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A one-pot process for the regioselective synthesis of 1,3,4-trisubstituted-1*H*-pyrazoles

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ABSTRACT

This Letter reports a facile and regioselective one-pot synthesis of 1,3,4-trisubstituted-1*H*-pyrazoles. It comprises a three-step telescoped sequence, which has been utilised in the production of a variety of differentially substituted pyrazoles.

As part of a current research programme, we required a robust and safe process to provide significant quantities of 1,3-dimethyl-1*H*-pyrazole-4-carbaldehyde **1** (Fig. 1). This important building block **1** has found use in the preparation of several pharmacologically active agents.[1] Furthermore, this general 1,3,4-substituted pyrazole motif is also an important constituent in several classes of pharmaceutically active compounds.[2]

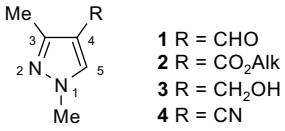


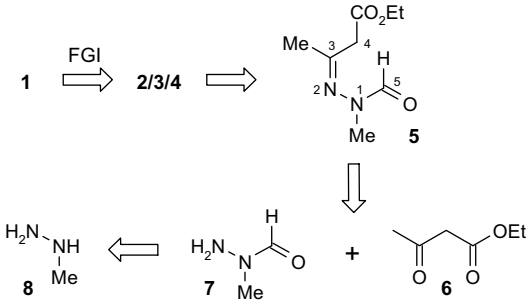
Figure 1.

Although a few syntheses of this compound have been reported in the literature,[3] these methods all have significant drawbacks. In some, the desired compound **1** is produced in low yield, as a regioisomeric mixture or, indeed, as a by-product.[3a,e] Those preparations that do give good yields and selectivity[3b–d] employ the Vilsmeier reagent or the Vilsmeier–Haack reaction to construct the heterocyclic system. Over and above the toxicity of the reagents and intermediates involved, the practicalities of this chemistry proved prohibitive: in our hands, the reaction mixtures were thick, immobile gels which produced significant exotherms, both during reaction and upon quenching.

Similarly, reported syntheses of the corresponding ester-substituted pyrazoles **2**[4] also suffer from drawbacks: product mixtures,[4a,c,d] diazotization steps,[4b,d] relatively high step-count or expensive raw materials.[4e] This also applies to the corresponding pyrazole acid **10**.[4d,e]

Lastly, the nitrile **4** has been reported as an isolated compound just once,[5] again as a regioisomeric mixture.

Ideally, we required a short, regioselective synthesis of pyrazoles of type **2** (e.g., Alk = Et) or **4** (which in turn would give access to **1**) that would be amenable to scale-up and avoided the use of Vilsmeier–Haack type chemistry. As discussed, none of the published methods satisfied those requirements, which led us to devise a novel approach to the construction of such pyrazoles, targeting ring-formation at the C4–C5 bond (Scheme 1).[6]



Scheme 1.

In this approach, a key intramolecular Knoevenagel-type condensation would allow incorporation of the C5 carbon into the molecule as a formyl moiety (it is C5 that is often introduced *via* Vilsmeier-type chemistry). Hydrazone **5** would be derived from ethyl acetoacetate **6** and the known 1-formyl-1-methylhydrazine **7**,[7] accessed in turn from commercially available methylhydrazine **8**.

In a wider context, the most prevalent approach to substituted pyrazoles is the reaction of hydrazine-derivatives with 1,3-diketones (comprising C3–C5 using the numbering above).[8] Given the importance of the pyrazole sub-unit in pharmaceutically active compounds, this classical method still attracts current industrial research interest.[9] Our proposed approach is complimentary to this

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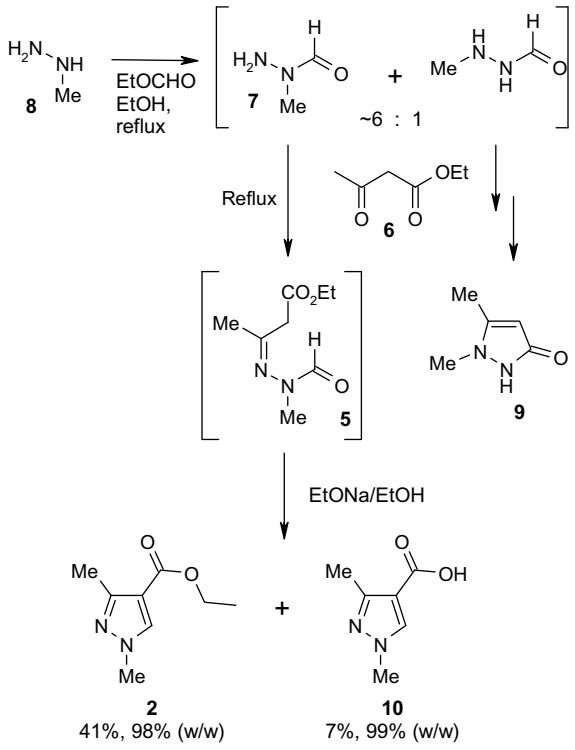
(with the C3–C5 unit being assembled in the ring-forming step) and would represent a useful tool in the heterocyclic synthetic arsenal.

We have shown that, in the forward direction, synthesis of **2** can be telescoped into one stage (Scheme 2): reaction of methylhydrazine **8** with ethyl formate gives 1-formyl-1-methylhydrazine **7** (accompanied by the regioisomer in a ratio of ~6.5:1, desired to undesired). Addition of ethyl acetoacetate **6** allows formation of hydrazone **5** and pyrazolone **9**. Finally, we were pleased to observe that base-induced cyclisation gave the desired pyrazole ester **2**, accompanied only by the corresponding acid **10**, thus proving our retrosynthetic rationale.



Scheme 2.

An operationally simple isolation of ester **2** was also developed: the reaction mixture was partitioned between *t*-butyl methyl ether (MTBE) and water to remove water-soluble by-products (including pyrazolone **9** and acid **10**). The organic solvent is then swapped from MTBE to *n*-heptane by distillation and product **2** crystallises from the solution on cooling, and is isolated in 41% yield, 98% (w/w).[10] Furthermore, simply acidifying the aqueous extract to pH 4 causes crystallisation of acid **10**, which can be isolated in 7% yield, 99% (w/w), if so desired.[11]

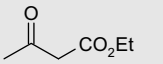
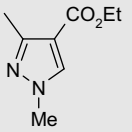
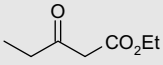
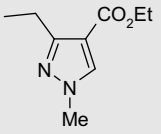
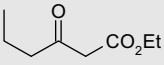
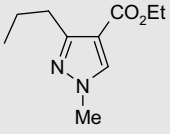
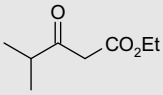
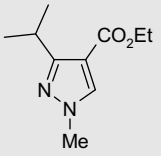
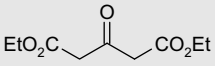
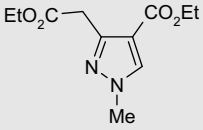
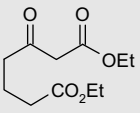
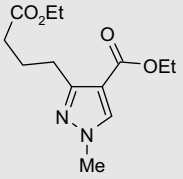
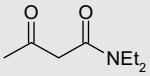
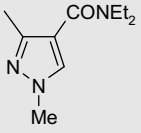
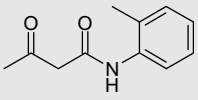
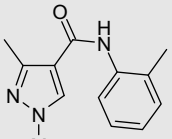
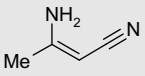
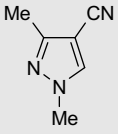
Though relatively low yields of **2** are obtained, this is an operationally simple three-step telescope, coupled with straightforward isolation of the product. The pyrazole produced is of high quality and, importantly, is regioisomerically pure.

Having established the methodology for the production of **2**, we were keen to explore its applicability to the regioselective synthesis of other 1,3,4-trisubstituted-1*H*-pyrazoles. To this end, several β-keto esters were exposed to the reaction sequence outlined in Scheme 1. The results are summarised in Table 1.

As can be seen, in terms of the ketone, primary alkyl (entries 1–3) and secondary alkyl (entry 4) substituents work well in this methodology. More complex ester substituents (entries 5 and 6) are also tolerated, though these are accompanied by significant hydrolysis of the side chain ester. As well as β-ketoesters, both secondary (entry 8) and tertiary (entry 7) β-ketoamides work well in this methodology, with aryl- and alkyl-amide functionalities being tolerated. Finally, β-ketonitrile equivalents, such as 3-aminocrotonitrile, also take part in this chemistry (entry 9), though these required slightly different reaction conditions to give optimum yield. We also have some evidence that alcoholysis or hydrolysis of the nitrile moiety occurs under these reaction conditions.

Unfortunately, other esters are not tolerated in this chemistry. For instance, when benzyl acetoacetate was employed, complete transesterification to the ethyl ester of the pyrazole product was

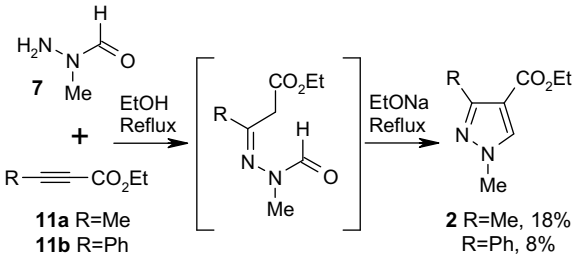
Table 1
1,3,4-Trisubstituted pyrazoles[10,12]

Entry	β-Keto ester	Pyrazole	Yield (%)
1			41
2			35
3			49
4			30
5			31 (+29% acid)
6			32 (+14% acid)
7			42
8			46
9			42[a]

[a] Hydrazone formation was carried out in AcOH. The mixture was diluted with IMS and basified with conc. NaOH to carry out the cyclisation step.

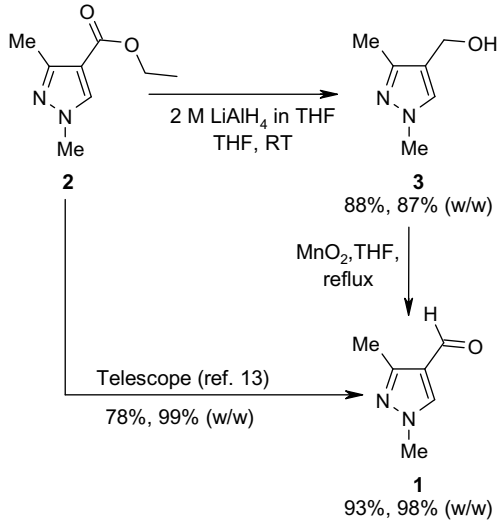
observed. Also, arylketones are conspicuous by their absence from the results shown in Table 1, the resonance deactivation of the carbonyl attenuating their reaction with the relatively unreactive 1-formyl-1-methyl hydrazine under a variety of conditions.

In an effort to address the non-participation of arylketones in this methodology, we also examined the reaction of substituted ethyl ynoates **11** with 1-formyl-1-methylhydrazine **7** (Scheme 3). Disappointingly, though the desired pyrazoles were indeed obtained, the yields were much lower than those seen with β-keto-esters. It is, however, encouraging that some of the desired pyrazoles were observed and optimisation of reaction conditions to allow efficient participation of conjugated alkynes in this type of chemistry is ongoing within our laboratories, to be reported in due course.



Scheme 3.

Finally, we have also demonstrated that ester **2** can indeed be converted easily to the target aldehyde **1** (Scheme 4). As shown, simple functional group interconversion gave access first to the alcohol **3**, then to aldehyde **1** in good yields. For our purposes, these steps were telescoped into a single stage, which gave **1** in 78% overall yield.[13]



Scheme 4.

In summary, we have developed a robust 3-step, 1-stage process for the synthesis of 1,3,4-trisubstituted-1*H*-pyrazoles which exploits a novel C4–C5 disconnection strategy and readily available raw materials. The chemistry is operationally simple and obviates the need to employ Vilsmeier-type chemistry. To demonstrate its synthetic utility, this methodology has been successfully applied to produce a range of pyrazoles (Table 1).

Acknowledgements

The authors would like to acknowledge Dr. Leigh Ferris (PR & D, AstraZeneca) and Dr. Barry Hayter (Medicinal Chemistry, AstraZeneca) for investigation of Vilsmeier-based approaches to **1**.

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9. For example, see: Heller, S. T.; Natarajan, S. R. *Org. Lett.* **2006**, *8*, 2675. It should be noted that, even in this methodology, the use of methylhydrazine gives poor regioselectivity at best.
10. Typical laboratory-scale procedure for **2**: To a cooled solution (0–5 °C) of methylhydrazine (660 mmol, 35.0 mL) in IMS (215 mL) was added ethyl formate (688 mmol, 55.5 mL) dropwise so that the temperature remained below 10 °C. Once the addition was complete, the solution was heated to reflux for 4 h. To the colourless solution was then added ethyl acetoacetate (550 mmol, 70.0 mL) and reflux continued for a further 4 h. The resulting yellow solution was cooled to ~55 °C and a solution of 21 wt % sodium ethoxide in IMS (550 mmol, 205.4 mL) was added dropwise so that a gentle reflux was maintained. Once addition was complete, reflux was maintained for 45 min. The suspension was then cooled to rt and diluted with 3 M ammonium chloride (360 mL) and brine (360 mL). The resulting solution was extracted with MTBE (2 × 360 and 1 × 180 mL). The combined organics were washed with saturated brine (180 mL) diluted with water (180 mL). The MTBE solution was concentrated by distillation to ~400 mL, then *n*-heptane (1200 mL) was added. Distillation was continued until the head temperature was constant at 97–99 °C and the volume in the vessel was 380 mL. The solution was allowed to cool to ambient temperature, then in an ice/water bath to 3–5 °C. The precipitated solid was collected by filtration, washed with cold *n*-heptane (2 × 80 mL) and dried in vacuo at ambient temperature to give the desired pyrazole ester **2** (38.32 g, 98 wt %, 223 mmol, 41% yield), as an off-white crystalline solid. The spectroscopic data for this material match those reported, see Ref. 4c.
11. Acid **10** has been shown to undergo the reduction–oxidation chemistry applied to ester **2** equally well.
12. All compounds gave satisfactory spectroscopic data.
13. Typical laboratory-scale procedure for **1**: To a solution of pyrazole ester **2** (204 mmol, 35.0 g) in THF (209 mL) at 0–3 °C was added a solution of 2.0 M $LiAlH_4$ in THF (204 mmol, 102 mL) dropwise so that the temperature remained below 10 °C. Once the addition was complete, the mixture was stirred at 0–3 °C

for 1 h, then warmed to ambient temperature. After a total of 3 h, the mixture was cooled in a water bath, and water (7.0 mL) was added dropwise [CAUTION—vigorous effervescence!] over 10 min. This was followed by dropwise addition of 1 M sodium hydroxide (7.0 mL) over 10 min, then more water (7.0 mL) over 1 min. Vigorous stirring was employed to maintain mobility. Harborlite-800 filter aid (30 g) was added to the mixture and the solid residues were removed by filtration. The cake was washed with THF (3 × 70 mL). To the combined organic solution (containing **3**) was added manganese dioxide [85%, activated <5 μm, Aldrich cat. 217646] (1020 mmol, 102.3 g) and the mixture heated to reflux. After 6 h, the mixture was cooled to room temperature and the solid residues were removed by filtration (double-thickness of Whatman GF/B paper in a split Buchner funnel). The cake was washed with THF (3 × 80 mL). The combined THF solution was concentrated by distillation to ~100 mL, then *n*-heptane (200 mL) was added. Distillation was continued until the head temperature was constant at 97–99 °C and the volume in the vessel was 160 mL. The solution was allowed to cool to 45 °C, which caused precipitation of the product as an oil which then crystallised. The mixture was then cooled in an ice/water bath to 3–5 °C. The solid was collected by filtration, washed with cold *n*-heptane (2 × 30 mL) and dried in vacuo at ambient temperature to give the desired pyrazole aldehyde **1** (19.82 g, 99 wt %, 158 mmol, 78% yield), as a white crystalline solid. The spectroscopic data for this material match those reported, see Ref. 3e.