



Three-component synthesis of substituted β -(trifluoromethyl)pyrroles via Grob cyclization of 1,1,1-trifluoro-3-nitrobut-2-ene with 1,3-dicarbonylic compounds and ammonia or primary amines

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ABSTRACT

A variety of substituted β -(trifluoromethyl)pyrroles were easily synthesized in good yields by a one-pot, three-component Grob cyclization of 1,1,1-trifluoro-3-nitrobut-2-ene with 1,3-dicarbonyls (ethyl acetoacetate, acetylacetone, benzoylacetone) and ammonia or primary aliphatic amines.

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1. Introduction

Much attention has been addressed to trifluoromethylated heterocyclic compounds because they often show unique biological and physiological activities [1]. In particular, trifluoromethyl-substituted pyrroles and other five-membered heterocycles have drawn considerable attention [2]. The search for a simple and efficient access to such compounds with a CF_3 group at a specific position is one of the important goals in this area. However, there are a limited number of regioselective syntheses of CF_3 -containing heteroaromatic compounds in good yield. In the case of β -(trifluoromethyl)pyrroles, only a few synthetic concepts have been developed [1e].

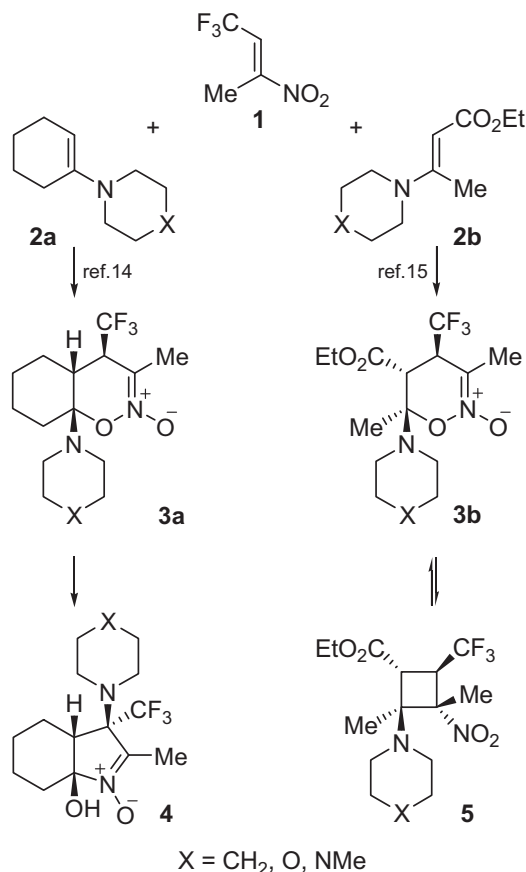
These compounds have been synthesized by the modified Knorr condensation from ethyl trifluoroacetoacetate and 1,3-dicarbonyls in strong acid media [3]. Reaction of α -(trifluoromethyl)alkenyl sulfones with ethyl isocynoacetate in the presence of a base gave 4-(trifluoromethyl)pyrrole-2-carboxylates in moderate to good yields [4]. A one-step formation of the pyrrole ring from Michael acceptors and tosylmethylisocyanide under basic conditions was reported by van Leusen et al. [5]. The application of this procedure to the alkyl (*E*)-4,4,4-trifluorobutenoates led to the corresponding 4-(trifluoromethyl)pyrrole-3-carboxylates [6]. Ogoshi and coworkers applied

this procedure to the preparation of 3-acetyl-4-(polyfluoroalkyl)pyrroles in somewhat lower yields [7]. 1,3-Dipolar cycloaddition of munchnones (1,3-oxazolium 5-olates) to β -chloro- β -(trifluoromethyl)vinyl phenyl ketone, butyl β -chloro- γ,γ,γ -trifluorocrotonate and polyfluoroacetylenic esters proceeds in a regiospecific manner under mild reaction conditions, followed by simultaneous decarboxylation to afford 4-(polyfluoroalkyl)pyrrole-3-carboxylate derivatives [8]. Cyclodehydration of the products obtained by oxygen-nitrogen exchange reaction of 4-alkoxy-1,1,1-trifluoro-3-buten-2-ones with esters of α -aminoacids, α -aminoacetophenone and 2,2-dimethoxyethylamine into fluorine-containing pyrroles is also described [9]. In addition, the introduction of a polyfluoroalkyl group in moderate yield was achieved by 1,2-addition of Me_3SiCN to β -alkoxyvinyl polyfluoroalkyl ketones, followed by reduction with LiAlH_4 and subsequent hydrolysis with intramolecular cyclization [10]. Although these reaction sequences have been developed for the regioselective introduction of a R^{F} group in the pyrrole ring, there are remaining problems to be solved, such as the handling of the materials and availability of reagents. Herein we wish to demonstrate utility of readily available (*E*)-1,1,1-trifluoro-3-nitrobut-2-ene **1** [11] as a novel building block for the construction of 4-(trifluoromethyl)pyrroles bearing different electron-withdrawing substituents at the 3-position via addition of push-pull enamines.

Nucleophilic addition of enamines to conjugated nitroalkenes is an efficient method for preparation of cyclobutanes, 1,2-oxazine *N*-oxides and nitroalkylated enamines or γ -nitroketones [12] that, in

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Scheme 1. Compounds 3–5 obtained previously from nitrobutene 1.

turn, are widely used in organic synthesis [12,13]. We have recently investigated the reaction of nitrobutene **1** with tertiary enamines **2a,b** and described the first example of spontaneous ring-contraction–rearrangement of 1,2-oxazine *N*-oxides **3a** into 1-pyrroline *N*-oxides **4** [14] and a new type of ring-ring tautomerism between 1,2-oxazine *N*-oxides **3b** and cyclobutanes **5** [15] (Scheme 1).

In this paper we report a general method for the preparation of β -(trifluoromethyl)pyrroles, which is based on the three-component variant of Grob cyclization. In this pyrrole synthesis, nitroalkenes are commonly employed because the nitro group can act both as a powerful stabilizer of the intermediate anion and as a good nucleofuge in the aromatization forming a pyrrole ring. In view of the utility of this reaction in synthetic chemistry [16], we envisioned the use of nitrobutene **1** as a synthon for trifluoromethylated pyrroles, some of which represent a new class of insect control agents [17]. Although there is one report on the preparation of β -(trifluoromethyl)pyrroles by reaction of active methylene compounds with 3,3,3-trifluoro-1-nitropropene, followed by the reduction of the nitro group and subsequent cyclization [18], the use of nitrobutene **1** in the synthesis of CF₃-containing heterocycles has not been reported, except for compounds **3** and **4**.

2. Results and discussion

We found that nitrobutene **1**, which is easily obtainable from fluoral hydrate and nitroethane [11], reacted with 1,3-dicarbonyls (ethyl acetoacetate, acetylacetone and benzoylacetone) and primary aliphatic amines at reflux in ethanol to give β -(trifluoromethyl)pyrroles **7** in 42–75% yields. In most cases, the

Table 1
Synthesis of compounds **7a–r**.

7	R ¹	R ²	Yield (%) ^a
a	OEt	H	28
b	OEt	Me	66
c	OEt	Et	42
d	OEt	HO(CH ₂) ₂	50
e	OEt	Bn	75
f	OEt	Ph(CH ₂) ₂	69
g	OEt	3,4-(MeO) ₂ C ₆ H ₃ (CH ₂) ₂	57
h	Me	H	24
i	Me	Me	48
j	Me	Et	51
k	Me	HO(CH ₂) ₂	66
l	Me	Bn	64
m	Me	Ph(CH ₂) ₂	52
n	Me	3,4-(MeO) ₂ C ₆ H ₃ (CH ₂) ₂	48
o	Ph	H	25 ^b
p	Ph	Bn	54
q	Ph	Ph(CH ₂) ₂	50
r	Ph	3,4-(MeO) ₂ C ₆ H ₃ (CH ₂) ₂	48

^a Isolated yield.

^b In propan-1-ol.

reaction was complete after 1 h and the products could be isolated by column chromatography over silica gel. The similar reaction of 25% aqueous solution of ammonia afforded *N*-unsubstituted pyrroles **7a,h,o**, albeit in lower yields (24–28%). The progress of the reaction was monitored by ¹H and ¹⁹F NMR spectroscopy, and the results are summarized in Table 1. In the case of benzoylacetone, the regiochemistry was controlled by the more reactive acetyl group, which underwent preferential attack on the amine. The structure of the benzoyl derivative **7q** was confirmed by X-ray crystal structure analysis (Fig. 1) [19]. A plausible pathway leading to the formation of these compounds via intermediate aminoenones **6** is outlined in Scheme 2 [16b]. In contrast to its homologue **1**, (*E*)-3,3,3-trifluoro-1-nitropropene, lacking the methyl group, failed to give the corresponding pyrroles on reaction with 1,3-dicarbonyls and aliphatic amines under the same conditions. This indicated that cyclization in the case of a primary nitronate is not efficient.

This approach is the first example of successful three-component Grob synthesis of fully substituted β -(trifluoromethyl)pyrroles **7** and has advantages with regard to ease of operation and the ready availability of starting materials. It should be noted that primary and secondary push–pull enamines **6** could be employed directly under these conditions to give pyrroles **7** in 40–65% yields, however, a one-pot three-component reaction is much more convenient. Note that in contrast to enamines **6**,

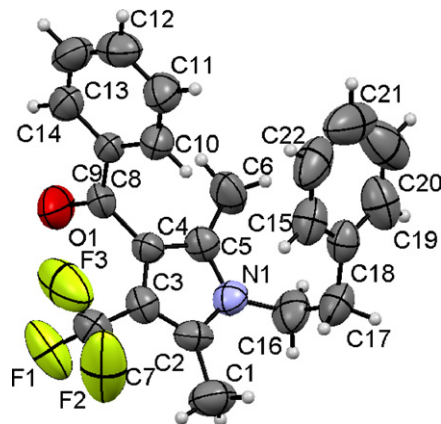


Fig. 1. Molecular structure of pyrrole **7q**.

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