ADAMANTYLATION OF *N*-UNSUBSTITUTED PYRAZOLE DERIVATIVES: MECHANISTIC AND STRUCTURAL STUDIES

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This manuscript is dedicated to Prof. Alan R. Katritzky on the occasion of his 65th birthday with friendship and respect

Abstract - Reaction of NH-pyrazoles with 1-bromoadamantane in a high pressure stainless steel autoclave gives regioselectively 1-(1-adamantyl)- or 4-(1-adamantyl)pyrazoles depending on the temperature. A series of cross-experiments allows to establish the mechanism of this reaction. The molecular structure of the most simple derivative, 4-(1-adamantyl) pyrazole (**3a**), has been determined. Intermolecular N-H···N hydrogen bonds hold the four independent molecules together in a helix system parallel to the **c** axis. The crystal is built up of two centrosymmetrically related helices.

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 either by treating 1-adamantylhydrazine with the suitable β-dicarbonyl compound,[1,2] or 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] The crystal geometries of the following derivatives were determined: 1-(1-adamantyl)- pyrazole (**2a**),[3] 1-(1-adamantyl)-3,5-dimethylpyrazole (**2c**),[5] 1-(1-adamantyl)-3,4,5-trimethyl-pyrazole,[5] and 1-(1-adamantyl-3-ol)-4-nitropyrazole.[3]

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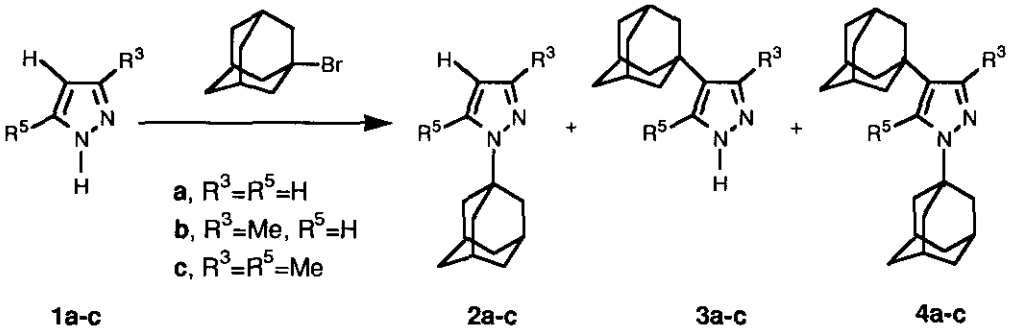
However, their corresponding isomers 4-(1-adamantyl)pyrazoles (**3**) have been scarcely mentioned in the literature. Only the preparation of **3a** from 1-adamantylcarboxaldehyde in a four step procedure[9] with a global yield of 11% (the total yield is even smaller due to the fact that 1-adamantanecarboxaldehyde is not a commercial product and has to be prepared by reduction of 1-adamantanecarboxylic acid) and the reaction of 1,3-disubstituted 2-(1-adamantyl)propane-1,3-diones with hydrazine and phenylhydrazine are known.[10]

We report here the direct adamantylation of NH-pyrazoles with BrAd, in 1-, 4- or 1,4-positions, depending on the reaction conditions, using a high pressure stainless steel autoclave (See Table 1).



Scheme 1

Synthesis. Heating NH-pyrazoles (**1a-c**) with 1-bromoadamantane in the conditions reported in Table 1 yields compounds (**2**), (**3**) and (**4**), depending on the experimental conditions.

Table 1. Experimental conditions

Series	Starting material (mmol)				T (°C)	Reaction	Product number[a]		
	1a	**1b**	**1c**	BrAd		time (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**[b]	25	--
b	--	20	--	10	230	4	7[b]	**90**	3
b	--	10	--	20	230	4	9[b]	26	**65**
c	--	--	10	10	120	5.5	**100**	--	--
c	--	--	10	10	230	4	--	**100**	--

[a]Relative amounts: [b]Compound (**2b**) is obtained (relative amount 96%) together with 1-(1-adamantyl)-5-methylpyrazole (**2d**) (R^3 = H, R^5 = Me, relative amount 4%).

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 yields when using two moles of alkylating agent against 1 mole of the N-unsubstituted pyrazole derivative. 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 mmol) with bromoadamantane (6 mmol) during 6 hours at normal pressure at 240°C.

Cross-experiments. We have carried out ten experiments to clarify the mechanism of the reactions summarized in Table 1. These experiments, labelled from ***1*** to ***10***, are collected in Table 2.

Table 2. *Summary of the reactions carried out with adamantylpyrazoles*

Exp.	Com-pounds[a]	Conditons[b]	Recovered starting material (%)	Isolated products[c]
1	**2a**	No acid	**2a**	------
2	**2a**	HCl	**2a**(12%)	**1a**(100%)
3	**2a** + **1a**	HCl	**2a** + **1a**	**3a**(100%)
4	**3a** + **1a**	HCl	**3a** + **1a**	------
5	**3a** + **1c**	HCl	**3a** + **1c**	------
6	**3c** + **1a**	HCl	**1a**(27%)+**3c**(4%)	**2a**(6%) + **3a**(73%) + **1c**(21%)
7	**4a**	HCl	**4a**(7%)	**2a**(4%) + **3a**(96%)
8	**4a** + **1a**	HCl	**1a**(22%)	**2a**(16%) + **3a**(84%)
9	**4a** + **1c**	HCl	**1c**(25%)	**2a**(15%) + **3a**(55%) + **2c**(22%) + **3c**(8%)
10	**4c** + **1a**	HCl	**1a**(13%)	**2a**(4%) + **3a**(10%) + **2c**(23%) + **3c**(63%)

[a]Always in equimolar ratios; [b]Always 4 h at 230 °C, either without acid or with 12 N HCl; [c]Relative amounts.

Experiment no. ***1*** shows that 1-(1-adamantyl)pyrazole is thermally stable and that apparently 4-(1-adamantyl)pyrazole is not formed by thermal isomerization of the N-substituted compound. However, in the conditions of the adamantylation reaction, hydrogen bromide is formed, and consequently, experiment no. ***2*** is more representative. Since in this experiment only starting material and pyrazole (**1a**) are recovered, the crucial role of HCl (or HBr) for the stability of adamantylpyrazoles is demonstrated.

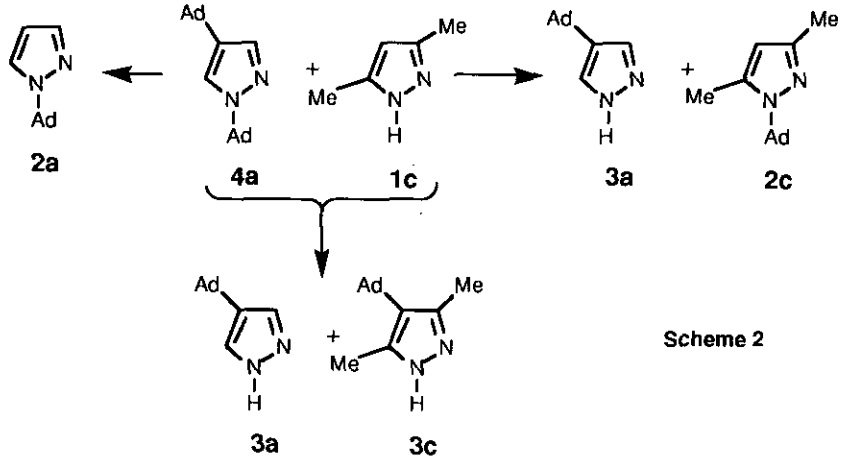
These experiments lead to the following conclusions:

1) By heating in the presence of protic acids, both 1-(1-adamantyl) and 4-(1-adamantyl) substituents are eliminated, the former more easily than the latter. Since 4-(1-adamantyl)pyrazoles are more stable than 1-(1-adamantyl)pyrazoles it is possible to carry out an *N*- vs *C*-isomerization but not the other way around.

2) *N*-(1-Adamantyl)pyrazoles are better adamantylating agents (both in positions 1 and 4) than *C*-(1-adamantyl)pyrazoles.

3) The reactivity of 4-(1-adamantyl)pyrazoles depends on the remaining substituents, only 4-(1-adamantyl)pyrazole (**3a**) is stable (Exp. no. ***5***). Other 4-derivatives either lose the adamantyl group (Exp. no. ***6***, ***9***, ***10***: **3c** → **1c**, **4a** → **2a**, **4c** → **2c**) or adamantylate other pyrazoles (Exp. no. ***6***, ***8***, ***9***: **3c** + **1a** → **2a** + **3a**, **4a** + **1c** → **2c** + **3c**, **4c** + **1a** → **2c** + **3a**).

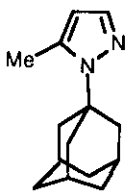
4) As an illustration of the complexity of these reactions, Scheme 2 summarizes the products obtained in experiment no. ***9***.



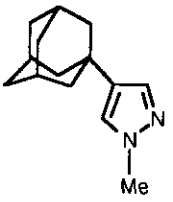
Scheme 2

The formation of the four different entities involves i) *C*-adamantylation, **3a** + **3c**; ii) *N*-adamantylation, **3a** + **2c**; iii) loss of the 4-adamantyl residue, **2a**.

Nmr studies in solution. The ^{1}H and ^{13}C nmr spectra of these compounds have been recorded in $CDCl_3$ and/or in DMSO-d_6 solution. The data are reported in the experimental part; in most cases assignments are based on two-dimensional (^{1}H-^{13}C) experiments. For comparative purposes, compound (**5**), 1-methyl-4-(1-adamantyl)pyrazole, was prepared by methylation of **3a**.



2d



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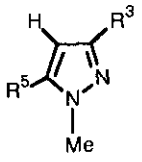
In carbon-13 nmr spectroscopy, the eleven compounds studied in this communication (**2a-2d**, **3a-3c**, **4a-4c** and **5**) can be compared with the corresponding methyl derivatives **6a-6d**, **7a-7c** and **8a-8c** whose data have been reported in the literature.[11]



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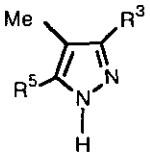

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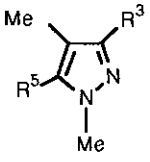

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a, $R^3 = R^5 = H$
b, $R^3 = Me$, $R^5 = H$
c, $R^3 = R^5 = Me$
d, $R^3 = H$, $R^5 = Me$

From the numerous possible comparisons, the following two conclusions can be drawn:

1) Most signals show **direct** relationships (positive slopes), i.e., the chemical shifts in both series of compounds change in the same direction. For instance: δC_4(4-Ad) = -62.9 + 1.70 δC_4(4-Me) [compounds **3a/7a**, **3b/7b**, **3c/7c**, **5/8a**, R = 0.99], δC_4(1,4-diAd) = -37.9 + 1.47 δC_4(1,4-diMe) and δC_5(1,4-diAd) = -185.0 + 2.37 δC_5(1,4-diMe) [compounds **4a/8a**, **4b/8b**, **4c/8c**, both R = 1.00]. The quality of these linear relationships is a supplementary proof of the correct assignment of adamantylpyrazoles.

2) The signals corresponding to C_α of the adamantyl substituent and to the methyl groups show **inverse** relationships (negative slopes): δC_α(*N*-Ad) = 94.5 - 0.97 δ(*N*-Me), R = 0.95 and δC_α(4-Ad) = 49.6 - 2.2 δ(4-Me), R = 0.86. This fact is due to steric shielding effects of the adamantyl substituent when there is another substituent near to it. These steric effects are also apparent in the signals of

the 5-methyl group [compare $\delta(C_5\text{-Me})$ for 1,3,5-trimethylpyrazole (**6c**)[11] 11.7 ppm, (**2c**) 14.3 ppm and (**4c**) 17.1 ppm].

Crystal and molecular structure of 4-(1-adamantyl)pyrazole (**3a**). Selected geometrical parameters are listed in Table 3. The compound crystallizes in the triclinic system P-1 with four molecules in the asymmetric unit. Figure 1 shows a perspective view of molecule (**1**) with the numbering scheme.[12]

Compound (**3a**) exhibits a disordered structure as it was observed in 1-(1-adamantyl)-3,5-dimethyl-pyrazole (**2c**).[5] Of the four independent adamantyl residues, two (those of molecules **2** and **4**) are disordered into two orientations (**A** and **B**) with respect to the pyrazole ring with population factors of 2/3 and 1/3 respectively. All but one pyrazole ring adopt the 'parallel' conformation with respect to the adamantyl residue (0, +/- 120° or +/-60, 180°) versus the perpendicular one (30, 150, -90°).[2] Both parallel conformations correspond to a twist of 60° around the C(4)-C(6) bond, both being present in the crystal, i.e., the C(5)/C(3)-C(4) bond is almost coincident with the C(6)-C(12) one in **1**, **2B**, **3/2A**, **4A** molecules while in **4B**, the C(5)-C(4) bond deviates, on average, 23.5(4)°.[13]

The bond linking the heterocycle and the carbocycle presents values close to the tabulated one [1.504(12) Å].[14] Distances and angles in the adamantyl residues are consistent with the values reported for other 1-(1-adamantyl)pyrazoles;[2,5] nevertheless, some discrepancies are displayed by molecules (**2B**) and (**4B**) due to crystallographic disorder. As far as the geometry of the pyrazole ring is concerned, some distortions are observed with regard to the geometry of pyrazole itself (**1a**).[15,16] The differences in bond distances are probably a consequence of the atomic displacement parameters of the nitrogen atoms, larger in molecules (**2**) and (**4**) than in **1** and **3**. The differences in angles, mainly at C(4) (up to 2.7°), can be due to the effect of the 4-(1-adamantyl) substituent.

As illustrated in Figure 2a, the N-H···N hydrogen bonds link the four independent molecules to form chains parallel to the **c** axis, in a manner similar to that of pyrazole itself, Figure 2b. In pairs, these bonds are respectively stronger and weaker than those of pyrazole [2.914(6), 2.902(6) Å].[16] The unit cell accommodates two centrosymmetrically related helices, Figure 2c, not bearing any significant interaction between themselves. The bulky adamantyl residue does not allow molecular stacking. In spite of the disorder and the low density of the compound, there are no voids in the structure, the packing coefficient being 0.64.[17]

The spectrum of **3a** has been recorded in the solid state (CPMAS technique). The spectrum is similar to that found in solution for the *N*-methyl derivative (**5**) (to avoid prototropic tautomerism): C_3 at 134.5

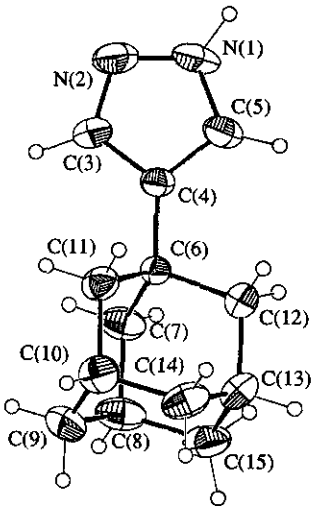
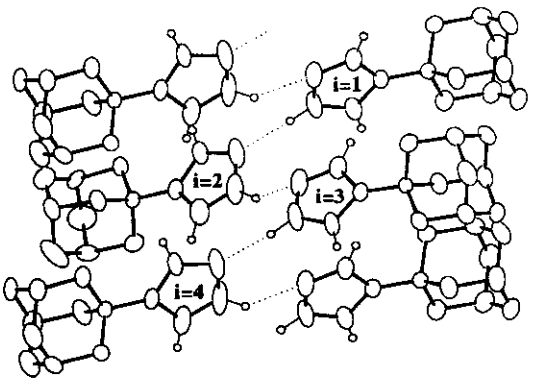


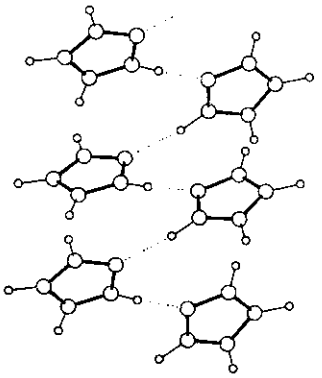
Figure 1. Molecular structure of molecule 1 showing de numbering system

Table 3. Selected bond distances, angles, torsion angles and intermolecular hydrogen bonds (Å,°).

	i=1	i=2		i=3	i=4	
		A	B		A	B
N(i01)-N(i02)	1.332(6)	1.309(7)		1.327(6)	1.304(8)	
N(i01)-C(i05)	1.343(5)	1.333(6)		1.353(5)	1.335(7)	
N(i02)-C(i03)	1.320(5)	1.323(5)		1.323(5)	1.325(5)	
C(i03)-C(i04)	1.402(5)	1.395(5)		1.406(5)	1.391(5)	
C(i04)-C(i05)	1.361(5)	1.368(5)		1.370(5)	1.367(6)	
C(i04)-C(i06)	1.512(4)	1.502(4)		1.502(4)	1.503(4)	
C(i06)-C(i07)	1.543(5)	1.534(7)	1.543(11)	1.542(5)	1.531(9)	1.544(18)
C(i06)-C(i11)	1.530(5)	1.534(6)	1.516(14)	1.527(4)	1.514(8)	1.519(25)
C(i06)-C(i12)	1.523(5)	1.549(6)	1.545(11)	1.532(5)	1.510(12)	1.559(16)
N(i02)-N(i01)-C(i05)	112.2(3)	113.3(4)		112.5(4)	112.8(4)	
N(i01)-N(i02)-C(i03)	103.8(3)	103.9(4)		104.7(3)	103.9(4)	
N(i02)-C(i03)-C(i04)	113.2(4)	112.9(4)		112.2(4)	113.3(4)	
C(i03)-C(i04)-C(i05)	102.5(3)	102.4(3)		103.5(3)	101.7(3)	
N(i01)-C(i05)-C(i04)	108.2(3)	107.6(4)		107.1(3)	108.3(5)	
C(i03)-C(i04)-C(i06)	129.0(3)	128.8(3)		127.9(3)	129.0(3)	
C(i05)-C(i04)-C(i06)	128.5(3)	128.8(3)		128.6(3)	129.2(4)	
C(i04)-C(i06)-C(i12)	110.7(3)	110.3(3)	108.9(4)	111.3(2)	110.5(4)	113.2(8)
C(i04)-C(i06)-C(i11)	110.7(3)	110.4(3)	109.8(5)	110.2(2)	109.6(4)	113.8(10)
C(i04)-C(i06)-C(i07)	110.5(3)	111.8(3)	111.1(4)	111.3(2)	109.8(4)	107.7(7)
C(i05)-C(i04)-C(i06)-C(i07)	-119.5(4)	-55.2(5)	-118.7(4)	-124.6(6)	-58.1(6)	-95.6(8)
C(i05)-C(i04)-C(i06)-C(i11)	120.6(4)	65.9(5)	121.7(4)	111.8(7)	59.7(6)	147.2(12)
C(i05)-C(i04)-C(i06)-C(i12)	0.0(5)	-174.8(4)	1.6(5)	-7.8(6)	-179.9(6)	22.4(11)
N-H···N	N-H		N···N	H···N		N-H···N
N(101)-H(101)···N(202)	*0.87(6)*		*2.856(5)*	*1.98(6)*		*159(6)*
N(201)-H(201)···N(302)	0.88(8)		3.023(5)	2.17(8)		162(7)
N(301)-H(301)···N(402)	0.84(5)		2.854(5)	2.01(5)		154(5)
N(401)-H(401)···N(102)(x,y,z+1)	0.79(8)		3.133(5)	2.39(8)		160(8)



(a)



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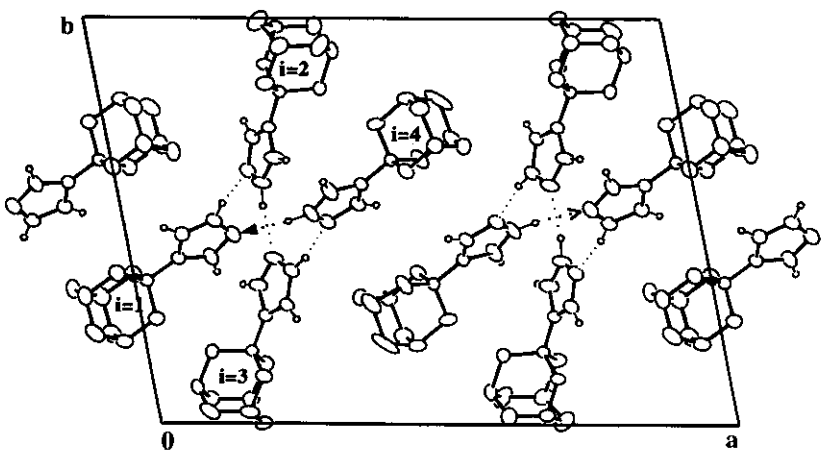

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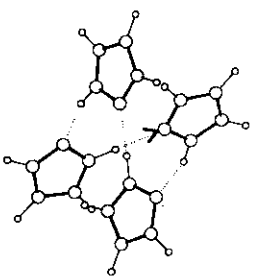

(d)

Figure 2. (a) Perspective view of the helix formed by the four independent molecules. For sake of clarity only the pyrazole hydrogen atoms and the most populated adamanthyl conformation are shown. (b) Helix of pyrazole molecules. (c) Crystal packing viewed down the c axis. (d) Analogous view for the pyrazole hydrogen bonded chain.

ppm (**5** 135.7 ppm), C_4 132.8 ppm (**5** 133.9, **3a** 132.7 ppm), C_5 123.0 and 124.4 ppm (**5** 125.6 ppm). The splitting of C_5 is certainly associated with the existence of two kinds of molecules (with ordered and disordered adamantyl residues respectively) in the crystal cell. Signals of C_3 and C_5 are broader than that of C_4. This observation together with the large thermal ellipsoids of N1 and N2 may be an indication of some disorder affecting the NH proton.

Conclusion. In conclusion, we propose i) a new method of preparation of very congested heterocycles, a subject of considerable interest: 3,4-di-(1-adamantyl)thiophene,[18] 4,5-di-(1-adamantyl)pyridazine,[18] 3,5-dimethyl-4-(1-adamantyl)pyrazole (**3c**),[10] and 1,3,4,5-tetra-*tert*-butyl-pyrazole.[19] ii) the relationships between pyrazoles *N*- and *C*-substituted by (1-adamantyl) residues and iii) the structural characteristics of one of such compounds, (**3a**).

EXPERIMENTAL

Melting points were determined in a capillary tube and are uncorrected. Column chromatography was performed on silica gel Merck 60 (70-230 mesh) using dichromethane as eluent. The Rf were measured on tlc aluminium sheets of silica gel 60 F_{254} (layer thickness 0.2 mm) either with CH_2Cl_2 or with CH_2Cl_2/EtOH (9:1) as eluents. The retention times (RT) in min were measured by gas chromatography (Hewlett Packard 5890 - series II) with a column HP-1 of cross linked methylsilicone (25 m x 0.2 mm x 0.3 mm film thickness) with a nitrogen pressure of 0.4 bar and oven temperature of 220 °C. ^{1}H Nmr (200.13 MHz) and ^{13}C nmr (50.32 MHz) spectra were obtained using a Bruker AC-200 instrument. Chemical shifts (δ) in ppm and coupling constants (J) in Hz were measured using Me_4Si as internal standard. The chemical shifts are accurate to 0.01 and 0.1 ppm for ^{1}H and ^{13}C nmr, respectively. Coupling constants are accurate to 0.2 Hz for ^{1}H nmr and 0.5 Hz for ^{13}C nmr. The starting pyrazole (**1a**), 3(5)-methylpyrazole (**1b**) and 3,5-dimethylpyrazole (**1c**) are commercial products.

General Procedure. 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 200 atm), was heated in an oven during the appropriate reaction time. Once the heating was finished, we allowed the reactor to reach room temperature and then the autoclave was opened and the reaction crude taken with 5 ml of ethanol and 500 ml 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. This procedure was followed for all compounds but **4c** and **5**.

1-(1-Adamantyl)pyrazole (**2a**). mp 51-53 °C (lit.,[1,3] 51-52 °C). Yield (isolated product) 61%. R_f (CH_2Cl_2) = 0.26; R_f (CH_2Cl_2/EtOH 9:1) 0.80, RT = 3.88.

1-(1-Adamantyl)-3-methylpyrazole (**2b**) and **1-(1-adamantyl)-5-methylpyrazole** (**2d**). Compound (**2b**). mp 83-86 °C. Yield (isolated product) 70%. R_f (CH_2Cl_2) = 0.25; R_f (CH_2Cl_2/EtOH 9:1) = 0.78; RT = 4.27. Molecular formula $C_{14}H_{20}N_2$. M^+(%) = 216 (74). Anal. Calcd for $C_{14}H_{20}N_2$: C, 77.74; H, 9.31; N, 12.95. Found: C, 77.9; H, 9.4; N, 12.8. ^{1}H-Nmr ($CDCl_3$) δ: 1.74 (6H, m, Hδ 1-Ad), 2.14 (6H, s, Hβ, 1-Ad), 2.19 (3H, s, Hγ 1-Ad), 2.29 (3H, s, 3-Me), 5.97 (1H, d, ^3J = 2.2, H_4), 7.37 (1H, d, ^3J = 2.2, H_5). ^{13}C-Nmr ($CDCl_3$) δ: 13.7 (^1J = 126.7 Hz, 3-Me), 57.7 (Cα 1-Ad), 42.8 (^1J = 129.1 Hz, Cβ 1-Ad), 29.5 (^1J = 132.8 Hz, Cγ 1-Ad), 36.1 (^1J = 128.2 Hz, Cδ 1-Ad), 147.4 (C_3), 103.7 (^1J = 173.5 Hz, ^2J = 8.0 Hz, ^3J = 3.4 Hz, C_4), 125.2 (^1J = 183.3 Hz, ^2J = 9.4 Hz, C_5). Compound (**2d**) (not isolated pure). R_f (CH_2Cl_2) = 0.23; R_f (CH_2Cl_2/EtOH 9:1) = 0.77; RT = 4.98. ^{1}H-Nmr ($CDCl_3$) δ : 1.71 (6H, m, Hδ 1-Ad), 2.11 (6H, s, Hβ 1-Ad), 2.16 (3H, s, Hγ 1-Ad), 7.30 (1H, d, ^3J = 2.0 Hz, H_3), 5.94 (1H, d, ^3J = 2.0 Hz, H_4), 2.26 (3H, s, 5-Me). ^{13}C-Nmr ($CDCl_3$) δ: 14.3 (^1J = 128.2, 5-Me), 60.5 (Cα 1-Ad), 41.8 (^1J = 129.5 Hz, Cβ 1-Ad), 29.6 (^1J = 132.2 Hz, Cγ 1-Ad), 35.9 (^1J = 127.0 Hz, Cδ 1-Ad), 136.2 (^1J = 188.4 Hz, ^2J = 5.5 Hz, C_3), 107.8 (^1J = 183.2 Hz, ^2J = 10.4 Hz, ^3J = 3.9 Hz, C_4), 137.3 (C_5).

1-(1-Adamantyl)-3,5-dimethylpyrazole (**2c**). mp 82-83 °C (lit.,[1] 81-83 °C). Yield (isolated product) 72%. R_f (CH_2Cl_2) = 0.23; R_f (CH_2Cl_2/EtOH 9:1) = 0.77; RT = 5.38.

4-(1-Adamantyl)pyrazole (**3a**). mp 200-202 °C (lit.,[9] 198-199 °C).Yield (isolated product) 78%.R_f (CH_2Cl_2) = 0.0; R_f (CH_2Cl_2/EtOH 9:1) = 0.43; RT = 6.44.

3-Methyl-4-(1-adamantyl)pyrazole (**3b**). mp 179-180 °C. Yield (isolated product) 79%.R_f (CH_2Cl_2) = 0.0; R_f (CH_2Cl_2/EtOH 9:1) = 0.42; RT = 7.99. Molecular formula $C_{14}H_{20}N_2$. M^+(%) = 216 (100). Anal. Calcd for $C_{14}H_{20}N_2$: C, 77.74; H, 9.31; N, 12.95. Found: C, 77.9; H, 9.4; N, 13.0. ^{1}H-Nmr ($CDCl_3$) δ: 10.33 (1H, s, NH), 1.74 (6H, m, Hδ 4-Ad), 1.92 (6H, s, Hβ 4-Ad), 2.03 (3H, s, Hγ 4-Ad), 2.40 (3H, s, 3-Me), 7.30 (1H, s, H_5). ^{13}C-Nmr ($CDCl_3$) δ: 13.2 (^1J = 127.4 Hz, 3-Me), 31.7 (Cα 4-Ad), 42.3 (^1J = 127.6 Hz, Cβ 4-Ad), 28.4 (^1J = 130.9 Hz, Cγ 4-Ad), 36.5 (^1J = 124.7 Hz, Cδ 4-Ad), 139.0 (C_3), 127.6 (C_4), 131.5 (^1J = 182.2 Hz, C_5).

3,5-Dimethyl-4-(1-adamantyl)pyrazole (**3c**). mp 220-221 °C (lit,[10] 220-221 °C). Yield (isolated product) 75%.R_f (CH_2Cl_2) = 0.0; R_f (CH_2Cl_2/EtOH 9:1) = 0.42; RT = 8.53.

1,4-Di-(1-adamantyl)pyrazole (**4a**). mp 257-259 °C. Yield (isolated product) 32%.R_f (CH_2Cl_2) =

0.51; R_f (CH_2Cl_2/EtOH 9:1) = 0.80; RT = 52.13. Molecular formula $C_{23}H_{32}N_2$. M^+(%) = 336 (88). Anal. Calcd for $C_{23}H_{32}N_2$: C, 82.10; H, 9.57; N, 8.32. Found: C, 82.2; H, 9.5; N, 8.4. ^{1}H-Nmr ($CDCl_3$) δ: 1.74 (6H, m, Hδ 4-Ad), 1.76 (6H, m, Hδ 1-Ad), 1.84 (6H, s, Hβ 4-Ad), 2.19 (6H, s, Hβ 1-Ad), 2.02 (3H, s, Hγ 4-Ad), 2.20 (3H, s, Hγ 1-Ad), 7.41 (1H, d, ^4J = 0.6 Hz, H_3), 7.28 (1H, d, ^4J = 0.6, H_5). ^{13}C-Nmr ($CDCl_3$) δ : 57.7 (Cα 1-Ad), 42.6 (^1J = 129.0 Hz, Cβ 1-Ad), 29.3 (^1J = 134.4 Hz, Cγ 1-Ad), 35.9 (^1J = 130.6, Cδ 1-Ad), 31.0 (Cα 4-Ad), 44.0 (^1J = 125.1 Hz, Cβ 4-Ad), 28.5 (^1J = 136.2 Hz, Cγ 4-Ad), 36.5 (^1J = 125.8 Hz, Cδ 4-Ad), 134.6 (^1J = 188.7 Hz, ^3J = 8.1 Hz, C_3), 132.1 (C_4), 120.1 (^1J = 185.7 Hz, ^3J = 4.1 Hz, C_5).

1,4-Di-(1-adamantyl)-3-methylpyrazole (**4b**). mp 182-185 °C. Yield (isolated product) 23%.R_f (CH_2Cl_2) = 0.50; R_f (CH_2Cl_2/EtOH 9:1) = 0.78; RT = 61.21. Molecular formula $C_{24}H_{34}N_2$. M^+(%) = 350 (100). Anal. Calcd for $C_{24}H_{34}N_2$: C, 82.24; H, 9.77; N, 7.99. Found: C, 82.2; H, 9.7; N, 8.1. ^{1}H-Nmr ($CDCl_3$) δ: 1.73 (6H, m, Hδ 1-Ad), 1.74 (6H, m, Hδ 4-Ad), 1.88 (6H, s, Hβ 4-Ad), 2.10 (6H, s, Hβ 1-Ad), 2.01 (3H, s, Hγ 4-Ad), 2.18 (3H, s, Hγ 1-Ad), 2.36 (3H, s, 3-Me), 7.13 (1H, s, H_5). ^{13}C-Nmr ($CDCl_3$) δ: 15.0 (^1J = 126.5, 3-Me), 57.1 (Cα 1-Ad), 42.6 (^1J = 129.3 Hz, Cβ 1-Ad), 28.5 (^1J = 132.6 Hz, Cγ 1-Ad), 36.6 (^1J = 127.0, Cδ 1-Ad), 31.8 (Cα 4-Ad), 42.2 (^1J = 126.8 Hz, Cβ 4-Ad), 29.3 (^1J = 133.3 Hz, Cγ 4-Ad), 36.0 (^1J = 126.7 Hz, Cδ 4-Ad), 143.6 (C_3), 127.6 (C_4), 121.6 (^1J = 180.8 Hz, C_5).

1,4-Di-(1-adamantyl)-3,5-dimethylpyrazole (**4c**). This compound was prepared by adamantylation of (**3c**). A mixture of 2.76 g (12 mmol) of **3c** and 1.29 g (6 mmol) of 1-bromoadamantane was heated with magnetical stirring 4 h at 240 °C. Purification was carried out by column chromatography (eluent: dichloromethane). mp 200-202 °C. Yield (isolated product) 415 mg, (19%). R_f (CH_2Cl_2) = 0.48; R_f (CH_2Cl_2/EtOH 9:1) = 0.77; RT = 67.13. Molecular formula $C_{25}H_{36}N_2$ M^+(%) = 364 (21). Anal. Calcd for $C_{25}H_{36}N_2$: C, 82.38; H, 9.94; N, 7.68. Found: C, 82.5; H, 10.1; N, 7.7. ^{1}H-Nmr ($CDCl_3$) δ: 1.74 (12H, m, Hδ 1-Ad + 4-Ad), 2.04 (9H, s, Hβ + Hγ 4-Ad), 2.19 (3H, s, Hγ 1-Ad), 2.31 (6H, s, Hβ 1-Ad), 2.36 (3H, s, 3-Me), 2.56 (3H, s, 5-Me). ^{13}C-Nmr ($CDCl_3$) δ: 15.5 (^1J = 111.2, 3-Me), 17.1 (^1J = 110.9, 5-Me), 60.4 (Cα 1-Ad), 42.3 (^1J = 126.5 Hz, Cβ 1-Ad), 28.7 (^1J = 132.5 Hz, Cγ 1-Ad), 36.7 (^1J = 127.6, Cδ 1-Ad), 34.0 (Cα 4-Ad), 41.8 (^1J = 126.7 Hz, Cβ 4-Ad), 29.8 (^1J = 133.3 Hz, Cγ 4-Ad), 36.0 (^1J = 126.7 Hz, Cδ 4-Ad), 141.9 (C_3), 124.3 (C_4), 134.8 (C_5).

1-Methyl-4-(1-adamantyl)pyrazole (**5**). This compound was prepared by methylation of 0.789 g (3.9 mmol) of **3a** with 0.568 g (4.0 mmol) of methyl iodide in acetone and in the presence of potassium hydroxide (0.224 g, 4.0 mmol) and potassium carbonate (0.553 g, 4.0 mmol). The reaction mixture was filtered off, the solvent evaporated at room temperature under reduced pressure and the residue

distilled. Liquid, $bp_{0.1}$ = 120 °C (Kugelrohr Büchi GKR-50). Yield (isolated product) 126.5 mg, (15 %). R_f (CH_2Cl_2) = 0.25; R_f (CH_2Cl_2/EtOH 9:1) = 0.68; RT = 5.50. Molecular formula $C_{14}H_{20}N_2$. M^+(%) = 216 (100). Anal. Calcd for $C_{14}H_{20}N_2$: C, 77.74; H, 9.31; N, 12.95. Found: C, 77.7; H, 9.2; N, 13.0. ^{1}H-Nmr ($CDCl_3$) δ: 3.84 (3H, s, 1-Me), 1.73 (6H, m, Hδ 4-Ad), 1.81 (6H, s, Hβ 4-Ad), 2.01 (3H, s, Hγ 4-Ad), 7.35 (1H, s, H_3), 7.10 (1H, s, H_5). ^{13}C-Nmr ($CDCl_3$) δ:38.6 (^1J = 139.3 Hz, 1-Me), 31.1 (Cα 4-Ad), 44.1 (^1J = 128.9 Hz, Cβ 4-Ad), 28.6 (^1J = 136.4 Hz, Cγ 4-Ad), 36.6 (^1J = 126.8 Hz, Cδ 4-Ad), 135.7 (^1J = 181.6 Hz, ^3J = 7.8 Hz, C_3), 133.9 (C_4), 125.6 (^1J = 182.8 Hz, ^3J = 3.8 Hz, C_5).

Table 4. Crystal analysis parameters at room temperature

Crystal data			
Chemical formula	$C_{13}H_{18}N_2$	Crystal system	Triclinic
Mr	202.30	Space group	*P–1*
a (Å)	21.9046(21)	α (°)	93.406(5)
b (Å)	16.1551(16)	β (°)	93.651(5)
c (Å)	6.6044(2)	γ (°)	101.032(10)
Z	8	*Dx* (gr/m^3)	1.177
V (Å^3)	2283.1(3)	Radiation	CuKα
Wavelength (Å)	1.5418	No. of reflections for	
θ range for lattice parameters (°)	2-45	lattice parameters:	73
Absorption coefficient (cm^{-1})	5.04	Temperature (K)	295
Crystal colour	colorless	Crystal description	prism
Crystal size (mm)	0.50 x 0.33 x 0.17		
Data collection			
Diffractometer type	Philips PW1100		
Collection method	ω/2θ scans	θ_{max} (°)	65
No. of independent reflections	6737	No. of observed reflections, I>3σ(I)	5250
No. of standard reflections (interval)	2 (90 min.). No variation		
Refinement			
Treatment of hydrogen atoms	all refined*	Refinement: Least-Squares on *Fo*. 5 blocks.*	
R	0.085	No. of parameters refined	873
wR	0.093	Degrees of freedom	4377
$(\Delta\rho)_{max}$ (e/Å^3)	0.44	Ratio of freedom	6.0
<Shift/error>	0.34	Max. thermal value (Å^2)	U22[C(409B)]=0.55(13)
Weighting scheme: Empirical as to give no trends in <ωΔ^{2}F> vs. <|Fobs|> and <sinθ/λ>.			

*See text.

X-Ray structure determination. The parameters of data collection and details of refinement are summarized in Table 4. The spectrum was collected in a four-circle Philips PW1100 diffractometer with graphite oriented monochromator, detector apertures of 1° x 1°, 1 min/reflection and scan width of 1.5°. The structure was solved by direct methods[20] and the refinements were carried out by block matrix least-squares methods on F. There are four molecules in the asymmetric unit and the adamantyl moieties of molecules (**2**) and (**4**) appear to be disordered. The occupancy factors refined to 2/3 and 1/3 for both molecules, see Table 5. Only those hydrogen atoms not involved in the

disorder were located in a Fourier difference synthesis. Five reflections were affected by secondary extinction and were considered as unobserved in the last cycles of refinement. The scattering factors were taken from the *International Tables*.[21] The positional and the equivalent isotropic parameters are listed in Table 5. The calculations were carried out on a Vax 6410 computer using the XRAY80,[22] and PARST[23] programs. Tabulations of hydrogen atomic coordinates, anisotropic thermal parameters and structure factors are available from one of the authors (C.F-F.).

Table 5. Final atomic coordinates and Ueq=(1/3)Σ[Uij·a_i*·a_j*·a_i·a_j·cos(a_i,a_j)]x10^3

Atom	x	y	z	Ueq	Atom	x	y	z	Ueq
N(101)	0.1586(2)	0.5015(2)	−0.1584(6)	78(1)	N(301)	0.2765(1)	0.3788(2)	0.3621(7)	81(1)
N(102)	0.1864(1)	0.4673(2)	−0.3067(6)	81(1)	N(302)	0.2502(2)	0.4092(2)	0.2036(7)	89(1)
C(103)	0.1408(2)	0.4113(2)	−0.4053(6)	71(1)	C(303)	0.2145(2)	0.3422(2)	0.1030(7)	74(1)
C(104)	0.0833(1)	0.4077(2)	−0.3212(5)	51(1)	C(304)	0.2173(1)	0.2673(2)	0.1982(5)	49(1)
C(105)	0.0977(2)	0.4669(2)	−0.1613(6)	65(1)	C(305)	0.2574(2)	0.2943(2)	0.3671(6)	64(1)
C(106)	0.0209(1)	0.3516(2)	−0.3888(4)	43(1)	C(306)	0.1823(1)	0.1794(2)	0.1333(4)	40(1)
C(107)	0.0252(2)	0.2576(2)	−0.3819(6)	67(1)	C(307)	0.2013(2)	0.1482(2)	−0.0743(5)	61(1)
C(108)	−0.0380(2)	0.2009(2)	−0.4510(8)	80(2)	C(308)	0.1642(2)	0.0591(2)	−0.1398(5)	63(1)
C(109)	−0.0569(2)	0.2187(3)	−0.6681(7)	84(2)	C(309)	0.0950(2)	0.0601(2)	−0.1570(5)	65(1)
C(110)	−0.0631(2)	0.3104(3)	−0.6727(5)	72(1)	C(310)	0.0756(1)	0.0889(2)	0.0458(6)	65(1)
C(111)	*0.0001(2)*	*0.3669(2)*	*−0.6066(5)*	*63(1)*	C(311)	0.1123(1)	0.1776(2)	0.1129(6)	58(1)
C(112)	−0.0288(2)	0.3688(2)	−0.2497(6)	67(1)	C(312)	0.1949(2)	0.1165(2)	0.2880(5)	60(1)
C(113)	−0.0916(2)	0.3114(3)	−0.3179(7)	77(1)	C(313)	0.1579(2)	0.0275(2)	0.2202(6)	71(1)
C(114)	−0.1106(2)	0.3291(3)	−0.5308(8)	82(2)	C(314)	0.0889(2)	0.0287(3)	0.2034(6)	79(1)
C(115)	−0.0862(2)	0.2207(3)	−0.3103(7)	87(2)	C(315)	0.1778(2)	−0.0011(2)	0.0177(7)	77(1)
N(201)	0.2547(2)	0.5959(2)	0.2949(9)	98(2)	N(401)	0.3302(2)	0.5213(3)	0.8070(10)	112(2)
N(202)	0.2346(2)	0.6244(2)	0.1269(8)	86(1)	N(402)	0.3554(2)	0.5006(2)	0.6425(8)	91(2)
C(203)	0.2536(2)	0.7074(2)	0.1559(6)	67(1)	C(403)	0.4133(2)	0.5445(2)	0.6684(6)	67(1)
C(204)	0.2861(1)	0.7324(2)	0.3449(5)	53(1)	C(404)	0.4259(1)	0.5937(2)	0.8519(5)	54(1)
C(205)	0.2854(2)	0.6570(2)	0.4291(8)	90(2)	C(405)	0.3699(2)	0.5756(3)	0.9363(9)	97(2)
C(206)	0.3167(1)	0.8198(2)	0.4304(4)	41(1)	C(406)	0.4849(1)	0.6534(2)	0.9324(4)	42(1)
C(207A)*	0.2955(3)	0.8402(3)	0.6414(9)	72(2)	C(407A)#	0.4720(4)	0.7428(5)	0.9669(17)	80(3)
C(208A)*	0.3322(3)	0.9321(4)	0.7226(8)	78(2)	C(408A)#	0.5333(6)	0.8056(5)	1.0503(27)	84(4)
C(209A)*	0.4018(4)	0.9332(6)	0.7395(14)	111(3)	C(409A)#	0.5535(9)	0.7803(10)	1.2454(33)	110(6)
C(210A)*	0.4205(2)	0.9208(4)	0.5254(12)	79(2)	C(410A)#	0.5670(4)	0.6904(6)	1.2230(14)	67(3)
C(211A)*	0.3879(2)	0.8290(3)	0.4475(9)	66(2)	C(411A)#	0.5073(3)	0.6272(5)	1.1359(12)	63(2)
C(212A)*	0.2998(2)	0.8866(3)	0.2891(8)	60(2)	C(412A)#	0.5351(6)	0.6529(9)	0.7861(14)	89(4)
C(213A)*	0.3317(3)	0.9774(3)	0.3832(9)	65(2)	C(413A)#	0.5996(6)	0.7020(10)	0.8821(26)	92(4)
C(214A)*	0.3984(3)	0.9801(4)	0.3914(11)	80(2)	C(414A)#	0.6155(5)	0.6882(7)	1.0904(30)	89(4)
C(215A)*	0.3066(9)	0.9914(10)	0.5830(27)	79(6)	C(415A)#	0.5862(11)	0.7988(13)	0.8936(26)	110(7)
C(207B)*	0.2690(4)	0.8787(5)	0.4381(18)	59(3)	C(407B)#	0.4856(7)	0.7383(9)	0.8357(36)	87(6)
C(208B)*	0.3056(7)	0.9695(12)	0.5191(31)	61(6)	C(408B)#	0.5484(10)	0.8076(12)	0.9231(53)	82(9)
C(209B)*	0.3546(10)	1.0012(7)	0.3728(25)	118(7)	C(409B)#	0.5421(19)	0.7964(57)	1.1683(105)	323(51)
C(210B)*	0.4086(5)	0.9489(11)	0.3780(25)	105(6)	C(410B)#	*0.6090(21)*	*0.6929(59)*	*0.9908(113)*	*280(53)*
C(211B)*	0.3704(7)	0.8547(8)	0.3062(19)	85(5)	C(411B)#	0.5439(10)	0.6246(15)	0.8744(55)	103(12)
C(212B)*	0.3419(5)	0.8153(6)	0.6525(16)	63(4)	C(412B)#	0.4892(12)	0.6726(17)	1.1675(23)	116(9)
C(213B)*	0.3768(4)	0.9156(9)	0.7355(14)	71(4)	C(413B)#	0.5541(21)	0.7491(39)	1.2432(45)	181(22)
C(214B)*	0.3244(6)	0.9577(11)	0.7505(24)	88(6)	C(414B)#	0.5964(24)	0.6969(28)	1.2290(99)	250(27)
C(215B)*	0.4289(6)	0.9334(9)	0.6136(20)	82(5)	C(415B)#	0.5961(14)	0.7560(30)	0.8521(42)	93(11)

*Population parameter: pp(A)=0.66(2), pp(B)=1−pp(A)
#Population parameter: pp(A)=0.65(2), pp(B)=1−pp(A)

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