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One-pot synthesis of 5-(substituted-amino)pyrazoles

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Abstract—An efficient and mild one-pot synthesis of substituted 5-alkylamino and/or 5-(arylamino)pyrazoles is described. A suitably decorated β-ketoamide, an aryl or alkyl hydrazine and Lawesson's reagent are suspended in THF/Py and gently heated to yield the requisite 5-aminopyrazoles.

Compounds containing the 5-alkyl/arylamino substituted pyrazole moiety (**1**, Fig. 1) have been exploited in the design of pharmaceutical[1] and agrochemical agents.[2] Although a number of methods for the synthesis of 5-alkyl/arylamino substituted pyrazoles have been reported,[1–3] we found that none were suitable for our purposes[4] and thus sought a general solution phase method that could also be applied to solid-supported synthesis. The known protocols required harsh reaction conditions[3,4a] or were limited to a defined set of starting materials having special electronic requirements.[1a,2,4b] The most versatile method[1b,c,d] involves the reaction of mono-substituted hydrazines with pregenerated β-ketothioamides to accomplish the cyclization but, as such, was not suitable for solid-phase synthesis. We herein describe a modification of the latter method[1b–d] that allows for the efficient installation of mono- and di-substituted-5-amino groups on pyrazole core **1** in a single final step. This protocol avoids the pregeneration of the β-ketothioamides and it is amendable to solid-supported synthesis.

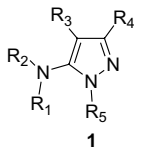

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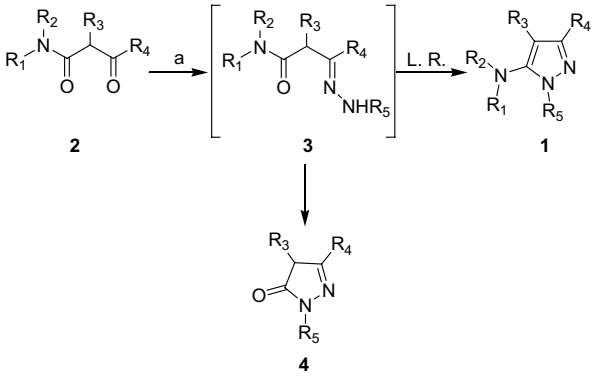
Figure 1. Substituted 5-(alkyl/arylamino)pyrazoles.

The 5-aminopyrazoles **1** (Scheme 1) are furnished by heating a mixture of the β-ketoamide,[5] aryl or alkyl hydrazines and Lawesson's reagent (L.R.) in dry THF/pyridine (95/5) at 55–60 °C.[6,7] The reaction proceeds by an initial formation of the intermediate hydrazone[7e,8] **3** followed by the reaction of the amide carbonyl with Lawesson's reagent. The reaction times range from 5 to 48 h[8] depending on the nature of the substrate but, in general, the reactions are complete within 12 h.[6–8] In those reactions that failed to give **1** in decent yields, pyrazolone **4** was identified as the major side product.[7b] In all cases only a single isomer was isolated.[6b] The



Scheme 1. Reagents and conditions: (a) 1.1 equiv $R_5NHNH_2 \times HCl$, 1.1 equiv Lawesson's reagent, THF/Py (95/5), 50–55 °C.

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method was found to be extremely versatile and can be applied to a diverse range of β-ketoamides and mono-substituted hydrazines.

The results of a representative study examining the reactivity of various secondary and tertiary amides (Table 1) with phenylhydrazine and benzylhydrazine are reported in Table 2.

In all cases the C-2 unsubstituted β-ketoamides **2a**–**f**, in which R_3 is H, consistently gave higher yields (respective products **1a**–**l**, Table 2) than their counterparts **2g**–**m**, where R_3 is Me or Ph (products **1m**–**u**, Table 2). Though the number of examples is limited, substrate **2g**, in which R_3 is Me, gave significantly better yields (products **1o** and **1p**) than substrate **2m**, where R_3 is a Ph[8] (product **1m** and **1n**, Table 2). As a general rule β-ketoamides where R_4 is Me (alkyl) reacted much faster and generally gave higher yields than substrates in which R_4 is Ph (aryl).[7c] As an example, β-ketoamide **2a** ($R_4 = Me$), when reacted with phenylhydrazine, gave product **1a** in 95% yield, whereas substrate **2b** ($R_4 = Ph$) reacted with phenylhydrazine to give product **1c** in only 65% yield. The initial transient hydrazone **3**, formed from the substrates where R_4 is Ph, took longer to cyclize and usually gave more of the pyrazoloneside product **4**.[7d,e]

Table 1. The β-ketoamides **2** used in the study[5]

Compound	R_1	R_2	R_3	R_4
2a	Et	Et	H	Me
2b	Et	Et	H	Ph
2c	Bn	H	H	Me
2d	Bn	H	H	Ph
2e	Ph	H	H	Me
2f	Ph	H	H	Ph
2g	Et	Et	Me	Me
2h	Et	Et	Me	Ph
2i	Bn	H	Me	Me
2j	Bn	H	Me	Ph
2k	Ph	Me	Me	Me
2l	Ph	Me	Me	Ph
2m	Et	Et	Ph	Me

Table 2. Yields of 5-aminopyrazoles **1**

Compound	R_1	R_2	R_3	R_4	R_5	Yield (%)[a,b]
1a	Et	Et	H	Me	Ph	95
1b	Et	Et	H	Me	Bn	87
1c	Et	Et	H	Ph	Ph	65
1d	Et	Et	H	Ph	Bn	52
1e	Bn	H	H	Me	Ph	91
1f	Bn	H	H	Me	Bn	87
1g	Bn	H	H	Ph	Ph	67
1h	Bn	H	H	Ph	Bn	50
1I	Ph	H	H	Me	Ph	95
1j	Ph	H	H	Ph	Ph	45
1k	Ph	Me	H	Me	Ph	92
1l	Ph	Me	H	Ph	Ph	40
1m	Et	Et	Ph	Me	Ph	13
1n	Et	Et	Ph	Me	Bn	15
1o	Et	Et	Me	Me	Ph	55
1p	Et	Et	Me	Me	Bn	60
1q	Et	Et	Me	Ph	Ph	32
1r	Bn	H	Me	Me	Ph	55
1s	Bn	H	Me	Ph	Ph	43
1t	Ph	H	Me	Me	Ph	30
1u	Ph	H	Me	Ph	Ph	26

[a] Purified using reverse phase preparative HPLC.
[b] Yield averaged from two runs.

In general, phenyl hydrazine gave slightly better yields with C-2 (R_3) unsubstituted β-ketoamides (**2a**–**f**) than did benzylhydrazine. Whereas, benzylhydrazine appeared to give slightly better yields with C-2 substituted substrates (**2g**–**m**) than did phenylhydrazine. Furthermore, it was noticed that the reaction with benzylhydrazine proceeded faster than with phenylhydrazine.

As for the substituents on the amide nitrogen or secondary versus tertiary amides **2**, the effect is not so clear cut and no trends were apparent. *N*-Aryl and *N*-alkyl substituents were tolerated equally well and the substitution pattern and the nature of the groups at C-2 (R_3) and C-4 (R_4) on the β-ketoamides appear to determine the fate of the reaction.

In summary, a mild one-pot procedure for the preparation of 5-*N*-mono- or 5-*N*,*N*-disubstituted-aminopyrazoles has been presented.[9] This protocol negates the need for pregeneration of β-ketothioamides as described previously[1b,c,d] and is thus easily adaptable for automated parallel synthesis. The versatility and mild nature of this method has also been exploited for the solid-supported synthesis of 5-(*N*-mono-substituted-amino)pyrazoles and will be reported in due course.

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4. (a) Method described in Ref. 3 requires the reaction of β-ketoamide with mono-substituted hydrazines under very harsh acidic conditions and/or very high temperatures to accomplish the cyclization in poor to moderate yields; (b) Method outlined in Refs. 2a,b,c, though very useful, is limited by the necessity of starting hydrazones that must be conjugated to an electron withdrawing group, to yield 5-(*N*-alkylamino)pyrazoles with electron-withdrawing groups at the C-4 position; (c) The method described in Refs. 1b,c,d takes advantage of the reaction between a 2-oxocarbo-thioamides (β-ketothioamides) with mono-substituted hydrazines to afford 5-(*N*-alkylamino)pyrazoles in good yield.
5. Some useful methods for the preparation of β-ketoamides include: (a) Miriyala, B.; Williamson, J. S. *Tetrahedron Lett.* **2003**, *44*, 7957; (b) Railard, S. P.; Chen, W.; Sullivan, E.; Bajjalieh, W.; Bhandari, A.; Baer, T. A. *J. Comb. Chem.* **2002**, *4*, 470; (c) Witzemanard, J. S.; Nottingham, W. D. *J. Org. Chem.* **1991**, *56*, 1715.
6. (a) Typical reaction conditions: To a mixture of the β-ketoamide **2a** (16 mg, 0.10 mmol), phenylhydrazine hydrochloride (16 mg, 0.11 mmol) and Lawesson's reagent (45 mg, 0.11 mmol) in a 1 dram vial was added 1.0 mL of dry THF/pyridine (95/5) solution. The reaction was stirred at room temperature for 15 min and the vial was transferred to a heating block. The vial was heated at 55 °C for 14 h and the solvents removed in vacuo. The resulting oil was resuspended in 1.0 mL of (1/4) DCE/heptane and loaded on a 500 mg prepacked silica cartridge and flushed with 6–7 mL of 1/1 diethyl ether/heptane. The filtrate is condensed in vacuo and purified using reverse-phase preparative HPLC to give **1a** (22 mg, 95%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57–7.55 (m, 2H), 7.51–7.44 (m, 3H), 5.71 (s, 3H), 3.00 (q, 4H, $J = 7.14$ Hz), 2.37 (s, 3H), 1.01 (t, 6H, $J = 7.14$ Hz); LCMS (m/z) 230 (M^++H); (b) The regiochemistry of the R_5 group was established using (2D) ^{1}H–^{13}C HMQC/HMBC and ^{1}H–^{15}N HMQC/HMBC as well as COSY and PSNOESY NMR experiments.
7. (a) Reactions also proceeded without the use of pyridine, but it was noticed that yields were slightly higher when pyridine was used as an additive, particularly for sluggish reactions. Dioxane can be substituted for THF; (b) The formation of the corresponding 5-pyrazolones **4** are monitored by LCMS; (c) For example, C-2 unsubstituted ($R_3 = H$) substrates such as **2a**, **2c** and **2e** with methyl groups at C-4 (R_4) reacted within as little as 5 h at 55 °C, where as substrates **2b**, **2d** and **2f** with phenyl at C-4 (R_4) required reaction times >12 h. For uniformity, all reactions were heated for 24 h;[8]; (d) Increasing reaction temperature did not enhance the yield. In fact, in some cases a decreased yield was observed due to an increase in the formation of the corresponding 5-pyrazolone **4**; (e) The hydrazones **3** were apparent by LCMS. Conversions to the thioamide intermediates were not observed.
8. It was noticed that the initial hydrazone intermediates **3** that are formed from **2m** are extremely stable (particularly those formed from phenylhydrazine). The reaction took >48 h at 60 °C to go to completion and resulted in a significant amount of the corresponding 5-pyrazolones **4**. Increasing the reaction temperatures (using 1,4-dioxane as the solvent) did not enhance the yield.
9. The reactivity of both electron rich and electron deficient hydrazines and β-ketoamides have also been examined. Though there were some combinations of hydrazines and β-ketoamides that were not compatible, on the whole most electronically diverse reagents were tolerated and gave reasonable yields and purity. The regioselectivity was independent of the electronic nature of the reactants.