β-Aminoenones in the regioselective synthesis of 1,3,5-trialkylpyrazoles. The influence of the substituents in the mechanism and the regioselectivity of the reaction

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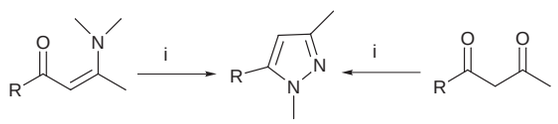
β-Aminoenones react with monoalkyl hydrazines to give regioselectively 1,3,5-trisubstituted pyrazoles. The mechanism and level of regioselectivity depend on both the substitution pattern of the substrates and the reaction conditions. When the least bulky substituent is attached at the β-position of the enone, a high regioselectivity is obtained, usually higher than that from equivalent β-diketones. If the β-substituent is the bulkiest group, the regioselectivity decreases. Nevertheless, in the conditions reported in this paper, it is possible to prepare pyrazoles not obtainable from β-diketones.

Introduction

The synthesis of pyrazoles starting from β-aminoenones has been previously reported.[1–4] In the cited β-aminoenones, the substituent α to the carbonyl group was normally an aromatic system or the bulkiest alkyl group. Their reaction with monosubstituted hydrazines lead regioselectively to a pyrazole with the bulky group at C-5, the same result as that obtained from their equivalent β-dicarbonyl compounds.

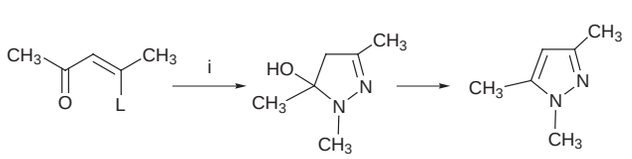


Reagent: i, NH_2–NH–.

Given that the type of substitution may be the cause of the observed selectivity, this paper studies the scope and limitations of the synthetic method, starting not only from the β-aminoenones normally used until now, but also from their regioisomers which should lead to other pyrazoles which are difficult to obtain from β-diketones. We also attempt to establish the reaction mechanism with the aims of justifying the observed results and predicting future behaviour.

Results and discussion

Preliminary experiments indicated that the nature of the nitrogen leaving group, together with the hydrazine substituent, solvent and catalyst have an important influence on the process. We studied their influence with acetylacetone derivatives (**1a**, L = NHC_6H_5; **1b**, L = $N(CH_2)_4$ and **1c**, L = NH_2), given that these compounds lead to a single pyrazole **3** (Scheme 1) which potentially makes it easier to identify the possible reaction intermediates.

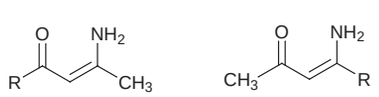


1a L= NHC_6H_5
1b L= $N(CH_2)_4$
1c L= NH_2

Scheme 1 *Reagents*: i, CH_3NHNH_2.

Their reactions with methylhydrazine in a solution of deuterated dimethyl sulfoxide were monitored by ^{1}H-NMR spectroscopy. The substrate reactivity was observed to change depending on L in the order: **1a** > **1b** > **1c**. In each case we detected the presence of 1,3,5-trimethyl-5-hydroxy-4,5-dihydro-1*H*-pyrazoline **2** as the only quantitatively significant intermediate. Given that the transformation into 1,3,5-trimethylpyrazole **3** (2nd step) is common to the three cases, the proportion of **2** is greater when the rate of the first step rises. In those experiments at temperatures above 20 °C or catalysed by deuterated hydrochloric or acetic acid or in deuterated methanol solution, the acceleration of the second step was greater than the first. As a consequence, the concentration of **2** decreased to levels where it was difficult to detect by ^{1}H-NMR spectroscopy.

The variety of factors which influence the process makes it advisable to pre-set some of them in order to investigate the regioselectivity. Thus, the convenience of comparing the effect of a single leaving group in all the substrates conditioned our choice. Although L = NH_2 is not the most efficient leaving group, it is the one which most easily allows the preparation of pairs of regioisomeric β-aminoenones by hydrogenation of the corresponding isoxazoles.[5] Their reactivity in dimethyl sulfoxide was considered sufficient and we resorted to other conditions only in extreme cases of low selectivity or reactivity. On the other hand, initially we only worked with alkyl-β-aminoenones (**1c**, **4**–**9**) to ensure that the influence exerted by the substituents of both substrates was due to steric effects.



4 R= $(CH_2)_2$-Ph
5 R= Pr^i
6 R= Bu^t

7 R= $(CH_2)_2$-Ph
8 R= Pr^i
9 R= Bu^t

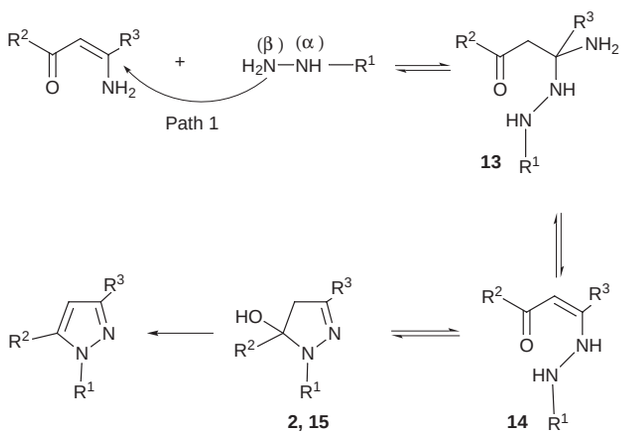
The β-aminoenones **4**, **5** and **6**, in which the β-substituent was the least bulky group (Me), reacted with alkylhydrazines (R^1 = Me, Bn, Bu^t) in dimethyl sulfoxide to yield pyrazoles **10** with a regioselectivity of over 90% (Table 1). We only observed the appearance of the regioisomer of the pyrazole **10** in the

reaction of methylhydrazine with **6** (86% of **10k**, 9% of **11k**, R^1 = Me, R = Bu^t).

When we moved from studying the β-aminoenones **4**, **5** and **6** to their regioisomers **7**, **8** and **9**, with a bulkier β-substituent, a decrease in reactivity was observed, but more important than this decrease in reactivity was the drop in regioselectivity. This phenomenon was greater when R and the alkylhydrazine were bulkier. Thus, while the selectivity in the preparation of **11e** [R^1 = Me, R = Ph(CH$_2$)$_2$], **11h** (R^1 = Me, R = Pr^i) and **11k** (R^1 = Me, R = Bu^t) may be considered very good, in **11l** (R^1 = Bn, R = Bu^t) it decreased to 2.4:1 (**11l**:**10l**) and in **11j** (R^1 = Bu^t, R = Pr^i) it was reversed to 1:9 (**11j**:**10j**) (Table 2). Various exploratory experiments were carried out with the aim of increasing the proportion of pyrazoles **11g** and **11j**, and this allowed us to establish that the selectivity improves if the reactions are catalysed with acetic acid either in dimethyl sulfoxide or ethanol. The decrease in reactivity of **7**, **8** and **9** can be compensated with a temperature increase, but a diminution in the proportion of the desired pyrazole takes place.

The mechanisms for this reaction which theoretically can be advanced are numerous, and are analogous to those previously reported for β-diketones.[6–10] We have studied the reactivity of the pairs **5**,**8** and **6**,**9** by ^{1}H-NMR (DMSO-d_6) spectroscopy and the information obtained from the relationship of the resulting regioisomeric pyrazoles, the relative rates of reaction and the identification of some of the intermediates allowed us to establish the most probable mechanism of these reactions (Schemes 2 and 3).

The process starts preferably by a conjugate addition of hydrazine nitrogen Nβ to the enone (Path 1, Scheme 2) to give the intermediate **13**, which rapidly evolves into **14** or **15**.

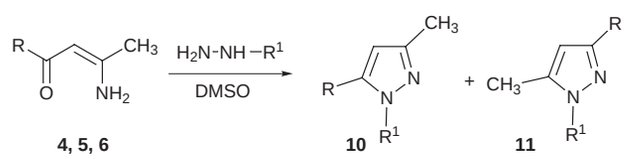


Scheme 2

If the R^1 and R^2 substituents are very bulky the cyclization is difficult and the reaction is partially stopped at intermediate **14** which very slowly transforms into the pyrazole. This behaviour can be seen in the evolution of the intermediate **14m** (R^1 = R^2 = Bu^t, R^3 = Me).

When one or both R^1 and R^2 substituents are less bulky, cyclization is easier and in several cases we were able to confirm the presence of pyrazoline intermediates. Thus, in the reactions of enones **1c**, **5** and **6** with methylhydrazine, 5-hydroxy-1,3,5-trimethyl-4,5-dihydro-1*H*-pyrazoline **2**, 1,3-dimethyl-5-hydroxy-5-isopropyl-4,5-dihydro-1*H*-pyrazoline **15h** and 5-*tert*-butyl-1,3-dimethyl-5-hydroxy-4,5-dihydro-1*H*-pyrazoline **15k** were clearly detected by ^{1}H-NMR. Its rate of transformation into pyrazole derivatives is dependent upon the steric hindrance: when this increases, the approach of the base (ammonia or methylhydrazine) at H-4 is more difficult during

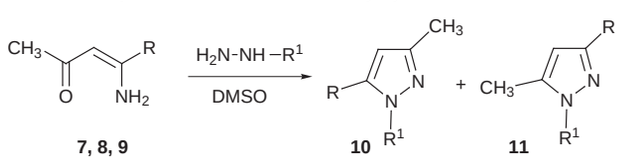
Table 1 Preparation of pyrazoles **3** and **10e**–**m** from β-aminoenones **1c**, **4**–**6** and alkylhydrazines



Starting material	R	R^1	*T*/°C	*t*/h	Yield (%)[a] [%][b]
1c	Me	Me	20	95	**3** (93) [77]
4	Ph(CH$_2$)$_2$	Me	80	12	**10e** (93) [81]
4	Ph(CH$_2$)$_2$	Bn[c]	20	2	**10f** (95) [83]
4	Ph(CH$_2$)$_2$	Bu^t[d]	37	72	**10g** (93) [78]
5	Pr^i	Me	80	16	**10h** (92) [84]
5	Pr^i	Bn[c]	20	2	**10i** (97) [83]
5	Pr^i	Bu^t[d]	60	48	**10j** (95) [86]
6	Bu^t	Me	80	16	**10k** (86) [72]
					11k (9) [—]
6	Bu^t	Bn	20	2	**10l** (98) [86]
6	Bu^t	Bu^t[d]	37	150	**10m** (78) [86][e]

[a] Estimated from NMR spectra of the reaction mixture. [b] Isolated yield. [c] Oxalate derivative. [d] Hydrochloride derivative. [e] The pyrazole **10m** is partially transformed (10%) into 3(5)-*tert*-butyl-5(3)-methylpyrazole **12**.

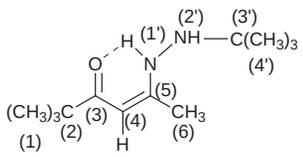
Table 2 Preparation of the pyrazoles **11e**–**l** from β-aminoenones **7**–**9** and alkylhydrazines



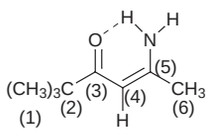
Starting material	R	R^1	*T*/°C	*t*/h	**11**:**10** (%)[a]	Pyrazole (%)[b]
7	Ph(CH$_2$)$_2$	Me	80	16	1:0 (92)	**11e** (81)
7	Ph(CH$_2$)$_2$	Bn[c]	20	20	6:1 (91)	**11f** (69)
7	Ph(CH$_2$)$_2$	Bu^t[d]	80	40	1:1.4 (86)	**11g** (23)
						10g (38)
7[e,f]	Ph(CH$_2$)$_2$	Bu^t[d]	80	40	1:0 (86)	**11g** (71)
8	Pr^i	Me	80	20	1:0 (85)	**11h** (71)
8	Pr^i	Bn[c]	20	24	8:1 (92)	**11i** (73)
8	Pr^i	Bu^t[d]	80	48	1:9 (86)	**11j** (—)
						10j (71)
8[g]	Pr^i	Bu^t[d]	80	48	6:1 (89)	**11j** (63)
9	Bu^t	Me	80	20	11:1 (83)	**11k** (65)
9	Bu^t	Bn[d]	80	30	2.4:1 (85)	**11l** (49)

[a] Total yield estimated from NMR of the reaction mixture. [b] Isolated yield. [c] Oxalate derivative. [d] Hydrochloride derivative. [e] In EtOH–AcOH (3:1). [f] Ratio **7**:*tert*-butylhydrazine, 1:3. [g] In DMSO–AcOH (3:1).

Table 3 ^{1}H and ^{13}C NMR data for **14m** and **6**



14m



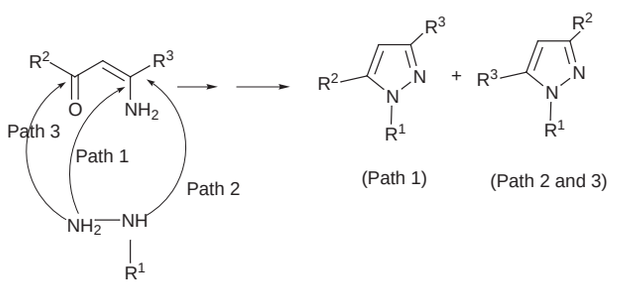
6

	δ_H					
	H-1	H-4	H-6	H-1′	H-2′	H-4′
14m	0.97	4.97	1.91	11.73	4.79	1.00
6	0.98	5.02	1.81	9.53, 4.79	—	—

	δ_C							
	C(1)	C(2)	C(3)	C(4)	C(5)	C(6)	C(3′)	C(4′)
14m	27.94	40.34	200.09	87.99	165.83	18.40	53.37	26.73
6	27.72	40.84	202.25	88.99	162.78	21.71	—	—

dehydration [10] and, moreover, the coplanarity of R^1 and R^2 will be even harder to obtain. The intermediate **15k** (R^1 = Me, R^2 = Bu^t) evolves so slowly that it becomes the rate-determining step.

The decrease in the rate of the mechanism which seems to have priority (Scheme 2), allows the appearance of the regioisomeric pyrazole *via* Paths 2 and 3 (Scheme 3).



Scheme 3

Thus, when the size of R^3 and R^1 increases, the conjugate addition becomes more difficult (Paths 1 and 2), allowing the initial attack of Nβ at the carbonyl group (Path 3). The variation in regioselectivity which we observed, starting from the enones **7**, **8** and **9** (Table 2), can be explained as a consequence of the competitive action of this mechanism.

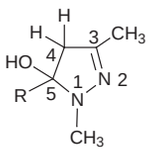
The same pyrazole can also be formed *via* an initial conjugated addition of Nα (Path 2). This will mainly occur when R^3 and R^1 are not very bulky [1,9] and the large size of R^2 retards the aromatization stage of the main process. In the reaction conditions, this mechanism appears to take place in a short extension. The formation of **14k** (9%) from **6** and methylhydrazine (Table 1) is a possible example of this behaviour.

Characterization of reaction intermediates

Detection by NMR confirms the presence of intermediates in numerous reactions. However, their structures can only be unequivocally established in those cases in which sufficient concentrations of the compounds are found and, moreover, their signals do not overlap or mask those of other compounds. In this respect, the intermediates **14m**, **2** and **15k** are especially interesting (Tables 3 and 4).

Contrary to that described by some authors [10] (for the derivatives of 4-nitrophenylhydrazine) the intermediate **14m** does not appear to be a hydrazone but rather its ene hydrazine tautomer. The spectrum, in which an olefinic methine (and not methylene) is observed, is comparable to that of the enone **6** from which it proceeds (Table 3).

Table 4 ^{1}H and ^{13}C NMR data for compounds **2** and **15k**

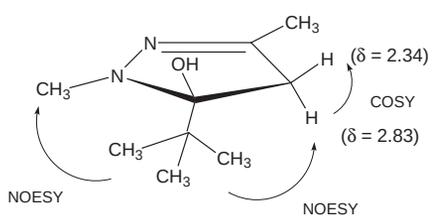


2, 15k

	δ_H			
	CH_3-N	CH_3-3	CH_2	R
2	2.59 s	1.81 s	2.50 d, 2.47 d, J = 16 Hz	1.34 s
15k	2.64 s	1.77 s	2.83 d, 2.34 d, J = 16 Hz	0.90 s

	δ_C					
	CH_3-N	C(3)	CH_3-3	C(4)	C(5)	R
2	32.91	147.91	15.99	50.59	92.67	24.04
15k	36.48	146.24	15.74	47.26	98.53	33.63, 26.43

On the other hand, the spectra of hydroxypyrazolines **2** and **15k** are similar to those reported in the literature for analogous compounds (Table 4).[6,8,10] The regioisomer pyrazoline of **15k** can be discarded because of the difference in the ^{1}H-chemical shift of the substituents CH_3-3 (sp^2) and CH_3-5 (sp^3) (see CH_3-3 and CH_3-5 in **2**, Table 4). Furthermore, the high yield of **2** and **15k** which can be detected starting from **1a** and **6** respectively (NMR experiments at 0–5 °C) allowed us to carry out NOESY, COSY experiments and inverse correlations which confirmed the structure and also allowed us to assign the *cis*- and *trans*-hydrogens at C-4.



15k

The similarity of the H-chemical shift observed in different 2-pyrazolines for CH_3-N and 3-CH_3-(sp^2) and the chemical shifts of 5-Pr^i-(sp^3) were used to detect and monitor the intermediate **15h**.

Conclusion

From a preparative point of view we can conclude that the reaction of β-aminoenones with monoalkylhydrazines in dimethyl sulfoxide solution can be widely used in the regioselective synthesis of 1,3,5-trialkylpyrazoles, many of which could not be prepared from β-diketones. As a limitation of the procedure, we should make reference to the β-aminoenones of the **7**–**9** type when they react with very bulky hydrazines (*e.g. tert*-butylhydrazine). In these cases the selectivity improves if the reactions are catalysed with acetic acid, whether in dimethyl sulfoxide or in ethanol.

Experimental

Melting points were measured on a Reichert-Jung Thermo Galen and are uncorrected. Boiling points correspond to the oven temperature in a Kugelrohr GKR-51. NMR spectra were recorded on a Bruker AC300 spectrometer, and chemical shifts are given downfield from $SiMe_4$ as an internal standard; ^{13}C-NMR spectra were carried out with complete ^{1}H decoupling and the assignments were made by additional DEPT experiments. Mass spectra were measured on a Hewlett-Packard 5988A mass spectrometer.

Starting compounds were prepared as previously described. Synthesis of **1a**, **1b** and **1c** involves the condensation of ammonia or amines with β-diketones.[11] β-Aminoenones **4**–**9** were obtained by catalytic hydrogenation[4,5,12] of 3,5-dialkylisoxazoles: these were prepared regioselectively by the procedure of Nitz *et al.*[13] from oximes and *N*-methoxy-*N*-methylalkylamides.

Reaction of β-aminoenones with monoalkylhydrazines. Synthesis of 1,3,5-trialkylpyrazoles

A mixture of β-aminoenone (2.8 mmol) and the hydrazine derivative (3.4 mmol) in 4 cm^3 of dimethyl sulfoxide were stirred under the conditions given in Tables 1 and 2. The solution was poured into water (20 cm^3) and extracted with methylene dichloride (3 × 20 cm^3). The organic layer was dried over anhydrous magnesium sulfate and the solvent was removed *in vacuo*. The residue was purified by recrystallization from hexane–toluene (**10e**, **10g** and **11e**), distillation (**10f**, **10h**, **10i**, **10j** and **10l**) or chromatographed on silica gel with methylene dichloride or methylene dichloride–diethyl ether (20:1) as eluents (**10k**, **10m**, **11f**, **11g**, **11h**, **11i**, **11j**, **11k** and **11l**).

1,3-Dimethyl-5-(2-phenylethyl)pyrazole 10e. Yield 81% (Table 1), mp 81–82 °C (Found: C, 77.85; H, 8.09; N, 14.06; $C_{13}H_{16}N_2$ requires C, 77.96; H, 8.05; N, 13.99%); δ_H(300 MHz; $CDCl_3$) 2.22 (3H, s), 2.88 (4H, m, A_2B_2), 3.58 (3H, s), 5.83 (1H, s) and 7.15–7.32 (5H, m); δ_C(75.4 MHz; $CDCl_3$) 13.5 (CH_3), 27.7 (CH_2), 35.1 (CH_2), 35.5 (CH_3), 103.8 (CH), 126.3 (CH), 128.3 (CH), 128.5 (CH), 140.7 (C), 142.8 (C) and 147.0 (C); *m*/*z* 200 (M^+, 23%) and 109 (100).

1-Benzyl-3-methyl-5-(2-phenylethyl)pyrazole 10f. Yield 83% (Table 1), bp 160–163 °C at 0.4 mmHg (Found: C, 82.62; H, 7.27; N, 10.11; $C_{19}H_{20}N_2$ requires C, 82.57; H, 7.29; N, 10.14%); δ_H(300 MHz; $CDCl_3$) 2.27 (3H, s), 2.77 (4H, m, A_2B_2), 5.14 (2H, s), 5.90 (1H, s) and 7.01–7.30 (10H, m); δ_C(75.4 MHz; $CDCl_3$) 13.5 (CH_3), 27.4 (CH_2), 34.8 (CH_2), 52.5 (CH_2), 104.5 (CH), 126.2 (CH), 126.4 (CH), 127.4 (CH), 128.2 (CH), 128.4 (CH), 128.6 (CH), 137.4 (C), 140.6 (C), 143.1 (C) and 147.5 (C); *m*/*z* 276 (M^+, 7%) and 91 (100).

1-*tert*-Butyl-3-methyl-5-(2-phenylethyl)pyrazole 10g. Yield 78% (Table 1), mp 87–89 °C (Found: C, 79.29; H, 9.11; N, 11.60; $C_{16}H_{22}N_2$ requires C, 79.29; H, 9.15; N, 11.56%); δ_H(300 MHz; $CDCl_3$) 1.61 (9H, s), 2.23 (3H, s), 3.01 (4H, m, A_2B_2), 5.95 (1H, s) and 7.22–7.34 (5H, m); δ_C(75.4 MHz; $CDCl_3$) 13.6 (CH_3), 30.2 (CH_2), 30.3 (CH_3), 35.6 (CH_2), 59.1 (C), 105.9 (CH), 126.2 (CH), 128.2 (CH), 128.5 (CH), 141.1 (C), 142.7 (C) and 144.8 (C); *m*/*z* 242 (M^+, 6%) and 95 (100).

1,3-Dimethyl-5-isopropylpyrazole 10h. Yield 84% (Table 1), bp 75–78 °C at 5.5 mmHg (Found: C, 69.52; H, 10.16; N, 20.32; $C_8H_{14}N_2$ requires C, 69.52; H, 10.21; N, 20.27%); δ_H(300 MHz; $CDCl_3$) 1.23 (6H, d, *J* 6.9), 2.22 (3H, s), 2.88 (1H, m, *J* 6.9), 3.74 (3H, s) and 5.80 (1H, s); δ_C(75.4 MHz; $CDCl_3$) 13.4 (CH_3), 22.3 (CH_3), 25.4 (CH), 35.6 (CH_3), 101.2 (CH), 147.0 (C) and 150.0 (C); *m*/*z* 138 (M^+, 26%) and 123 (100).

1-Benzyl-5-isopropyl-3-methylpyrazole 10i. Yield 83% (Table 1), bp 105–110 °C at 0.3 mmHg (Found: C, 78.39; H, 8.50; N, 13.11; $C_{14}H_{18}N_2$ requires C, 78.46; H, 8.47; N, 13.07%); δ_H(300 MHz; $CDCl_3$) 1.12 (6H, d, *J* 6.8), 2.26 (3H, s), 2.80 (1H, m, *J* 6.8), 5.25 (2H, s), 5.87 (1H, s) and 7.02–7.30 (5H, m); δ_C(75.4 MHz; $CDCl_3$) 13.6 (CH_3), 22.9 (CH_3), 25.3 (CH), 52.3 (CH_2), 101.8 (CH), 126.3 (CH), 127.3 (CH), 128.6 (CH), 137.9 (C), 147.6 (C) and 150.5 (C); *m*/*z* 214 (M^+, 11%) and 91 (100).

1-*tert*-Butyl-5-isopropyl-3-methylpyrazole 10j. Yield 86% (Table 1), bp 90–92 °C at 2 mmHg (Found: C, 73.38; H, 11.14; N, 15.48; $C_{11}H_{20}N_2$ requires C, 73.28; H, 11.18; N, 15.54%); δ_H(300 MHz; $CDCl_3$) 1.25 (6H, d, *J* 6.8), 1.63 (9H, s), 2.21 (3H, s), 3.32 (1H, m, *J* 6.8) and 5.91 (1H, s); δ_C(75.4 MHz; $CDCl_3$) 13.6 (CH_3), 24.5 (CH_3), 26.9 (CH), 30.7 (CH_3), 59.0 (C), 103.6 (CH), 145.0 (C) and 150.9 (C); *m*/*z* 180 (M^+, 11%) and 109 (100).

5-*tert*-Butyl-1,3-dimethylpyrazole 10k. Yield 72% (Table 1), bp 80–83 °C at 0.8 mmHg (Found: C, 70.97; H, 10.55; N, 18.48; $C_9H_{16}N_2$ requires C, 71.01; H, 10.59; N, 18.40%); δ_H(300 MHz; $CDCl_3$) 1.31 (9H, s), 2.16 (3H, s), 3.86 (3H, s) and 5.77 (1H, s); δ_C(75.4 MHz; $CDCl_3$) 13.2 (CH_3), 29.5 (CH_3), 31.0 (C), 38.8 (CH_3), 103.0 (CH), 146.1 (C) and 151.7 (C); *m*/*z* 152 (M^+, 23%) and 137 (100).

1-Benzyl-5-*tert*-butyl-3-methylpyrazole 10l. Yield 86% (Table 1), bp 150–152 °C at 2 mmHg (Found: C, 78.99; H, 8.79; N, 12.22; $C_{15}H_{20}N_2$ requires C, 78.90; H, 8.83; N, 12.27%); δ_H(300 MHz; $CDCl_3$) 1.19 (9H, s), 2.16 (3H, s), 5.36 (2H, s), 5.80 (1H, s) and 6.83–7.21 (5H, m); δ_C(75.4 MHz; $CDCl_3$) 13.5 (CH_3), 30.2 (CH_3), 31.2 (C), 53.9 (CH_2), 103.3 (CH), 125.8 (CH), 126.9 (CH), 128.3 (CH), 138.5 (C), 147.1 (C) and 152.5 (C); *m*/*z* 228 (M^+, 4%) and 91 (100).

1,5-Di-*tert*-butyl-3-methylpyrazole 10m. Yield 86% (Table 1), bp 110–115 °C at 3 mmHg (Found: C, 74.20; H, 11.44; N, 14.36; $C_{12}H_{22}N_2$ requires C, 74.17; H, 11.41; N, 14.42%); δ_H(300 MHz; $CDCl_3$) 1.45 (9H, s), 1.69 (9H, s), 2.19 (3H, s) and 5.96 (1H, s); δ_C(75.4 MHz; $CDCl_3$) 13.4 (CH_3), 31.9 (CH_3), 32.5 (CH_3), 32.7 (C), 60.9 (C), 106.9 (CH), 143.7 (C) and 152.9 (C); *m*/*z* 194 (M^+, 9%) and 123 (100).

1,5-Dimethyl-3-(2-phenylethyl)pyrazole 11e. Yield 81% (Table 2), mp 85–86 °C (Found: C, 78.06; H, 8.02; N, 13.92; $C_{13}H_{16}N_2$ requires C, 77.96; H, 8.05; N, 13.99%); δ_H(300 MHz; $CDCl_3$) 2.18 (3H, s), 2.89 (4H, m, A_2B_2), 3.68 (3H, s), 5.78 (1H, s) and 7.14–7.29 (5H, m); δ_C(75.4 MHz; $CDCl_3$) 11.0 (CH_3), 30.0 (CH_2), 35.4 (CH_3), 36.0 (CH_2), 103.8 (CH), 5.7 (CH), 128.1 (CH), 128.2 (CH), 138.7 (C), 141.8 (C) and 150.8 (C); *m*/*z* 200 (M^+, 31%) and 109 (100).

1-Benzyl-5-methyl-3-(2-phenylethyl)pyrazole 11f. Yield 69% (Table 2), bp 155–157 °C at 0.6 mmHg (Found: C, 82.59; H, 7.31; N, 10.09; $C_{19}H_{20}N_2$ requires C, 82.57; H, 7.29; N, 10.14%); δ_H(300 MHz; $CDCl_3$) 2.11 (3H, s), 2.93 (4H, m, A_2B_2), 5.21 (2H, s), 5.84 (1H, s) and 6.99–7.30 (10H, m); δ_C(75.4 MHz; $CDCl_3$) 11.1 (CH_3), 30.1 (CH_2), 36.0 (CH_2), 52.6 (CH_2), 104.6 (CH), 125.7 (CH), 126.4 (CH), 127.3 (CH), 128.2 (CH), 128.4 (CH), 128.6 (CH), 137.3 (C), 138.9 (C), 141.8 (C) and 151.3 (C); *m*/*z* 276 (M^+, 12%) and 277 (100).

1-*tert*-Butyl-5-methyl-3-(2-phenylethyl)pyrazole 11g. Yield 23% (Table 2), bp 228–230 °C at 1 mmHg (Found: C, 79.28; H, 9.18; N, 11.54; $C_{16}H_{22}N_2$ requires C, 79.29; H, 9.15; N, 11.56%); δ_H(300 MHz; $CDCl_3$) 1.53 (9H, s), 2.30 (3H, s), 2.80 (4H, m, A_2B_2), 5.71 (1H, s) and 7.08–7.18 (5H, m); δ_C(75.4 MHz; $CDCl_3$) 14.7 (CH_3), 30.0 (CH_2), 30.1 (CH_3), 35.9 (CH_2), 59.2 (C), 106.7 (CH), 125.7 (CH), 128.2 (CH), 128.4 (CH), 138.2 (C), 142.2 (C) and 149.0 (C); *m*/*z* 242 (M^+, 43%) and 95 (100).

1,5-Dimethyl-3-isopropylpyrazole 11h. Yield 71% (Table 2), bp 65–67 °C at 5 mmHg (Found: C, 69.46; H, 10.18; N, 20.36; $C_8H_{14}N_2$ requires C, 69.52; H, 10.21; N, 20.27%); δ_H(300 MHz; $CDCl_3$) 1.23 (6H, d, *J* 7.0), 2.19 (3H, s), 2.90 (1H, m, *J* 7.0), 3.67 (3H, s) and 5.79 (1H, s); δ_C(75.4 MHz; $CDCl_3$) 10.6 (CH_3), 22.6 (CH_3), 27.3 (CH), 35.1 (CH_3), 101.3 (CH), 138.0 (C) and 157.2 (C); *m*/*z* 138 (M^+, 29%) and 123 (100).

1-Benzyl-3-isopropyl-5-methylpyrazole 11i. Yield 73% (Table 2), bp 100–105 °C at 0.4 mmHg (Found: C, 78.55; H, 8.44; N,

13.01; $C_{14}H_{18}N_2$ requires C, 78.46; H, 8.47; N, 13.07%); δ_H(300 MHz; $CDCl_3$) 1.26 (6H, d, *J* 6.9), 2.12 (3H, s), 2.97 (1H, m, *J* 6.9), 5.22 (2H, s), 5.88 (1H, s) and 7.02–7.30 (5H, m); δ_C(75.4 MHz; $CDCl_3$) 11.2 (CH_3), 23.1 (CH_3), 27.8 (CH), 52.6 (CH_2), 102.4 (CH), 126.5 (CH), 127.3 (CH), 128.6 (CH), 137.5 (C), 138.8 (C) and 158.3 (C); *m*/*z* 214 (M^+, 28%) and 91 (100).

1-*tert*-Butyl-3-isopropyl-5-methylpyrazole 11j. Yield 63% (Table 3), bp 95–96 °C at 3 mmHg (Found: C, 73.23; H, 11.22; N, 15.55; $C_{11}H_{20}N_2$ requires C, 73.28; H, 11.18; N, 15.54%); δ_H(300 MHz; $CDCl_3$) 1.22 (6H, d, *J* 6.9), 1.61 (9H, s), 2.40 (3H, s), 2.91 (1H, m, *J* 6.9) and 5.82 (1H, s); δ_C(75.4 MHz; $CDCl_3$) 14.7 (CH_3), 23.1 (CH_3), 27.8 (CH), 30.1 (CH_3), 59.0 (C), 104.3 (CH), 137.8 (C) and 155.5 (C); *m*/*z* 180 (M^+, 21%) and 109 (100).

3-*tert*-Butyl-1,5-dimethylpyrazole 11k. Yield 65% (Table 2), bp 70–73 °C at 0.7 mmHg (Found: C, 70.99; H, 10.57; N, 18.44; $C_9H_{16}N_2$ requires C, 71.01; H, 10.59; N, 18.40%); δ_H(300 MHz; $CDCl_3$) 1.28 (9H, s), 2.22 (3H, s), 3.71 (3H, s) and 5.85 (1H, s); δ_C(75.4 MHz; $CDCl_3$) 11.1 (CH_3), 30.6 (CH_3), 31.8 (C), 35.7 (CH_3), 101.4 (CH), 138.4 (C) and 160.5 (C); *m*/*z* 152 (M^+, 24%) and 137 (100).

1-Benzyl-3-*tert*-butyl-5-methylpyrazole 11l. Yield 49% (Table 2), bp 160–163 °C at 2.5 mmHg (Found: C, 78.98; H, 8.79; N, 12.23; $C_{15}H_{20}N_2$ requires C, 78.90; H, 8.83; N, 12.27%); δ_H(300 MHz; $CDCl_3$) 1.32 (9H, s), 2.10 (3H, s), 5.24 (2H, s), 5.91 (1H, s) and 6.99–7.30 (5H, m); δ_C(75.4 MHz; $CDCl_3$) 11.2 (CH_3), 30.6 (CH_3), 31.9 (C), 52.7 (CH_2), 102.3 (CH), 126.4 (CH), 127.2 (CH), 128.5 (CH), 137.6 (C), 138.5 (C) and 160.9 (C); *m*/*z* 228 (M^+, 7%) and 91 (100).

3(5)-*tert*-Butyl-5(3)-methylpyrazole 12. Mp 152–153 °C (lit.,[10] 145–146 °C; lit.,[14] 169–171 °C) (Found: C, 69.58; H, 10.25; N, 20.17; $C_8H_{14}N_2$ requires C, 69.52; H, 10.21; N, 20.27%); δ_H(300 MHz; $CDCl_3$) 1.30 (9H, s), 2.27 (3H, s), 5.87 (1H, s) and 8.80 (1H, br s, NH); δ_C(75.4 MHz; $CDCl_3$) 12.3 (CH_3), 30.3 (CH_3), 31.3 (C), 100.9 (CH), 144.4 (C) and 157.5 (C); *m*/*z* 138 (M^+, 25%) and 123 (100).

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Paper 8/07692H