JOURNAL OF THE CHEMICAL SOCIETY

Chemical Communications

Number 2
1993

A Convenient Synthesis of 2-Trifluoromethylpyrroles *via* Base-promoted Cyclocondensation of Trifluoromethyloxazolones with Electron-deficient Alkenes

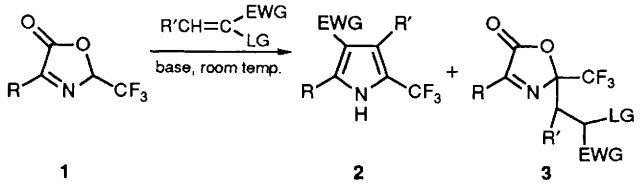
Wei-sheng Tian,* Yong-rong Luo, Yu-qun Chen and Ai-jun Yu

Shanghai Institute of Organic Chemistry, Academia Sinica, 345 Lingling Lu Shanghai 200032, PR China

The cyclocondensation of trifluoromethyloxazolones with electron-deficient alkenes in the presence of base gives 2-trifluoromethylpyrroles and related heterocyclic compounds in good yields; the reaction involves the tandem Michael addition of trifluoromethyloxazoles to electron-deficient alkenes, intramolecular cyclization and decarboxylation.

The development of synthetic methodology for heterocyclic compounds bearing a trifluoromethyl group has received current interest because of their ability to enhance biological activity.[1] The synthesis of trifluoromethyl heterocyclic compounds using a synthon with a trifluoromethyl group has often been found to be superior to either selective introduction of a trifluoromethyl group into heterocyclic compounds or conversion of a carboxy group into the trifluoromethyl group.[2] Choosing a readily available synthon with a trifluoromethyl group is also very important for successful synthesis of trifluoromethyl heterocyclic compounds. It was known that trifluoromethyloxazolones could easily be prepared from a suitable α-amino acid and trifluoroacetic anhydride,[3] which have been used for the synthesis of a peptide and γ-keto ester.[4] As an equivalent of the 1,3-dipole with a trifluoromethyl group, we have used Δ^3-trifluoromethyloxazolones to synthesize the trifluoromethylpyrroles *via* 1,3-dipolar cycloaddition and decarboxylation.[5] Here, we report a new versatile synthesis of trifluoromethylpyrroles from trifluoromethyloxazolones *via* the base-promoted tandem cyclocondensation under mild conditions and in good yields (Scheme 1).

In the presence of organic base, Michael addition of oxazolones to activated unsaturated bonds has been reported.[3] However, treatment of the trifluoromethyl group of oxazolone **1a** (R = Ph) and α-chloroacrylonitrile with triethylamine, gave 2-trifluoromethylpyrrole **2a** as the main reaction product instead of the Michael adduct **3a**. The reaction conditions were very mild and the yield was good. It is obvious that the difference between of our result and that reported in literature is due to the presence of the trifluoromethyl group in oxazolone. The reaction is also suitable for other trifluoromethyloxazolones and compounds containing unsaturated bonds. Some examples are summarized in Table 1.

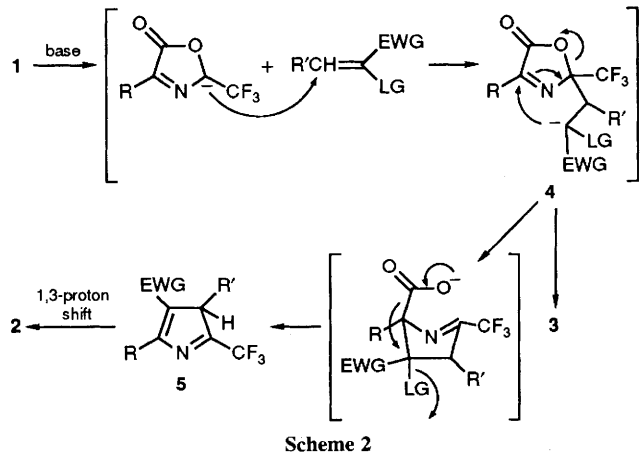


1 2 3

Scheme 1

A plausible mechanism for this reaction is suggested in Scheme 2. The carbanion of **1**, generated by treatment of **1** with organic base, is added to the activated alkene to yield a new carbanion intermediate **4**. Usually **4** can accept a proton to give Michael adduct **3**, but in the case of oxazolones with a trifluoromethyl group tandem intramolecular cyclization, involving a Mannich-like reaction, decarboxylation and elimination, occurred with intermediate **4**. The reaction gave 3*H*-pyrrole **5** that underwent a 1,3-proton shift to produce 1*H*-trifluoromethylpyrrole **2**.

The reaction was found to be influenced by the R group in **1** and the base used. In general, an electron-withdrawing group R in **1** and the stronger the base used in the reaction were favourable for the formation of 2-trifluoromethylpyrroles **2**. Otherwise, the Michael adduct was the main product instead of **2**. The reaction product was also influenced by the electron-withdrawing group (EWG) and the leaving group (LG) in the alkenes. In entry 5 (Table 1), the main product was trifluoromethylpyrrole **2e**. In the same reaction, when the CN group in the alkene was replaced by CO_2Me, the Michael adduct **3** was the only product obtained in high yield. The tandem cyclocondensation reaction of **1a** and methyl acrylate can occur by raising the reaction temperature and by using a stronger base such as 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU).



1 2 3 4 5

Scheme 2

Table 1 Tandem cyclocondensation of trifluoromethyloxazolones with electron-deficient alkenes in the presence of base[a]

Entry	R	R′	EWG	LG	Base	*t*/h	Product[b]	Yield (%)[d]
1	Ph	H	CN	Cl	Et_3N	4	**2a**[c]	70
2	*p*-BrC_6H_4	H	CN	Cl	Et_3N	4	**2b**	65
3	*p*-$MeOC_6H_4$	H	CN	Cl	DBU	5.5	**2c**	74
4	Ph	H	CF_3	Br	DBU	3	**2d**	87
5	Ph	H	CN	H	Et_3N	11.5	**2e**	55
6	$PhCH_2$	H	CN	Cl	DBU	6	**2f**	58

[a] *General procedure*:[3] To a solution of **1** (1 mmol) and the alkene (1–10 mmol) in dry dichloromethane (1.5 ml) was added base (1 mmol). The mixture was then stirred at room temp. until the TLC spot of **1** disappeared. Removal of solvent under reduced pressure gave the crude product, which was purified on a silica gel column to give **2** or **3**. [b] M.p.s, MS, IR and ^1H NMR spectra of the products were identifcal with those of authentic samples. [c] *Selected spectroscopic data* for **2a**: m.p. 218–219 °C. IR γ cm^{-1} (KCl): 2200 (CN). ^1H NMR (90 MHz, $CDCl_3$): δ 7.78 (2H, dd, *J* 8 and 1.6 Hz, Ar-H), 7.54 (3H, m, Ar-H), 7.28 (1H, br s). ^{19}F NMR (ext. ref. TFA, positive for upfield shifts) (60 MHz, $DCCl_3$): δ −16.6 (s, CF_3). MS *m/z*: 237 ($M^+ + 1$), 236 (M^+), 216 ($M^+ - HF$); satisfactory elemental analyses were obtained. [d] Isolated yield.

The reaction can be used for the synthesis of trifluoromethylpyrroles with a variety of substituents at C-3, C-4 and C-5 by choosing the appropriate **1** and activated alkenes. Some 2,4-bis(trifluoromethyl)pyrroles were synthesized by the reaction of **1** and 1,1,1-trifluoro-2-bromopropene as entry 4 in Table 1. This reaction was also suitable for the synthesis of 2-trifluoromethylpyrrolines (see entry 5, Table 1).

We thank the National Science Foundation of China for financial support.

Received, 6th July 1992; Com. 2/03553G

References

1 J. H. Welch, *Tetrahedron*, 1987, **43**, 3123; R. Filler and Y. Kobayashi, *Biomedicinal aspects of fluorine chemistry*, Kodasha Ltd, Tokyo, 1982; H. Yoshioka, C. Takayama and N. Matsuo, *J. Synth. Org. Chem. Jpn.*, 1984, **42**, 809.
2 H. Ono, Y. Shiraishi and H. Sujuki, *Bull. Chem. Soc. Jpn.*, 1989, 3386; G. B. Blachwell, R. N. Haszeldine and D. R. Taylor, *J. Chem. Soc., Perkin Trans. 1*, 1982, 2207.
3 T. Weygand, W. Steglich and H. Tanner, *Liebigs Ann. Chem.*, 1962, 658, 128.
4 J. Bergmann and G. Lingren, *Tetrahedron Lett.*, 1989, **30**, 4597.
5 W. S. Tian, Y. Q. Chen, Y. R. Luo, X. W. Deng, *Chin. Chem. Lett.*, 1991, **2**, 217.