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Regiospecific Synthesis of 4-Alkoxy and 4-Amino Substituted 2-Trifluoromethyl Pyrroles

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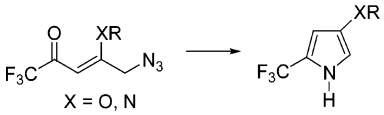

A simple and regiospecific synthesis of 4-alkoxy(amino)-2-trifluoromethyl pyrroles from 5-azido-4-alkoxy-(amino)-1,1,1-trifluoro-pent-3-en-2-ones by an aza-Wittig cyclization of aminophosphoranes is described. The structures of the pyrroles and their synthetic intermediates were supported by NMR and HRMS analysis.

The development of a methodology for synthesizing heterocyclic compounds bearing a trifluoromethyl group has received much attention recently, because the introduction of halogenated groups in organic molecules often improves their biological activity, probably because of the high lipophilicity of the trifluoromethyl group.[1] The most convenient method to construct halogenated compounds is to make use of halogen-containing building blocks as starting reagents.[2] Trifluoromethylated 4-alkoxyvinyl ketones represent interesting precursors for the synthesis of trifluoromethyl containing compounds, especially heterocyclic systems.[3]

Among the numerous heterocycles, the pyrrole core has been one of the most prominent, because this structure is present in many important classes of natural products,[4] and many pyrrole derivatives exhibit interesting biological activities.[5] Other examples of simple pyrrole derivatives that exhibit remarkable activity[6] are antibiotics, such as pyrrolnitrine and verrucarin E,[7] and pheromones, such as methyl 4-methylpyrrole-2-carboxylate,[8] the trail marker of the Texas leaf-cutting ant (*Atta texana*), just to name a few. Furthermore, trifluoromethyl substituted pyrroles

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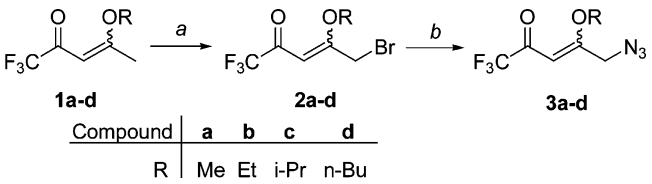
SCHEME 1



Reagents and conditions. (a) (1) Br_2, CH_2Cl_2, 0 °C to rt, 2 h; (2) Py, 0 °C to rt, 1 h. (b) NaN_3, acetone, 0 °C to rt, 1 h.

are rare compounds; however, they have been shown to exhibit significant insecticidal and acaricidal activity.[9]

The 2- or 5-substituted pyrroles are easily synthesized by aromatic electrophilic substitution,[10] whereas a special strategy is necessary to obtain 3- or 4-substituted pyrroles.[11] Furthermore, pyrroles bearing electron-donor substituents are not very stable.[12] Probably for this reason, alkoxy and alkylamino substituted pyrroles are not as often reported as the pyrroles bearing electron-withdrawing substituents.[13] Therefore, it is important to note that there is a clear demand for the development of a modular and simple reaction to strategically access substituted pyrroles.[14]

In this paper, we wish to report a simple and regiospecific synthesis of new 4-alkoxy and 4-amino substituted 2-trifluoromethyl pyrroles from the Staudinger reaction of the readily available 5-azido-1,1,1-trifluoro-4-alkoxy(amino)-pent-3-en-2-ones with triphenyl- or trimethyl-phosphine, followed by an intramolecular aza-Wittig cyclization of iminophosphoranes. To the best of our knowledge, no description of the use of such compounds for the synthesis of 4-alkoxy or 4-amino substituted 2-trifluoromethyl pyrroles has been reported.

Scheme 1 outlines the synthesis of the key intermediates **3a**−**d**, which starts with the preparation of the enone **1a**, whose synthesis has been published previously.[15] To increase the number of substituents (R), *trans*-etherification reactions of **1a** were performed with alcohols such as ethanol, 2-propanol, and butanol with a catalytic amount of *p*-toluenesulfonic acid, furnishing compounds **1b**−**d**.[16] The brominated compounds **2a**−**d** were prepared in good yields from the reaction of **1a**−**d** with bromine and pyridine in dichloromethane.[17] The subsequent reaction with sodium azide furnished the 5-azido-4-alkoxy-1,1,1-trifluoro-methyl-pent-3-en-2-ones **3a**−**d** (Scheme 1, Table 1).[17]

TABLE 1. Reaction Conditions and Yields for the Synthesis of Compounds 2 and 3

compd	R	reaction conditions[a]	yield (%)[b]	product
1a	Me	a	95	**2a**
1b	Et	a	94	**2b**
1c	*i*-Pr	a	93	**2c**
1d	*n*-Bu	a	93	**2d**
2a	Me	b	90	**3a**
2b	Et	b	70	**3b**
2c	*i*-Pr	b	88	**3c**
2d	*n*-Bu	b	74	**3d**

[a] Reaction conditions: (a) (1) Br_2, CH_2Cl_2, 0 °C to rt, 2 h; (2) Py, 0 °C to rt, 1 h. (b) NaN_3, acetone, 0 °C to rt, 1 h. [b] Yields of pure isolated products.

TABLE 2. Reaction Conditions and Yields for the Synthesis of Compounds 5a−f and 6a−f

compd	R^1	R^2	reaction conditions[a]	yield (%)[b]	product
3a	Me	Me	c	79	**5a**
3b	Et	Et	c	89	**5b**
3c	$-(CH_2)_4-$		c	82	**5c**
3d	$-(CH_2)_5-$		c	90	**5d**
3e	$-(CH_2)_2-O-(CH_2)_2-$		c	92	**5e**
3f	Bn	Bn	c	76	**5f**
5a	Me	Me	d	72	**6a**
5b	Et	Et	d	78	**6b**
5c	$-(CH_2)_4-$		d	81	**6c**
5d	$-(CH_2)_5-$		d	61	**6d**
5e	$-(CH_2)_2-O-(CH_2)_2-$		d	64	**6e**
5f	Bn	Bn	d	77	**6f**

[a] Reaction conditions: (c) HNR^1R^2, CH_3CN, 0 °C to rt, 8 h; (d) Me_3P, THF, 0 °C to rt, 8 h. [b] Yields of pure isolated compounds.

In a second strategy, the bromination of **1a** was carried out first, followed by the *trans*-etherification of the brominated **2a** with alcohols. In addition, the *trans*-etherification reaction was performed on the azido compound **3a** to reduce the number of reactions. However, the *trans*-etherification reaction using both **2a** and **3a** gave a complex mixture of products, proving to be impractical.

Having obtained the 5-azido-1,1,1-trifluoro-4-methoxy-pent-3-en-2-ones **3**, we concentrated our efforts on the synthesis of the pyrrole rings. The reaction was initially carried out with the azido compound **3a**, to determine the best reaction conditions (Table 2). It is well-known that the azido function can be easily reduced with phosphines to iminophosphoranes, which can effect an aza-Wittig attack on an electron-deficient carbon.[18]

A similar reaction was presented by Montforts et al.,[12a] where 2-azido-ethylidene-malonic acid methyl esters reacted with triphenylphosphine to give a series of 2-methoxy-1-*H*-pyrrole-3-carboxylic acid methyl esters. According to the study of Dieter and Yu,[13] the inability to control olefin stereochemistry in the γ-amino-α,β-enone adduct **I** (Figure 1) could pose serious problems to the pyrrole formation, unless both stereoisomers could be cyclized to the corresponding pyrrole as is possible

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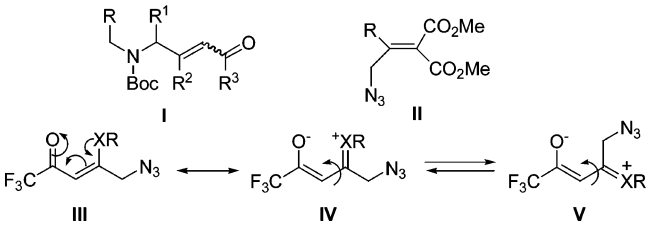


FIGURE 1. Structures of precursors used in the synthesis of pyrroles.

for the compounds in structure **II** (Figure 1). An anti relationship between the carbon−carbon double bond of the methyl azido and the carbonyl groups of intermediate **III** could hinder the formation of the corresponding pyrroles. However, the low energy barrier of the carbon−carbon double bond observed in compounds such as **3** and **5** (Schemes 2 and 3, respectively), which is driven by the electron "push−pull" effect of the carbonyl (π-acceptor) and the 4-alkoxy or 4-amino groups (π-donor), allows one to draw resonance structures such as **III** and **IV** (Figure 1), where the rotation around the C3−C4 bond is less restricted. Thus, because of the easy interconversion between the *E* and *Z* isomers (structures **IV** and **V**), the azido intermediates **3** and **5** can be completely converted to the corresponding pyrroles **4** and **6** regardless of the configuration of the carbon−carbon double bond.

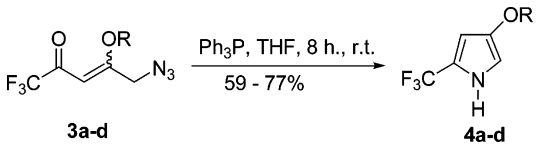
Thus, through the reaction of compounds **3** with an equimolar amount of triphenylphosphine in THF, the desired 4-alkoxy-2-trifluoromethyl pyrroles **4a**−**d** were isolated in moderate to good yields after short reaction times (Scheme 2).

We attempted to improve the yields by changing reaction conditions, such as temperature, reaction times, and amount of phosphine. It was observed that the utilization of 2 equiv of phosphine did not improve the yields and, when the reaction was carried out in THF under reflux, the product was not observed, probably owing to the decomposition of the starting material. Compounds **4a**−**d** that resulted in oils after purification were not very stable and needed storage at −4 °C.

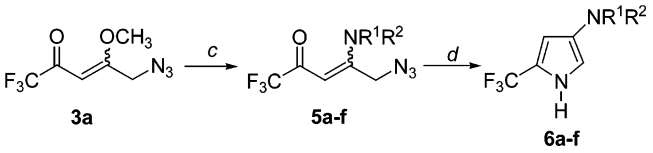
We observed that the methoxy group of **3a** could also be replaced by an amino group, to obtain 4-amino substituted 2-trifluoromethyl pyrroles. The precursors for these derivatives were achieved when compound **3a** underwent a reaction with a series of secondary amines in acetonitrile[19] (Scheme 3). Initially, the cyclization step was also performed using triphenylphosphine as the azido reducing agent. However, the triphenylphosphin-oxide byproduct formed during the course of the cyclization reaction was very difficult to separate from the obtained 4-amino pyrroles **6** by means of column chromatography, distillation, or recrystallization.

This problem was circumvented by changing the triphenylphosphine reagent to trimethylphosphine. Since the trimethylphosphinoxide is soluble in water, it was easily removed by the extraction step, and products were further purified by distillation in a Kugelrohr oven and recrystallization from a dichloromethane/hexane mixture. The 4-amino pyrrole products **6a**−**f** were obtained in better yields (Table 2) than the 4-alkoxy pyrrole derivatives **4a**−**d**, probably because compounds **6** are more stable than compounds **4**. However, the attempted cyclization of **5**, derived of primary amines, rendered a complex mixture of products.

SCHEME 2



SCHEME 3



In summary, we have developed a simple, efficient, and regiospecific synthetic procedure for the preparation of new 4-alkoxy and 4-dialkylamino substituted 2-trifluoromethyl pyrroles, using mild conditions in order to not set off the decomposition of the products. In addition, this study showed that 5-azido-1,1,1-trifluoro-4-alkoxy(amino)-pent-3-en-2-ones **3** and **5** are convenient key intermediates for the synthesis of 4-alkoxy and 4-dialkylamino substituted 2-trifluoromethyl pyrroles, since they are easily obtained in good yields and the cyclization step does not depend on the *E/Z* configuration of the carbon−carbon double bond of **3** and **5** for the cyclization to take place.

Experimental Section

General Procedure for the Synthesis of 4-Alkoxy-pyrroles 4a−d. A solution of Ph_3P in THF (1M, 1.0 mL) was slowly added to a stirred solution of azido compounds **3** (1.0 mmol) in dry THF (4 mL) with a syringe at room temperature. After 8 h, the THF was removed in vacuo, and the oil residue was distilled in a Kugelrohr glass oven, affording the pyrroles as yellow oils.

General Procedure for the Synthesis of 4-Dialkylamino-pyrroles 6a−f. In a 25 mL round-bottom flask, a solution of azido compounds **5** (1.0 mmol) in dry THF (5 mL) was cooled to 0 °C with an ice bath. Me_3P (1 M in THF, 1.0 mL) was slowly added to this solution with a syringe. The reaction was allowed to reach room temperature, and stirring was continued for an additional 8 h. The THF was removed in vacuo, and the residue (for **6a**, and **6c**−**f**) was dissolved in a 1:1 mixture of hexane/CH_2Cl_2 (2 mL) for crystallization by cooling. Compound **6b** was purified in a Kugelrohr glass oven and obtained as an orange oil.

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Supporting Information Available: Representative experimental procedure, characterization data (^1H and ^{13}C NMR, HRMS-(ESI), and IR), and selected ^1H and ^{13}C NMR and HRMS spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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