Tetrahedron Letters,Vol.30,No.16,pp 2049-2052,1989 0040-4039/89 $3.00 + .00
Printed in Great Britain Pergamon Press plc

An Efficient Method for the Synthesis of Trifluoromethyl Substituted Heterocycles

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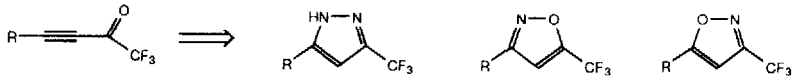
Abstract: Trifluoromethyl substituted pyrazoles and isoxazoles have been prepared regiospecifically in high yield from trifluoroacetyl acetylenes.

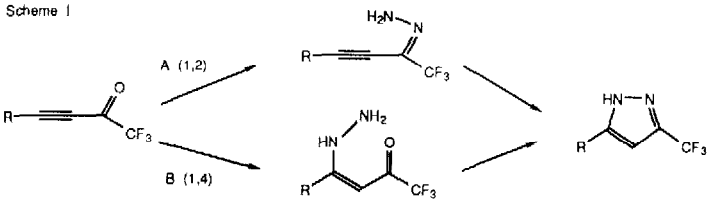
The development of new and more efficient methods for the synthesis of trifluoromethyl substituted aromatic and heteroaromatic compounds are currently of considerable interest.[1] Agrochemicals such as Fluoemturon and Trifluralin, and pharmaceuticals such as Penfluridol and Mefloquine serve to illustrate the basis for this interest as well as to demonstrate the unique biological activities exhibited by these compounds.[2] However, high yielding regiospecific methods for the synthesis of trifluoromethyl substituted heteroaromatic compounds are still quite limited. We have recently studied the regiospecificity of organocuprate addition to trifluoroacetyl acetylenes and addressed the issue of 1,2 vs 1,4-selectivity.[3] We now wish to report some preliminary results on the regiospecific synthesis of trifluoromethyl substituted pyrazoles and isoxazoles from trifluoroacetyl acetylenes. Although acetylenic ketone derivatives are well known precursors for the synthesis of a variety of heterocyclic compounds, this methodology has surprisingly not been extended to fluorinated compounds.[4]



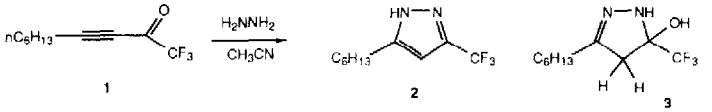
Trifluoromethyl substituted pyrazoles were readily prepared by reaction of hydrazine and a trifluoroacetyl acetylene in refluxing benzene with azeotropic removal of water. The reaction was equally efficient for difluoroacetyl acetylenes, providing the corresponding pyrazoles in 76-92% yield, see Table. The reaction could potentially take two pathways: by nucleophilic attack at the electrophilic trifluoromethyl substituted carbonyl,[5] or by an

initial Michael reaction and subsequent ring closure and aromatization, Scheme 1, path A and B, respectively. Reaction of the acetylene 1 and hydrazine in acetonitrile at room

Scheme I

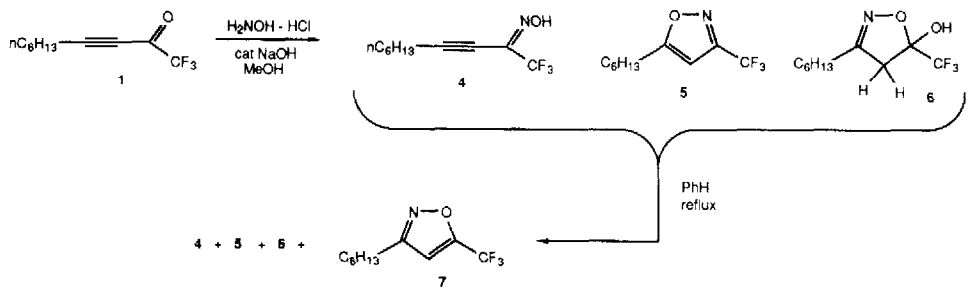


temperature provided a mixture of the pyrazole 2 and the hydroxy substituted pyrazoline 3 which was readily identified by NMR. Compound 3 exhibited an AB quartet at 2.8 ppm in the ^{1}H-NMR, as well as a ^{19}F-NMR signal at -82.0 ppm. The aromatic pyrazole 2 ^{19}F-NMR signal appeared at -62.5 ppm.[6] This observation clearly indicates that initial hydrazone formation is not the sole reaction pathway, yet, cannot rule out hydrazone formation. Studies with hydroxylamine hydrochloride were then undertaken to probe the initial regioselectivity of addition.



1 2 3

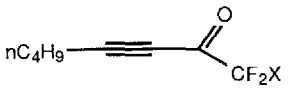
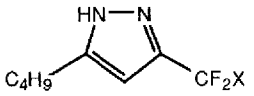
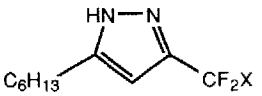
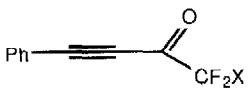
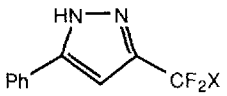
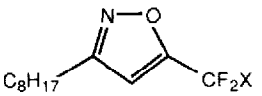
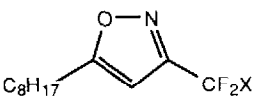
Reaction of acetylene 1 with hydroxylamine hydrochloride in methanol with a catalytic amount of sodium hydroxide lead to the isolation of a mixture of the oxime 4, the 3-trifluoromethyl substituted isoxazole 5, and the 5-trifluoromethyl-3-hydroxyisoxazoline derivative 6 in a ratio of 1:2:2.3, respectively. 6 exhibited the same characteristic AB quartet in the ^{1}H-NMR (3.15 ppm) as did the hydroxy pyrazoline 3. Further treatment of the crude reaction product in refluxing benzene provided a mixture of four compounds, 4, 5, 6, and the 5-trifluoromethyl substituted isoxazole 7. The regioisomeric isoxazoles 5 and 7 were distinguishable by ^{19}F-NMR (-64.0 ppm and -65.0 ppm for 5 and 7, respectively) and were easily



1 4 5 6 7

separated on capillary GC. After several trials, reaction conditions leading only to the oxime 4 (AcOH,cat 10%HCl,RT,15h) and conditions leading only to the isoxazoline 6 (MeONa/MeOH,Δ,2h) were determined. Subjecting the clean oxime 4 to refluxing benzene with azeotropic removal of water resulted in the formation of only the 3-trifluoromethyl substituted isoxazole 5. Similarly, isoxazoline 6 provided only the 5-trifluoromethyl regioisomer 7. The regioselectivity of the reaction of a heterocyclic nucleophile with a trifluoroacetyl acetylene can therefore be controlled by the choice of reaction conditions (acidic or basic). An additional example of regiospecfic isoxazole synthesis is given in the Table.

TABLE SYNTHESIS OF TRI- AND DIFLUOROMETHYL SUBSTITUTED HETEROCYCLES

Entry	Acetylene	Product	Yield, %[a]
1			X = F 92 X = H 78
2			X = F 86 X = H 89
3			X = F 76 X = H 82
4			X = F 64[b] X = H 70[b]
5			X = F 80[c] X = H 74[c]

[a] Isolated yield after chromatography. All new compounds exhibited correct spectral and combustion analytical data. [b] Reaction carried out under basic conditions (see text). [c] Reaction carried out under acidic conditions (see text).

In summary, we have developed a highly efficient regiospecific synthetic procedure for the preparation of trifluoromethyl substituted pyrazoles and isoxazoles ultimately derived from ethyl trifluoroacetate in two steps. Further studies on the generality of this process in the synthesis of other heteroaromatic compounds is underway.

Acknowledgments Dr. Kirollos would like to thank the Fulbright Scholar Program for a Research Scholar Award.

References and Footnotes

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4. For a review, see M. V. George, S. K. Kheton, R. K. Gupta, Adv. Heterocyclic Chem., 19, 279 (1976). We have reported [3] an efficient method for the preparative scale production of trifluoroacetyl acetylenes.

5. Trifluoromethyl carbonyl compounds readily undergo nucleophilic addition at the carbonyl by a variety of nucleophilic species. In water, the carbonyl is essentially completely hydrated, see C. D. Ritchie, J. Am. Chem. Soc., 106, 7187 (1984).

6. Trifluoromethyl pyrazoles have been prepared from 2,2,2-trifluorodiazoethane; however, this compound is nearly as explosive as TNT. R. Fields, J. P. Tomlinson, J. Fluorine Chem., 13, 147 (1979).

(Received in USA 23 January 1989)