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Enol ethers and acetals: acylation with dichloroacetyl, acetyl and benzoyl chloride in ionic liquid medium

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ABSTRACT

Synthesis of 4-alkoxy-1,1-dichloro-3-alken-2-ones [$CHCl_2C(O)C(R^2)=C(R^1)$-OR, where R, R^1, R^2 = Et, H, H; Me, Me, H; Et, H, Me; Me, $-(CH_2)_2-$; Me, $-(CH_2)_3-$; Et, Et, H; Et, Bu, H; Et, *i*-Pr, H; Et, *i*-Bu, H; Me, Ph, H; Me, thien-2-yl, H] from acylation of enol ethers and acetals with dichloroacetyl chloride, in ionic liquid ([BMIM][BF_4] or [BMIM][PF_6]) is reported. The synthesis of alkenones [R^3–C(O)C(R^2)=C(R^1)-OR], where R/R^1/R^2/R^3 = Et/H/H/Ph, *t*-Bu/H/H/Ph, Me/-$(CH_2)_4$/Ph, Me/-$(CH_2)_4$/Me] from the reaction of enol ethers with benzoyl chloride or acetyl chloride, in ionic liquid [BMIM][BF_4], is also reported. Last products are described for the first time.

The usefulness of β-alkoxyvinyl ketones (alkenones) in heterocyclic synthesis, for example, isoxazoles, pyrazoles, pyrroles, pyrimidines, pyridines, thiazines and diazepines, has been extensively described by some research groups.[1–5] The acylation reaction of enol ethers, isolated or generated in situ (from acetals), is the main procedure to obtain alkenones.[1] However, taking into account that enol ethers show low reactivity when compared to enamines, it should be noted that direct acylation involves problems such as: (i) the requirement of strongly activated acylating agents, for example, carbonyl carbon containing electronegative substituents attached, such as trifluoro- or trichloro-methyl groups[6–9]; and (ii) the use of Friedel–Crafts catalysts, which is naturally limited to enol ethers with a high polymerization tendency.[10] In 1964, Maier[11] demonstrated how the course of the reaction depends on the electrophilic potential of the acylant agent: while acetyl chloride does not react with ethyl vinyl ether and chloroacetyl chloride causes polymerization; dichloroacetyl chloride gives the addition product, and trichloroacetyl chloride gives the substitution product. On the other hand, Youssefyeh[10] published a work showing that bulky enol ether or acetal of the cholestan-3-one ethylene was acylated with acetic anhydride, using boron trifluoride Friedel–Crafts catalyst. Halberg and Andersson[12] described the reaction of butylvinylether with benzoyl chloride using palladium catalysis; the use of metal was required, since the reaction would not occur without the use of this catalyst.

Our research group has systematically studied the acylation reaction of enol ether, isolated or from acetals, for about twenty years and has developed a classical method for the acylation of enol ethers and acetals with trihalomethylated acylants to obtain a series of 4-alkoxy-1,1,1-trihalo-3-alken-2-ones in the presence of pyridine and under anhydrous atmosphere, with dichloromethane as solvent.[1,9] However, this procedure is tedious and the reaction is relatively time-consuming (16–48 h).[9] Recently, we reported a method of acylation for enol ethers[13] and acetals[14] with trihalomethylated acylants to obtain a series of 4-alkoxy-1,1,1-trihalo-3-alken-2-ones in the presence of pyridine, using ionic liquid in catalytic conditions. This procedure induces faster reaction times, easy work up, easier purification of products and better yields than the classical methods.

Considering the importance of 4-alkoxy-3-alken-2-ones in heterocyclic synthesis, there is a scarcity of literature reporting promising methods to synthesize these compounds from the acylation of enol ethers. Due to the positive results we achieved using ionic liquids in the acylation reaction of enol ether and acetal with strong trihalomethylated acylating agents,[13,14] the aim of this work is to evaluate the ability of the ionic liquid to promote these reactions with moderate or weak acylating agents that require some kind of activation, such as 1,1-dichloroacetyl, benzoyl and acetyl chlorides.

The reaction was very successful for a range of enol ethers and acetals, as shown in Table 1. Enol ethers (**1a–c**), dichloroacetyl

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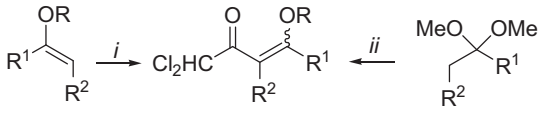
Table 1
Yields of 4-alkoxy-1,1-dichloro-3-alken-2-ones **3** obtained from acylation reaction of enol ethers or acetals



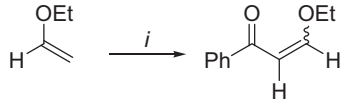
1a-e **3a-k** **2f-k**

i: $Cl_2CHC(O)Cl$, Py, IL, 0-40 °C, 3 h.
ii: $Cl_2CHC(O)Cl$, Py, IL, 0-50 °C, 6-8 h.

Reactant	R	R^2	R^1	Product	Yield[a] (%)	
					IL: [BMIM][BF_4]	IL: [BMIM][PF_6]
1a	Et	H	H	**3a**	75	68
1b	Me	H	Me	**3b**	77	79
1c	Et	Me	H	**3c**	52	10
1d	$-(CH_2)_2-$		H	**3d**	70	69
1e	$-(CH_2)_3-$		H	**3e**	71	41
2f	Et	H	Et	**3f**	48	46
2g	Et	H	Bu	**3g**	52	53
2h	Et	H	*i*-Pr	**3h**	64	62
2i	Et	H	*i*-Bu	**3i**	48	47
2j	Me	H	Ph	**3j**	49	50
2k	Me	H	Thien-2-yl	**3k**	52	51

[a] Yield of isolated product.

Table 2
Optimization of acylation reaction of enol ether **1a** with benzoyl chloride



1a **4a**

i: PhC(O)Cl, Py, IL: [BMIM][BF_4]

Entry	Pyridine:acylant:IL molar ratio	Addition order[a]	Addition temp. (°C)	Time (h)	Yield[b] (%)
1	1.0:1.0:0.1	I	25	14	–
2	1.0:1.0:0.1	I	0	14	–
3	1.0:1.0:1.0	II	0	16	Traces
4	1.0:1.0:1.0	I	0	16	10
5	1.0:1.0:1.0	III	0	16	12

[a] I: Acylant in the glass followed by sluggish addition of other reagents and IL. II: Reagents and IL in the flask by sluggish addition of acylant. III: Acylant and IL in the glass by sluggish addition of other reagents.
[b] Yield of isolated product.

chloride and benzoyl chloride are commercially available. Enol ethers (**1d,e**) and the acetals (**2f–k**) were prepared according to the procedure described in the literature.[15] The reaction of dichloroacetyl chloride with **1,2** was performed by slowly adding a mixture of pyridine and **1,2** to the mixture of acylant and IL in an ice bath. Two equivalents of the acylating agent per acetal were required to obtain the 4-alkoxy-1,1-dichloro-3-alken-2-ones (**3**), since one molecule of the acylant promotes the formation of the enol ether in situ by trapping the alkoxide group released by the acetal, and the second molecule of the acylant promotes acylation.[16–20] The *E*-isomer was the only product observed.[17–20] Products **3** were extracted from the reaction media with diethyl ether and were obtained without further purification. The IL was completely recovered by the addition of CH_2Cl_2, filtration of the precipitate and evaporation of the solvent. The compound structures were determined by ^1H and ^{13}C NMR spectroscopy and data of compounds **3a–k** are given in the Supplementary data.

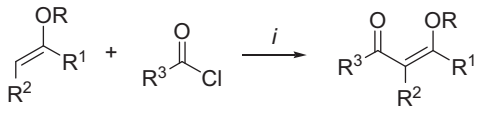
Data from the literature[21,22] have demonstrated that in the Friedel–Crafts acylation in ionic liquids in the presence of a Lewis acid, the acylation rate depends on the Lewis acid/IL molar ratio and that almost no reaction occurs if this ratio is $\leqslant 0.5$.[21,22] In the present study, an additional Lewis acid was not necessary for the acylation reaction. However, the 1:1 reactant/IL ratio seems to be critical for conversion into the desired products. The acetal acylation in equimolar amounts of ILs allowed the formation of alkenones **3**,**4**,**5**. The results from the present study in regard to the reactant/IL ratio differ from those published by us for enol ether acylation,[13] where less than an equimolar proportion of the ionic liquid was sufficient to obtain optimum results beyond which there was no further increase of conversion.

Reactions yields were higher in [BMIM][BF_4] than in [BMIM][PF_6], probably because of the better solubility of reagents in [BMIM][BF_4]. It is noteworthy that products **3a**,**b**,**d** and **e** were already synthesized using a classical method,[23,24] however their yields and spectral data are not described in literature.

We started the evaluation of reaction of enol ethers **1a**,**l**,**m** with weakly acylating agents like benzoyl chloride and acetyl chloride, by the reaction of ethyl vinyl ether (**1a**) and benzoyl chloride (Table 2) in [BMIM][BF_4].

The use of [BMIM][BF_4] in 0.1 equiv in relation to the acylant was not effective in promoting the reaction, with addition at 25 °C (entry 1) or 0 °C (entry 2). The addition of an equimolar

Table 3
Yields of 4-alkoxy-3-alken-2-ones **4,5** obtained from acylation reaction of enol ethers or acetals



1a,l,m **4a,l,m, 5m**

i : Py, [BMIM][BF_4], 0-40 °C, 14-16 h.

Acylant R^3	Enol ether	R	R^2	R^1	Product	Yield[a] (%)
Ph	**1a**	Et	H	H	**4a**	12
Ph	**1l**	*t*-Bu	H	H	**4l**	16
Ph	**1m**	Me	$-(CH_2)_4-$		**4m**	34
Me	**1m**	Me	$-(CH_2)_4-$		**5m**	22

[a] Yield of isolated product.

amount of [BMIM][BF_4] and a slight increase of the reaction time allowed the observation of traces of product **4a** (entry 3). Taking into account that [BMIM][BF_4] could change the coordinate of the reaction by an interaction with reactants, we tested two reactant addition orders. Both reactant addition orders provided very similar results in the yields (entries 4 and 5). Thus we decided to perform the reaction using the reactant addition order III, which was shown to be better to handle [BMIM][BF_4].

With these results in hand, we performed the acylation reaction with enol ethers **1a,l,m** (Table 3). The yields of products were low, but the products were obtained for the first time using this method. In addition, the bulkiness of the enol ether structure seems to have led to the better yields. Theoretically, it is expected that these enol ethers are less reactive to polymerization than those that are less substituted and, additionally, they remain available for the acylation reaction.

These results are preliminary and we have already extended our study to C-acylation of enamino compounds using acylating agents that require strong activation, such as 4-nitrobenzoyl-, 4-chloro-3-nitrobenzoyl- and 3,5-dinitrobenzoyl chlorides. The initial results show that this method provides good yields of products. These data will be communicated hereafter.

The results of this work suggest that the presence of IL in this medium affords strong stabilization of the reaction intermediates and activated complexes. Accordingly, the enhanced rate of the reactions is due to the decreased activation energy of the slow reaction step.[25] This behaviour is in agreement with the general IL effect that can be expected for reactions involving highly polar or charged intermediates, such as carbocations or carbanions, and activated complexes which could become more stable and long-lived in IL media.[25]

In summary, the method proposed in this study allows for the preparation of β-alkoxyvinyl ketones in short times and with moderate yields. In addition, it was demonstrated that the method of acylation of enol ethers or acetals in ionic liquids was efficient for the acylation of enol ethers using acylating agents that require strong activation, like benzoyl and acetyl chloride. Our results show the promising role of [BMIM][BF_4] in promoting an acylation reaction that does not work with molecular solvents.

Unless otherwise indicated, all common reagents and solvents were used as obtained from commercial suppliers without further purification. ^1H and ^{13}C NMR spectra were recorded on a Bruker DPX-400 (^1H at 400.13 MHz and ^{13}C at 100.62 MHz) in 5-mm sample tubes at 298 K in $CDCl_3$/TMS solutions. The general reproducibility of chemical shift data was estimated to be better than ±0.01 ppm. The ^1H and ^{13}C NMR data of the compounds **3a–k, 4a,l,m** and **5m** are given in the Supplementary data.[13,14]

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Supplementary data

Supplementary data (general procedures and characterization data (^1H NMR, ^{13}C NMR, GC/MS and melting points) of compounds **3a–l**) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.10.163.

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