Efficient preparation of novel *N*-propargylic β-enaminones from the reaction of β-alkoxyvinyltrihalomethyl[carboxy]ketones and propargylamines

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Abstract

Fifteen *N*-propargylic β-enaminones were synthesized from the reaction of propargyl amines [4-X-PhNHCH$_2$C≡CH, where X = H, Me] and 4-alkoxy-1,1,1-trihalo[ethoxy]-3-alken-2-ones [RC(O)CH=C(R^1)OMe, where R = CF_3, CCl_3, CO_2Et and R^1 = Me, Et, Pr, Bu, *i*-Pent, $CH_2CH_2CO_2Me$]. The methodology described herein proceeded smoothly and furnished the products in good to high yields (70-95%).

Keywords: Enones, propargyl amines, *N*-propargylic β-enaminones

Introduction

β-Enaminones are an important class of organic synthetic intermediates for the synthesis of a variety of heterocycles and pharmaceutical compounds. Their basic structural units, N–C=C–C=O, are responsible for the synthesis of many therapeutic agents of both natural and synthetic sources, including taxol, anticonvulsants, anti-inflammatory agents and ducarmycin classes of anti-tumor agents, as well as quinoline antibacterial and quinoline antimalarial agents.[1-3] They are also intermediates for the synthesis of several amino acids, aminols, peptides and alkaloids.[4-6]

The most well-known and exploited route to synthesize β-enaminones involves the direct condensation of β-dicarbonyl compounds with amines in refluxing aromatic hydrocarbons with azeotropic removal of water.[7] Improved procedures have been subsequently reported and include the reaction of amines with β-dicarbonyl compounds on solid supports[8] and the use of catalysts,[9-11] among others.[12] However, the main disadvantage of some of the existing methods is that the catalysts are destroyed in the work-up procedure and cannot be recovered or reused.[13]

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On the other hand, it is well known that the introduction of halogens and halogenated groups into organic molecules often confers significant and useful changes in their chemical and physical properties.[14] Thus, the development of β-enaminones containing halomethyl groups is still in demand. Some of the methods described in the literature include the reaction of propargyl amines with α,β-acetylenic- or α,β-unsaturated ketones,[15,16] condensation of amines with 1,3-dicarbonyl compounds[17] gold- or CAN-catalyzed reaction,[18] Sonogashira cross-coupling of terminal alkynes with acyl chlorides[19] and *N*-alkylation of β-enaminones with 3-bromopropyne.[20] No reports have demonstrated the use of secondary amines, since they are less reactive than primary amines in the synthesis of *N*-propargylic β-enaminones, which are extremely important building blocks in organic synthesis.

As a part of our program aiming at developing selective and safe methodologies for the preparation of new building blocks, herein we describe the synthesis of a series of *N*,*N*-aryl-propargylic β-enamino trihalomethyl[ethoxy]ketones from the reaction between 4-alkoxy-1,1,1-trihalo[ethoxy]-3-alken-2-ones and propargyl amines.

Results and Discussion

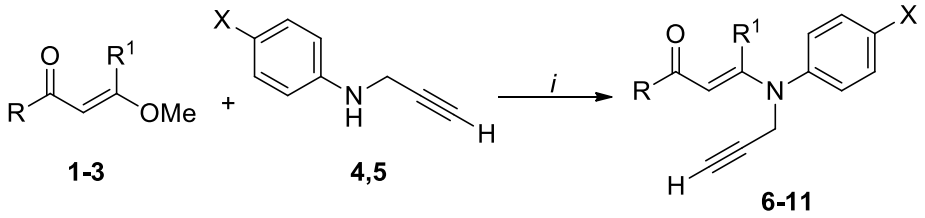
The starting materials, 4-alkoxy-1,1,1-trihalo[ethoxy]-3-alken-2-ones **1-3**, were synthesized from the acylation reaction of the respective enol ether or acetal with trifluoroacetic anhydride, trichloroacetyl chloride or ethyl oxalyl chloride.[14,21] Propargyl amines were prepared from the reaction of 1-methanesulfonate 2-propin-1-ol with primary amines, although they are commercially available. 1-Methanesulfonate 2-propin-1-ol was synthesized as described in the literature.[22]

We began our study by investigating the reaction of enone **1a** with *N*-phenyl-*N*-prop-2-yn-1-amine **4** in equimolar amounts. For this purpose, we evaluated different alternative methodologies, including microwave irradiation, ultrasound irradiation and ionic liquids. In general, data from the literature have demonstrated that reactions under these conditions present a lower reaction time, however the employment of such methodologies even after 1 h at 73 °C did not lead to the total conversion of the starting materials into the desired products. In addition, changing the solvent (ethanol, acetonitrile, [BMIM][BF_4]) did not influence the rate of conversion for either microwave or ultrasound irradiation. This reaction was also performed using conventional thermal heating with [BMIM][BF_4] or acetonitrile as solvent at 80 °C during 24 h. In the first case, the extraction step, necessary for ionic liquid removal, was determining in relation to the acetonitrile methodology, mainly due to the yield decrease observed. Thus, we extended this synthetic methodology for the entire product series **6-11** (Table 1).

The time required for the total conversion of the starting materials may be related to the substituents present in the propargyl amine, which would generate a steric hindrance and mainly due to the lone pair of electrons of the nitrogen-atom being engaged with the aryl groups, which

would make this atom less nucleophilic. Other *N*-propargylic β-enaminones have been reported in the literature, however only with primary amines.[15-18]

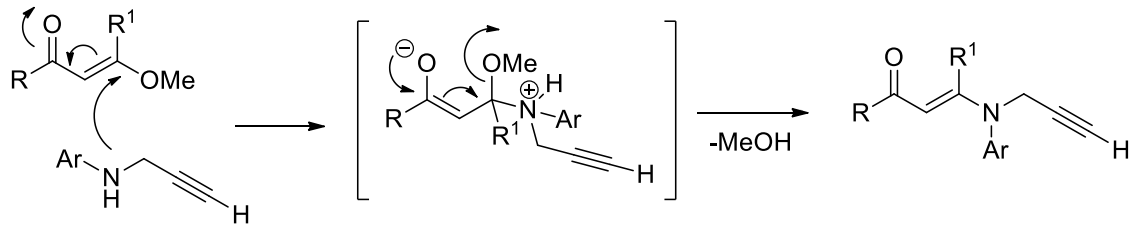
Table 1. Reaction conditions employed for the synthesis of compounds **6**-**11**.



i: MeCN, 80 °C, 24 h (70-95%)

Reactants					Product	Yield
Enone	R	R^1	Amine	X		(%)
1a	CF_3	Me	**4**	H	**6a**	95
1b	CF_3	Et	**4**	H	**6b**	83
1c	CF_3	Pr	**4**	H	**6c**	90
1d	CF_3	Bu	**4**	H	**6d**	91
1e	CF_3	*i*-Pent	**4**	H	**6e**	88
1f	CF_3	$(CH_2)_2CO_2Me$	**4**	H	**6f**	75
1a	CF_3	Me	**5**	Me	**7a**	86
1b	CF_3	Et	**5**	Me	**7b**	90
1c	CF_3	Pr	**5**	Me	**7c**	88
1d	CF_3	Bu	**5**	Me	**7d**	86
1e	CF_3	*i*-Pent	**5**	Me	**7e**	80
2a	CCl_3	Me	**4**	H	**8a**	90
2a	CCl_3	Me	**5**	Me	**9a**	80
3a	CO_2Et	Me	**4**	H	**10a**	70
3a	CO_2Et	Me	**5**	Me	**11a**	75

Thus, based on previous works,[23] the following sequence of steps appears to afford a satisfactory explanation for the mechanism of formation of the *N*,*N*-arylpropargylic β-enaminones (Scheme 1). This reaction involves the initial attack of the amine nitrogen atom on the enone β-carbon with a charge delocalization to the carbonyl group and a subsequent elimination of the alcohol molecule to furnish the desired products.



Scheme 1

In general, the β-enaminones which presented the NH-group in their structures have been obtained in solution in the *Z*-configuration on the double bond. This fact is attributed to the formation of intramolecular hydrogen bonds between the NH- and oxygen of the carbonyl-group (N-H···O) producing a stable pseudo six-membered ring. On the other hand, for β-enaminones that did not show NH-groups, a preference for the *E*-configuration has been observed because the steric hindrance then becomes a factor of greater importance.[24] In this paper, the β-enaminones **6-10** did not present the NH-group and thus were probably obtained in the *E*-configuration.

In all cases, some common features were obtained for ^{1}H and ^{13}C NMR chemical shifts. The ^{1}H NMR spectra of *N*,*N*-aryl-propargylic β-enamino trihalomethyl [ethoxy] ketones presented two signals related to the coupling between H6 and H8 as one of the main characteristics for these compounds. Hydrogen H6 was observed as a doublet while H8 was observed as a triplet, both with a coupling constant of ^{4}J = 2 Hz (Figure 1). Vinyl hydrogen (H3) showed a chemical shift in the range of 5.48-5.54 ppm (CF_3), 5.97-5.98 (CCl_3) and 6.13-6.14 (CO_2Et) in accordance with the R^3 substituent present in the enaminone. In addition, H9 showed as characteristic signal, a broad singlet for almost all compounds. This behavior is probably due the alkyl chain (R^1) which lead to the slow rotation on the N - C bond and, consequently, the coalescence of the NMR signals. The ^{13}C NMR spectra showed characteristic signals for C-6 in the range of 43.1-43.8 ppm, for C-8 at 73.8-74.6 ppm, for C-7 at 76.2-77.5 ppm and for C-3 at 85.9-88.4 ppm. Carbon C-1 presented a signal at 164.7 ppm (CO_2Et), 99.0-99.3 ppm (CCl_3) and 117.3-118.4 ppm (CF_3). Carbon C-2 presented a chemical shift in the range of 175.5-177.8 ppm when R^3 = CF_3, 179.4-179.7 ppm, when R^3 = CCl_3 and 178.4-178.5, when R^3 = CO_2Et. C1 (CF_3) was observed as a quartet due to the coupling between the carbon atom and the fluor atoms, with a coupling constant of ^{1}J = 289 Hz. This behavior was also observed for C2 (C=O), nevertheless the coupling constant was of ^{2}J = 33 Hz.

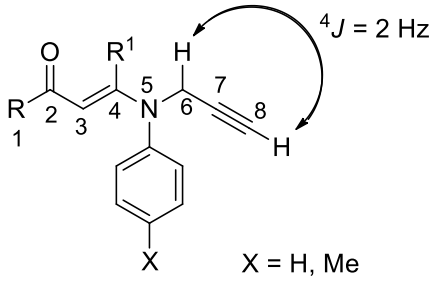


Figure 1. Typical coupling constant of *N*-propargylic β-enamino trihalomethyl[ethoxy]ketones.

Conclusions

In summary, we have developed a simple synthetic route to obtain a series of new *N*-propargylic β-enaminones from the reaction of 4-alkoxy-1,1,1-trihalo[ethoxy]-3-alken-2-ones with propargyl amines. Moreover, we have demonstrated for the first time the use of secondary amines containing the propargyl group. All products were obtained in good to high yields.

Experimental Section

General. Unless otherwise indicated, all common reactants were used as obtained from commercial suppliers without further purification. All melting points were measured using a Reichert-Thermovar apparatus. ^{1}H and ^{13}C NMR spectra were acquired on a Bruker DPX 200 or Bruker DPX 400 spectrometer (^{1}H at 200.13 MHz or 400.13 MHz and ^{13}C at 50.32 MHz or 100.13 MHz, respectively) at 300 K, 5 mm sample tubes, and with digital resolution of ±0.01 ppm. $CDCl_3$, or DMSO-d_6 were used as solvents containing TMS as internal standard. GC-MS EI was registered in an Agilent 6890N series connected to an Agilent G1530CN GC and interfaced by a Pentium PC. The GC was equipped with a split-splitless injector, autosampler cross-linked HP-5 capillary column (30 m, 0.32 mm i.d.), and He was used as the carrier gas.

General procedure for the synthesis of 1-methanesulfonate 2-propin-1-ol
1-Methanesulfonate 2-propin-1-ol was synthesized according to the methodology described in the literature.[22]

General procedure for the synthesis of propargyl amines (4, 5)
To a stirred solution of amine (aniline, *p*-toluidine, 100 mmol) in THF (40 mL) at room temperature, 1-methanesulfonate 2-propin-1-ol (50 mmol) was added. The mixture was stirred for 4 h at room temperature, when using propylamine or benzylamine, reflux during 4 h was required for aniline and *p*-toluidine. Sodium bicarbonate solution (3 × 50 mL) was added and the

products **4, 5** were extracted with diethyl ether (3 × 30 mL). The solvent was evaporated in a rotary evaporator and the products **4, 5** were purified by distillation under reduced pressure. The complete spectroscopy data for these compounds can be found in the reference 25.

General procedure for the synthesis of *N*-propargylic β-enaminones (6-11)

Propargyl amines **4** or **5** (1 mmol) were slowly (drop-by-drop) added to a round-bottomed flask containing enone **1**, **2** or **3** (1 mmol) and acetonitrile (2 mL), under magnetic stirring. After the addition, the mixture was kept under stirring at 80 °C during 24 h. The solvent was removed in a rotary evaporator and the products were purified by chromatographic column, using deactivated silica and a mixture of ethyl acetate/hexane (1:10) as the eluent.

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Supplementary material

The NMR spectra of all the compounds associated with this article can be found as supplementary material.

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