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Synthesis of linked heterocycles via use of bis-acetylenic compounds

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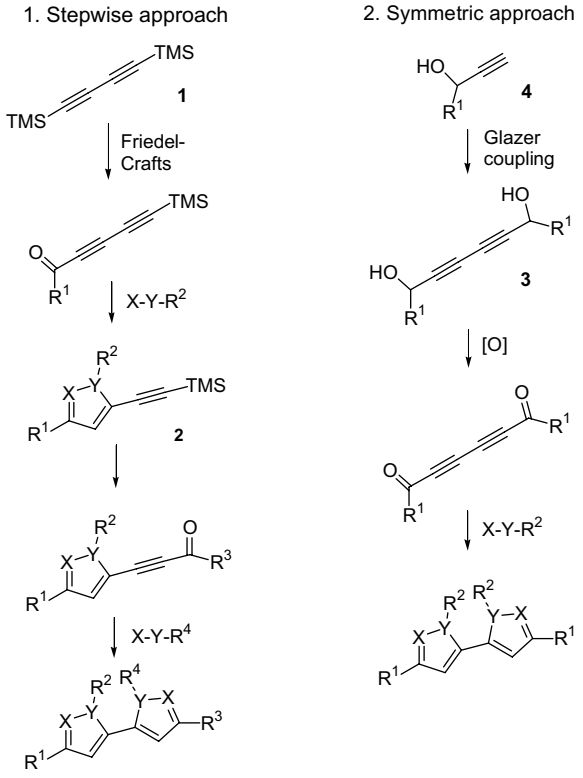
Abstract—Linked bis-pyrazoles, a pyrazolyl-isoxazole, a pyrazolyl-pyrimidine and a pyrazolyl-triazole were synthesized starting with commercially available 1,4-bis(trimethylsilyl)-1,3-butadiyne **1** or readily available bis-acetylenic diketone **22**. A stepwise approach based on the use of **1** allowed the synthesis of nonsymmetrically substituted bis-pyrazoles and linked heterocycles with two different cores whereas a symmetric approach based on the use of **22** allowed a very short synthesis of symmetric bis-pyrazoles.

1. Introduction

The synthesis of linked small ring heterocycles has attracted much attention in recent years due to their interesting biological properties.[1,2] Substituted pyrazoles and isoxazoles play key pharmacophore functions in many pharmaceuticals.[3–5] Moreover, linked heterocycles have found application in asymmetric catalysis.[6,7] Previous approaches to C–C linked heterocycles were predominantly based on cross-coupling strategies.[7,8] Our previous experience in the use of 1,4-bis(trimethylsilyl)-1,3-butadiyne **1** in the synthesis of 1*H*-pyrazolo[4,3-*c*]pyridines[9] has prompted us to investigate alternative applications of bis-acetylenic compounds for the synthesis of new heterocycles.

Two strategies were originally proposed. The first (Scheme 1), allowed the synthesis of nonsymmetric linked heterocycles and envisaged stepwise formation of the first ring, possessing the acetylenic substituent **2**, followed by condensation of the second ring. The second strategy was based on the use of the bis-acetylenic diketone **3**, which on condensation with hydrazines or hydroxylamines would give symmetric bis-pyrazoles or bis-isoxazoles. The first pathway, although longer than the second, would provide access to previously unknown pyrrazolyl-isoxazoles, pyrazolyl-pyrimidines and pyrazolyl-triazoles. It was proposed to access the diketone **3** via Glazer type oxidative coupling[10] of propargylic alcohols **4**.



Scheme 1. Proposed approaches to linked heterocycles.

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We present the initial results of our investigation of both pathways in this letter.

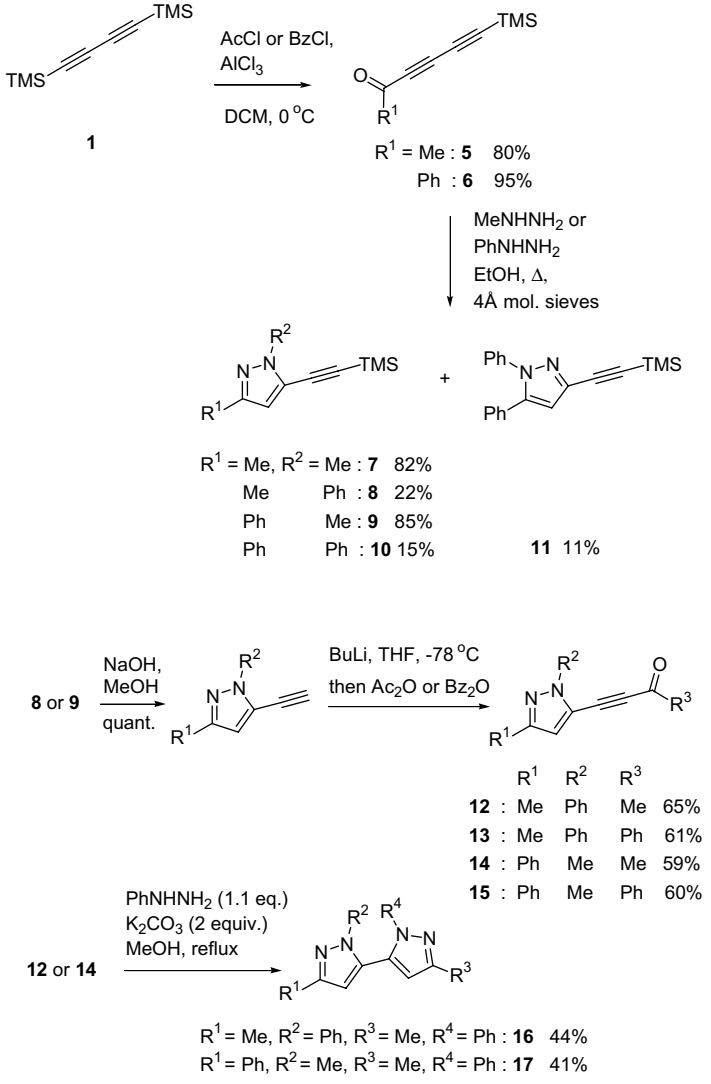
2. The stepwise approach

The initial acylation of the 1,4-bis(trimethylsilyl)-1,3-butadiyne **1** was carried out according to the literature procedure[11] resulting in near quantitative isolation of the acetylenic ketones **5** and **6**. Direct formation of the pyrazoles on treatment of ketones **5** and **6** with methyl and phenyl hydrazines in refluxing ethanol[12] in the presence of molecular sieves led to compounds **7**, **8**, **9** and **10** in varying yields.[13] It was observed that condensations with methyl hydrazine proceeded in higher yields and regioselectivity. Reaction of phenyl hydrazine with ketone **6** gave a significant amount of the regioisomeric pyrazole **11**, formation of which was attributed to stabilizing π-stacking of the two phenyl rings in **11**. Attempts to perform Friedel–Crafts acylation of the alkyne in either ketones **5** and **6** or acetylenic pyrazoles **7**, **8** or **9** were unsuccessful. Alternatively, cleavage of the TMS group in **8** or **9** with methanolic sodium hydroxide[14] followed by lithiation and quench of the acetylides with acetic or benzoic anhydrides led to formation of ketones **12**, **13**, **14** and **15** (Scheme 2).

Heating of the acetylenic ketones **12** and **14** with phenyl hydrazine hydrochloride and potassium carbonate in methanol led to formation of bis-pyrazoles **16** and **17** in moderate yields. The structure of **16** was confirmed by single crystal X-ray diffraction (Fig. 1). It is interesting to note that the two phenyl rings appear to be π-bonded, thus influencing the dihedral angle between the pyrazole nitrogens.

Next, we attempted formation of a pyrazolyl-isoxazole. The acetylenic ketone **12** was treated with hydroxylamine hydrochloride in acetonitrile.[15] The reaction took two days to reach completion and the linked heterocycle **18** was isolated in satisfactory yield as a single regioisomer (Scheme 3).[16]

Treatment of **12** with benzamidine hydrogen chloride salt in acetonitrile[17] produced a linked pyrazolyl-pyrimidine **19**, whereas treatment of the acetylenic pyrazole **20**



Scheme 2. Stepwise approach to bis-pyrazoles.

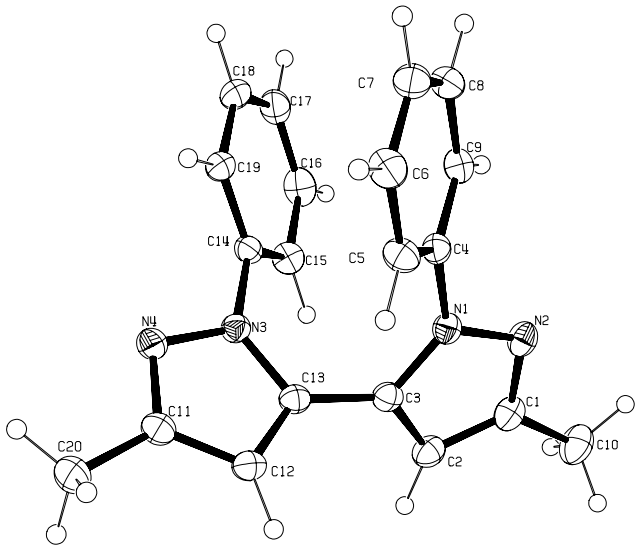
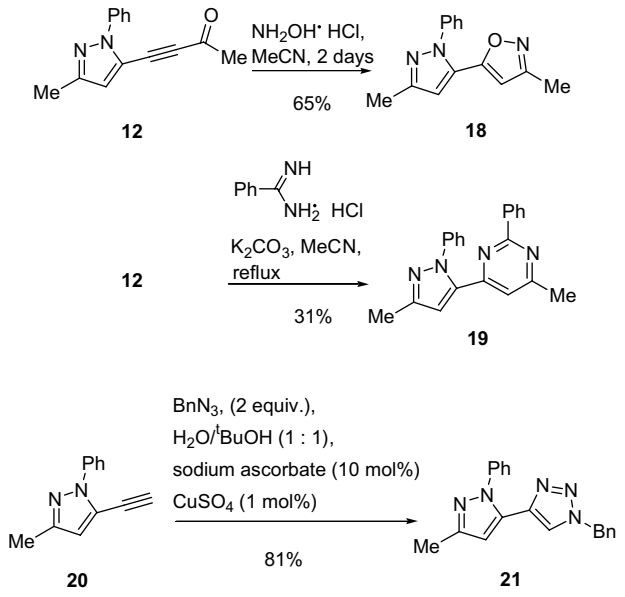


Figure 1. X-ray structure of bis-pyrazole **16.**

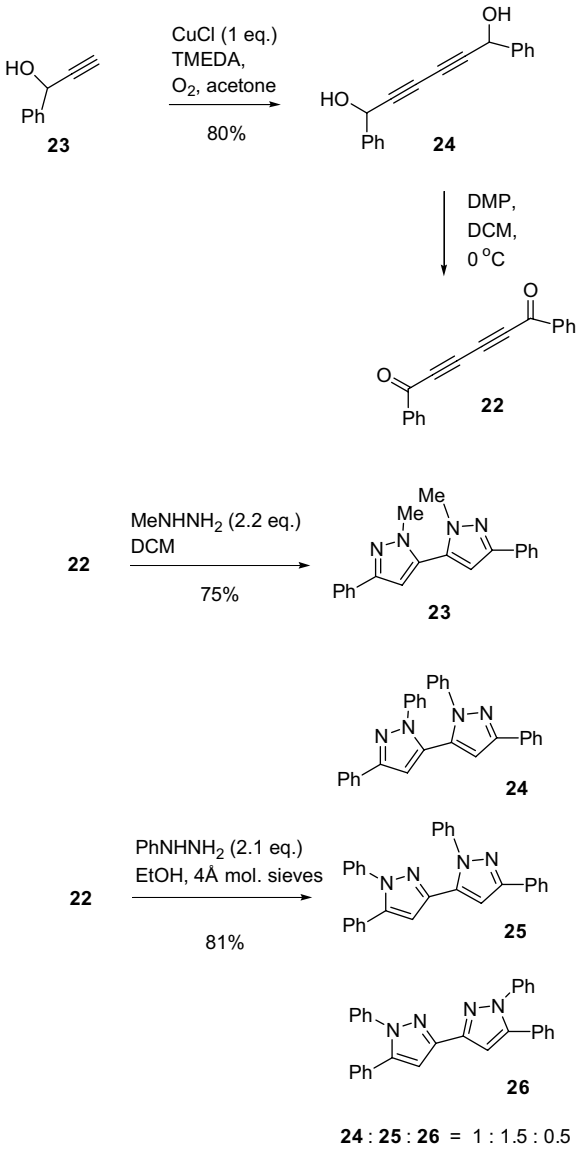


Scheme 3. Synthesis of novel linked heterocycles.

derived from **8** with benzyl azide in the presence of a copper catalyst, following the method published by Sharpless and co-workers[18] resulted in formation of a pyrazolyl-triazole **21** in a satisfactory yield as a single regioisomer. The structure of **21** was assigned according to the published mechanism for the copper catalysed Huisgen cycloaddition.[18]

3. The symmetric approach

Next, we investigated the symmetric approach to linked heterocycles. According to our original strategy the bis-acetylenic diketone **22** was synthesised via Glazer-type coupling[10] of propargylic alcohol **23** followed by mild Dess–Martin oxidation[19] of the diol **24** (Scheme 4).



Scheme 4. Symmetric synthesis of bis-pyrazoles.

On treatment with methyl hydrazine in DCM diketone **22** gave symmetric bis-pyrazole **23** in a satisfying yield. Reaction of **22** with phenyl hydrazine, on the other hand, produced a mixture of regioisomeric bis-pyrazoles **24**, **25** and **26** tentatively assigned in a 1:1.5:0.5 ratio as judged by integration of resonances in the crude ^{1}H NMR. The low regioselectivity in this case follows our observation of poor control in the case of formation of **10** and **11** as discussed previously. Due to their similar polarity the three regioisomeric bis-pyrazoles were never fully separated and were characterised as major components in mixtures with the isomeric analogues.

In conclusion, we have demonstrated the application of bis-acetylenic compounds **1** and **24** in syntheses of linked heterocycles. Two strategies—stepwise and symmetrical were investigated producing six substituted bis-pyrazoles and three novel pyrazolyl derivatives **18**, **19** and **21**. Further investigation will be focussed on

synthesis of a wider range of linked heterocycles as well as further optimisation of reaction conditions.

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