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β-Bromodifluoromethyl β-enaminoketones: versatile synthetic intermediates for synthesis of CF_2-containing compounds

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Abstract—A series of *N*-aryl β-bromodifluoromethyl β-enaminoketones were regioselectively synthesized in good yield by the reaction of *N*-aryl bromodifluoroacetimidoyl chlorides with methyl ketones. β-Bromodifluoromethyl β-enaminoketones smoothly cyclized to give a novel class of cyclic (2,2-difluoro-5-phenyl-furan-3-ylidene)-aryl-amines under basic condition. An intramolecular halophilic substitution mechanism was proposed.

1. Introduction

The synthesis and reactivity of β-enaminoketones represent an active investigation area in organic chemistry.[1] These compounds have remarkable properties and they are valuable intermediates for the synthesis of several interesting compounds.[2] They can also be used as starting materials for the stereoselective preparation of γ-amino alcohol.[3]

β-Enaminoketones can usually be prepared in several ways. The simplest is the direct condensation of the appropriate amine with symmetrical β-dicarbonyl compounds,[4] while the acylation of lithium imines with ester is another approach to the regioselective preparation.[5]

In recent years, the introduction of the difluoromethylene segment into organic compounds has been proved to be attractive due to the potential biological activities of such molecules.[6] Bromodifluoroacetate, chlorodifluoromethyl ketones and bromodifluoromethyl acetylene are widely used as reagents for the introduction of a CF_2 moiety.[7] In search for new CF_2-containing reactive synthetic intermediates,[8] we have found that β-bromodifluoromethyl β-enaminoketones showed unique properties compared with their non-fluorinated analogues because of the existence of $BrCF_2$ moiety. Herein, we would like to report the regioselective synthesis of β-bromodifluoromethyl β-enaminoketones and further conversion to some interesting CF_2-containing compounds.

2. Regioselective synthesis of β-bromodifluoromethyl β-enaminoketones

The β-bromodifluoromethyl β-enaminoketones can be prepared by the reaction of bromodifluoroacetimidoyl chlorides **1**[8] with the carbanion of methyl ketones.[9] The treatment of bromodifluoroacetimidoyl chloride **1** and acetophenone with NaH as base in dry Et_2O at 0 °C for 24 h, gave the desired β-enaminoketone in 78% isolated yield (Scheme 1).

This method is successfully extended to the synthesis of other β-bromodifluoromethyl β-enaminoketones,[10] as illustrated in Table 1. However, the reaction of 3,3-dimethyl-2-butanone or acetone with NaH as base was inefficient, and the desired product was isolated in low yield. Interestingly, when LDA was used instead of NaH, the reaction worked very well. It was worth noting that bromodifluoroacetimidoyl chlorides **1** reacted with methyl ketones under basic conditions to provide the enamino tautomer exclusively, but the possible imine tautomer was not observed in product **2** according to the ^1H, ^{19}F NMR analysis.

The configuration of the enamino double bond in product **2** was also studied. The down-field chemical shift of

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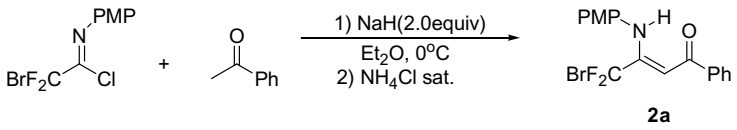
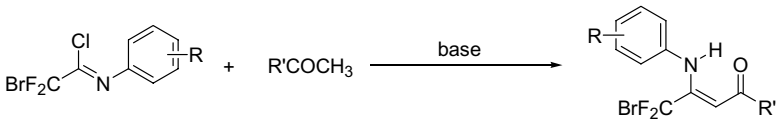


2a

Scheme 1. Synthesis of β-bromodifluoromethyl β-enaminoketones.

Table 1. The reaction of bromodifluoroacetimidoyl chlorides with methyl ketones



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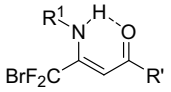
Entry	R	R′	Base	Product	Yield (%)
1	*p*-OCH_3	Ph	NaH	**2a**	78
2	*o*-Br	Ph	NaH	**2b**	62
3	*o*-Cl	Ph	NaH	**2c**	74
4	*o*-CH_3, *p*-Br	Ph	NaH	**2d**	71
5	*p*-OCH_3	*t*-Bu	LDA	**2e**	67
6	*o*-CH_3, *p*-Br	*t*-Bu	LDA	**2f**	63
7	*p*-OCH_3	CH_3	LDA	**2g**	54



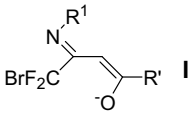
1 ***Z*** **(*s-cis*)**

Figure 1.

the N–H proton (δ >12 ppm) is a typical feature of a hydrogen bond with oxygen in carbonyl group, showing a chelated configuration, *Z*, *s-cis* form (Fig. 1).

3. Cyclization of β-bromodifluoromethyl β-enaminoketones

Because of the unique properties of CF_2Br moiety in β-bromodifluoromethyl β-enaminoketones **2**, generally speaking, the CF_2Br group could undergo two different types of reactions, that is, substitution via single electron transfer (SET) course or halophilic mechanism,[11] and radical addition to unsaturated compounds. We reasoned that β-enaminoketones **2** could be readily converted to enolate (I) under basic conditions (Fig. 2).[12] Once enolate (I) is formed in proper reaction conditions, intramolecular cyclization might occur.



I

Figure 2.

When a mixture of β-enaminoketones **2a** and triethylamine was heated in dry DMF at 100 °C for 12 h, no reaction occurred and **2a** was recovered quantitatively. However, when DMAP was used as a base, a crystalline solid was isolated in 22% yield after standard work up. An X-ray diffraction study confirmed the unique structure of the product (Fig. 3).[13] So the intramolecular cyclization indeed occurred.

Further experimental study revealed that K_2CO_3 was a suitable base for the intramolecular cyclization[14] (Scheme 2). When the reaction was carried out under strong basic conditions (NaH or NaOH as base), the reaction mixture turned dark and the desired product

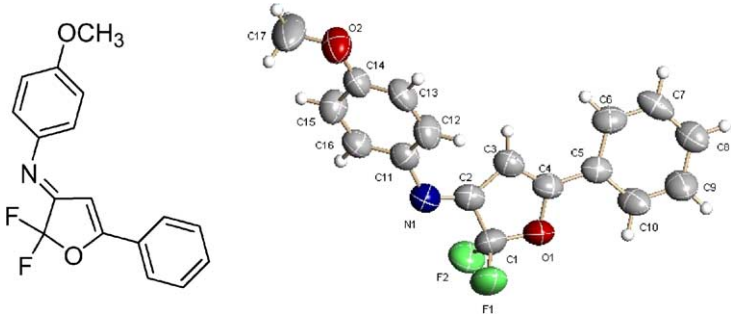


Figure 3. Crystal structure of the cyclization product.