with *tert*-butyl chloride which affords 1-*tert*-butylpyrazole (45%), 4-*tert*-butylpyrazole (20%), 1,4-di*tert*-butylpyrazole (24%) and unreacted pyrazole (11%). As it can be inferred from the Table 1 in the case of adamantane the regioselectivity control is higher than in the case of *tert*-butyl. Steric factors are crucial, so to get compound **4c** we had to react the previously isolated 3,5-dimethyl-4-(1-adamantyl)pyrazole **3c** (12 mmoles) with BrAd (6 mmoles) during 6 hours under normal pressure at 240°C. Formation of 4-(1-adamantyl)pyrazoles **3a-c** is favoured at high temperatures and with molar ratios NH-pyrazole/BrAd (2:1). By decreasing the temperature 1-(1-adamantyl)pyrazoles **2a-c** are obtained. The di(1-adamantyl)pyrazoles **4a-b** are only isolated in good proportion when using two moles of alkylating agent against 1 mole of the N-unsubstituted pyrazole derivative.

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Table 1. Some typical experimental conditions.[12]

Series	Starting Materials (mmol)				T	Reaction Time	Product Number [Distribution Data]		
	1a	**1b**	**1c**	BrAd	(°C)	(h)	**2**	**3**	**4**
a	20	-	-	10	120	4	***100***	-	-
a	20	-	-	10	230	4	13	***86***	1
a	10	-	-	20	230	1	14	37	***49***
b	-	10	-	10	230	4	***75***[a]	25	-
b	-	20	-	10	230	4	7[a]	***90***	3
b	-	10	-	20	230	4	9[a]	26	***65***
c	-	-	10	10	120	5.5	***100***	-	-
c	-	-	10	10	230	4	-	***100***	-

[a]Compound **2b** is obtained together with a small amount of 1-(1-adamantyl)-5-methylpyrazole (4%)

The ^1H and ^{13}C NMR spectra of these compounds have been recorded in $CDCl_3$. The steric hindrance of compound **4c** is apparent in the ^{13}C chemical shift of the 5-methyl group: compare 1,3,5-trimethylpyrazole (3-Me at 14.0 ppm, 5-Me at **11.7** ppm),[13] 1-(1-adamantyl)-3,5-dimethylpyrazole (3-Me at 13.3 ppm, 5-Me at **14.3** ppm)[13] and 1,4-di(1-adamantyl)-3,5-dimethylpyrazole **4c** (3-Me at 15.5 ppm, 5-Me at **17.1** ppm). In conclusion, we propose a new method of preparation of very congested heterocycles, a subject of several recent papers.[14,15]

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12. The *typical procedure* is as follows: A mixture of the N-unsubstituted pyrazole **1** and 1-bromoadamantane in the proportions stated in Table 1 in a high pressure stainless steel autoclave of 250 ml (maximum working pressure of 200 atm), was heated in an oven during the appropriate reaction time. Once the heating was finished, we allowed the reactor to reach the room temperature and then the autoclave was opened and the reaction crude taken with 5ml of ethanol and 500ml of water. The acidic solution was neutralized with 1N NaOH. A precipitate was formed, filtered, dried and column chromatographed on silica gel Merck 60 (230-400 mesh) with CH_2Cl_2 or CH_2Cl_2/EtOH as eluents. *Isolated yields* (%): **2a**, 61; **2b**, 70; **2c**, 72; **3a**, 78; **3b**, 79; **3c**, 75; **4a**, 32; **4b**, 23; and **4c**, 19.
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