ORGANIC LETTERS

2010
Vol. 12, No. 21
4776−4779

New Synthesis of 3-Trifluoromethylpyrroles by Condensation of Mesoionic 4-Trifluoroacetyl-1,3-oxazolium-5-olates with Phosphorus Ylides

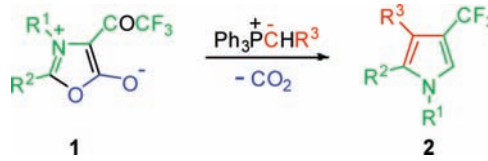
Ryosuke Saijo, Yuri Hagimoto, and Masami Kawase*

Faculty of Pharmaceutical Sciences, Matsuyama University, Matsuyama, Ehime 790-8578, Japan

kawase@cc.matsuyama-u.ac.jp

Received August 10, 2010

ABSTRACT



Mesoionic 4-trifluoroacetyl-1,3-oxazolium-5-olates (1), obtained from the reaction of *N*-acyl-*N*-alkylglycines with trifluoroacetic anhydride, react with phosphorus ylides to give *β*-trifluoromethylpyrroles (2) in good yields. The novel ring transformations of 1 into 2 occur via an initial attack of the ylide anions on the C-2 position of the ring.

The development of a methodology for the synthesis of heterocyclic compounds bearing a trifluoromethyl or perfluoroalkyl group has received much attention recently since the introduction of these groups in organic molecules often improves their biological activities for medicines and agrochemicals.[1] Pyrroles are important heterocycles in bioorganic chemistry and are present in many natural products and pharmaceuticals.[2] In particular, trifluoromethylated pyrroles have drawn considerable attention.[3] The 2-trifluoromethylpyrroles are easily synthesized by electrophilic aromatic substitution,[4] whereas a special strategy is necessary to obtain 3-trifluoromethylpyrroles.[3] Therefore, several methods for the synthesis of 3-trifluoromethylpyrroles have been described in the literature:[3] (a) 1,3-dipolar cycloadditions using trifluoromethylated dipolarophiles,[5] (b) condensation of electron-deficient alkenes with isocyanomethylide anions,[6] (c) a classical approach using α,*β*-unsaturated trifluoromethyl ketones as building blocks,[7] (d) coupling cyclization reaction of 1,3-diketones with appropriate amines,[8] (e) the Paal−Knorr synthesis using 1,4-dicarbonyl precursors,[9] and (f) Knorr synthesis using *β*-keto esters and α-amino ketones.[10] Whereas these methods have proven very useful for the synthesis of 3-trifluoromethylpyrroles, they generally involve multistep

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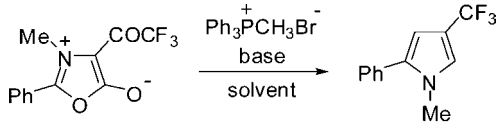
10.1021/ol1018689
Published on Web 10/05/2010

synthetic operations that limit the scope of these reactions. Indeed, it is still desirable to develop an efficient method for the synthesis of 3-trifluoromethylpyrroles.[3] In this paper, we wish to report a simple and regioselective synthesis of β-trifluoromethylpyrroles from the Wittig reaction of the readily available 4-trifluoroacetyl-1,3-oxazolium-5-olates **1**, obtained from the reaction of *N*-acyl-*N*-alkylglycines with trifluoroacetic anhydride.

Mesoionic oxazoles **1** with 4-trifluoroacetyl group are commonly known as munchnone derivatives[11] and represent interesting precursors for the synthesis of trifluoromethyl containing compounds, especially heterocyclic systems.[12−15] In general, the munchnones are too unstable to be isolated, whereas 4-trifluoroacetylated **1** can be isolated and stored for several months. In principle, the addition of nucleophiles to **1** can a priori be expected to occur at three different positions (C-2, C-5, or $COCF_3$). We have previously demonstrated the remarkable ability of phenylhydrazine to react with **1** at three different positions, depending on the nature of the solvent and reaction temperature.[12] *N*-Nucleophiles such as ammonia[13] and amidines[14] attacked at C-2 position of **1**. These data are consistent with the previous MO study that *N*-nucleophiles attack at C-2 in the mesoionic oxazole **1** on the basis of the HSAB theory.[15] We now examined the question which position of mesoionic **1** would be attacked by phosphorus (P)-ylides in the Wittig reaction.

We found that, upon treatment of **1a** with the ylide, methylenetriphenylphosphorane, generated from methyltriphenylphosphonium bromide (2.4 molar equiv) using *n*-BuLi (2.2 molar equiv) at −20 °C, a clean reaction occurred, leading to the 4-trifluoromethyl-1-methyl-2-phenylpyrrole **2a** in 74% yield (Table 1, entry 4). The effect of

Table 1. Conditions Tested for the Wittig Reactions



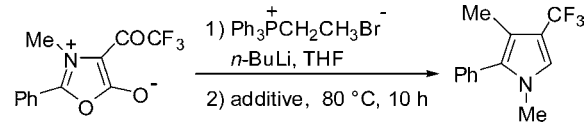
1a **2a**

entry	P^+ (equiv)	base (equiv)	solvent	conditions (temp (°C), time (h))	yield (%)
1	1.4	*n*-BuLi (1.2)	THF	−20 to rt, 20	34
2	1.2	*t*-BuOK (3)	DMF	rt, 15	15
3	1.2	NaH (3)	THF	rt, 25	
4	2.4	*n*-BuLi (2.2)	THF	−20 to rt, 10	74
5	2.4	*n*-BuLi (2.2)	THF	−78 to rt, 10	43
6	3.4	*n*-BuLi (3.2)	THF	−20 to rt, 10	65

the base, molar ratio of the reagents, and reaction temperature on the yield of **2a** were briefly investigated.

A 2.4 equiv portion of the ylide against **1a** was needed to obtain a high yield of **2a**, as 1.2 equiv reduced the yield. The use of 3.4 equiv did not improve the yield. The use of *t*-BuOK at rt in DMF or NaH at rt in THF afforded inferior results. Using the same reaction conditions (Table 1, entry 4), the reaction of **1a** with ethyltriphenylphosphonium bromide was performed to give a poor yield (14%) of the corresponding pyrrole **2b** (Table 2, entry 1). In the reaction,

Table 2. Wittig Reaction Optimized Studies[a]



1a **2b**

entry	additive	yield (%)
1	none	14
2	none[b]	18
3	AcOH	87
4	$(CF_3)_2CHOH$	83
5	TFA	49
6	EtOH	33
7	BuOH	29
8	5% H_2SO_4	19
9	pyridine	10
10	5% NaOH	8

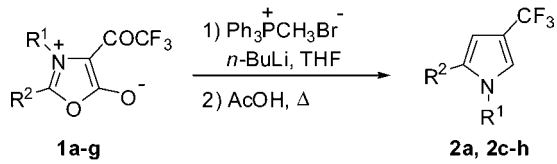
[a] 2.4 equiv of phosphonium salt and 2.2 equiv of *n*-BuLi were used. [b] Reflux, 10 h.

significant amounts of more polar products were detected by TLC after the Wittig reaction. Therefore, the subsequent addition of AcOH to the reaction mixture and heating the mixture at 80 °C led to clean formation of the pyrrole **2b** in a high yield (87%) (Table 2, entry 3). Among the examined additives (Table 2, entries 3−10) after the reaction, hexafluoro-2-propanol and AcOH gave good results: conducting the reaction in the presence of other additives (e.g., EtOH, BuOH, TFA, 5% H_2SO_4, pyridine, 5% NaOH) afforded lower yields (Table 2, entries 5−10); the best result was obtained in the addition of AcOH.

Having established the optimal reaction conditions (Table 2, entry 3), we studied the use of various mesoionic oxazoles **1b**−**g** (Table 3) as well as different Wittig reagents (Table 4) to synthesize a variety of 1,2-disubstituted or 1,2,3-trisubstituted 4-trifluoromethylpyrrole derivatives. As shown in Table 3, the one-pot protocol (method 2) by the addition of a ylide followed by AcOH (Table 2, entry 3) afforded improved yields of the pyrroles **2**, compared with the conditions (method 1) in entry 4 of Table 1. The yield with those of a linear alkyl chain is good (Table 4, entries 1−4), but the reaction with the ylide having a branch is poor (Table 4, entry 9). Benzylphosphonium ylide, a semistabilized ylide, gave poor yield (Table 4, entry 10). Most probably, the steric hindrance is responsible for the low reactivity, and the known low reactivity of the ylides can explain the result.

3-Substituents in the pyrroles **2** were changed by choosing the R group of the ylides ($Ph_3P{=}CHR$). However, in the case of α-substituted Wittig reagents ($Ph_3P^+CH_2R$, R = OCH_3, SCH_3, and $Si(CH_3)_3$), the corresponding pyrroles were obtained in poor yields (Table 4, entries 5−8).

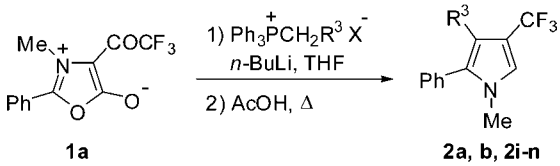
Table 3. Yields of 1,2-Disubstituted 4-Trifluoromethylpyrroles



				product (yield, %)	
entry	**1**	R^1	R^2	method 1[a]	method 2[a]
1	**1a**	Me	Ph	**2a** (74)	**2a** (90)
2	**1b**	Ph	Ph	**2c** (19)	**2c** (70)
3	**1c**	Ph	Me	**2d** (14)	**2d** (60)
4	**1d**	Bn	PMP	**2e** (80)	**2e** (88)
5	**1e**	Bn	Ph		**2f** (87)
6	**1f**	PMB	Ph		**2g** (87)
7	**1g**	Me	*t*-Bu	**2h** (3)	**2h** (32)

[a] Method 1: using the conditions in entry 4 of Table 1. Method 2: using the conditions in entry 3 of Table 2.

Table 4. Yields of 1,2,3-Trisubstituted 4-Trifluoromethylpyrroles



entry	R^3	X^-	product (yield, %)
1	H	Br^-	**2a** (90)
2	Me	Br^-	**2b** (87)
3	Pr	Br^-	**2i** (57)
4	Oct	Br^-	**2j** (53)
5	OMe	Cl^-	**2k** (33) + **2i** (26)[a]
6	OMe	Cl^-	**2k** (45)[b]
7	SMe	Cl^-	**2l** (22)
8	TMS	I^-	**2a** (47)[c]
9	*i*-Pr	Br^-	**2m** (6)
10	Ph	Br^-	**2n** (6)

[a] R^3 = Pr. [b] PhLi was used instead of *n*-BuLi. [c] R^3 = H.

In the reaction of **1a** and $Ph_3P^+CH_2OCH_3\ Br^-$ using *n*-BuLi as a base, the expected 4-trifluoromethyl-3-methoxy-1-methyl-2-phenylpyrrole **2k** and 4-trifluoromethyl-1-methyl-2-phenyl-3-propylpyrrole **2i** were isolated in 33% and 26% yields, respectively. The side product **2i** was identical with the product obtained by the reaction of **1a** and $Ph_3P{=}CHC_3H_7$ (Table 4, entry 3). It is reported that the reaction of $Ph_3P^+CH_2OCH_3\ Cl^-$ with *n*-BuLi produces $Ph_2(CH_3OCH_2)P{=}CHC_3H_7$, which accounts for the observed butylidene products of **2i**.[16] After the brief optimization was then made by screening of base, solvent, and reaction temperature, it was determined that use of phenyllithium instead of *n*-BuLi as a base led to the production of **2k** in a slight higher chemical yield (45%) (Table 4, entry 6). Treatment of **1a** with $Ph_3P^+CH_2Si(CH_3)_3\ I^-$ gave the desilylated product **2a** in 47% yield,[17] which was the same product as that obtained by the reaction of **1a** and $Ph_3P{=}CH_2$.

The structures of **2** were supported by the spectral data. For example, the ^{1}H NMR spectrum of **2a** exhibited the signal of C-3 proton at δ 6.37 (d) and C-5 proton at δ 7.01 (s), and other products (**2c**−**h**) also had the characteristic aromatic proton at the almost same position. In the ^{13}C NMR spectra of **2a**, the pyrrole ring carbon atoms C-2, C-3, C-4 and C-5 appear at δ 136, 106 ($^3J_{C-F}$ = 2.4 Hz), 114 ($^2J_{C-F}$ = 37 Hz), and 122 ($^3J_{C-F}$ = 4.9 Hz), respectively. The carbon of CF_3 group in **2** appears at around δ 124 ppm ($^1J_{C-F}$ = 266 Hz). The ultimate proof of the structure of **2a** rests upon its conversion into the known ethyl 1-methyl-2-phenylpyrrole-4-carboxylate **3**,[18] in which the conversion of **2a** to **3** is effected by the treatment with TFA and EtOH in 80% yield.[19] The hydrolytic instability of β-trifluoromethylpyrroles has recently been reported.[7]

A possible mechanism for the formation of 4-trifluoromethylpyrroles **2** is proposed in Scheme 1. Thus, initial nucleophilic attack of ylide on C-2 of **1** gives rise to an adduct **4** which is converted to **5** via a proton transfer. Then, equilibration gives a ylide **6** which seems to be stable in an aprotic solvent, and the thermal decarboxylation in protic solvent such as AcOH may be necessary to afford a phosphonium salt **7**. The driving force of the decarboxylation is probably due to the electron-donating ylide anion and the electron-withdrawing trifluoromethyl ketone. In the step of the formation of **8** from **7**, the nucleophilic attack of the carbonyl oxygen to phosphorus occurs to form the P−O bond, due to the greater affinity of phosphorus for oxygen. A similar transformation was postulated in the intramolecular Wittig reaction leading to indole derivatives.[20] The last step involves thermal elimination of triphenylphosphine oxide to afford the pyrroles **2**.

In conclusion, starting from the mesoionic **1** and ylides, a new, experimentally very simple, and efficient synthesis of 1,2-disubstituted and 1,2,3-trisubstituted β-trifluoromethylpyrroles has been described. The principal advantage of using mesoionic oxazoles **1** is the great variety of substituents available for R^1 and R^2. Thus, this flexibility in the type of substituents in **1** will be reflected in the corresponding substitution of the resulting pyrrole **2**. By this methodology, the 1-, 2- and 3-substituents in the pyrrole ring can be readily varied simply by choosing the appropiate *N*-acyl-*N*-alkylg-

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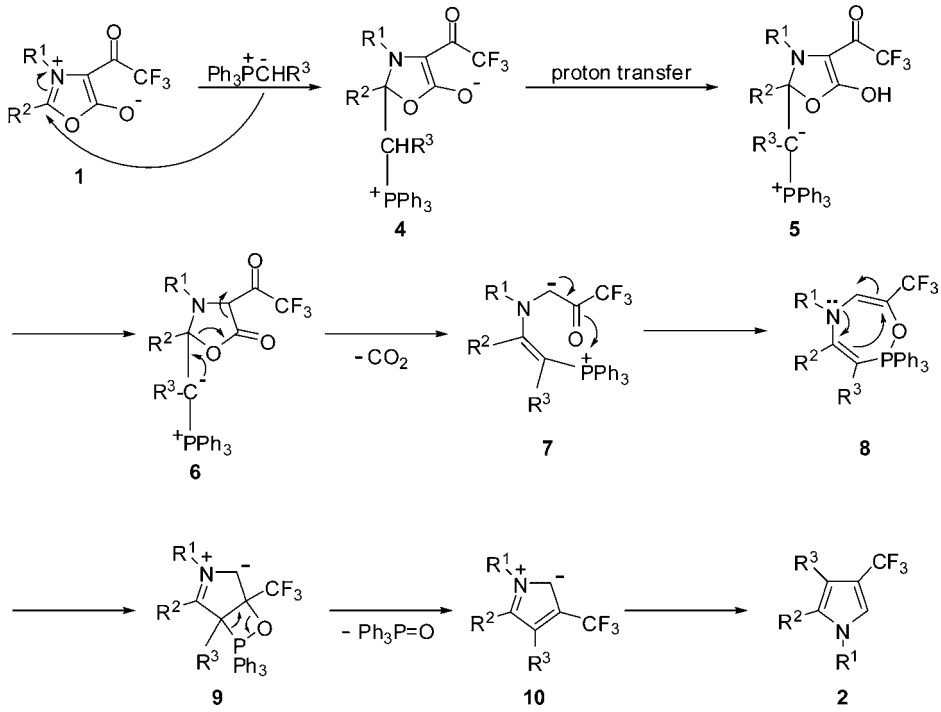
Scheme 1



lycines as the starting material and also the ylides. It should be emphasized that the simplicity of the method and the ready availability of the starting material and the Wittig reagent make this a practical approach to substituted β-trifluoromethylpyrroles.

Acknowledgment. Financial support in the form of a Grant-in-Aid for Scientific Research (C) (Kawase No. 20590114) from the Japan Society for the Promotion of Science (JSPS) is greatly acknowledged.

Supporting Information Available: Experimental procedures and characterization data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL1018689