Synthesis of 1,1,1-trichloro[fluoro]-3-alken-2-ones using ionic liquids

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Abstract

The synthesis of a series of ten 1,1,1-trichloro[fluoro]-3-alken-2-ones [$CX_3C(O)C(R^2)$=$C(R^1)OR$, where X = Cl and F; $R^1/R^2/R$ = H/H/Et, Me/H/Me, H/Me/Et, H/−$(CH_2)_2$− and H/−$(CH_2)_3$−] from the acylation reactions of enol ethers with trichloroacetyl chloride or trifluoroacetic anhydride in the presence of equimolar amounts of pyridine and 10% mol-equiv. of imidazolium based ionic liquid [BMIM]·BF_4 or [BMIM]·PF_6 is reported. The reaction time, the ionic liquid recyclation and yields were investigated and this method showed advantages over the methods described in the literature.

1. Introduction

The 1,1,1-trihalo-3-alken-2-ones are one of the most important synthetic intermediates for the synthesis of innumerous halo-substituted heterocycles [1]. In recent years, our groups has developed a general method of synthesis of these compounds and demonstrated their use in the preparation of heterocycles such as isoxazoles, pyrazoles, pyrazolium chlorides, pyrrolidinones, pyrimidines, pyridines, thiazines and diazepines [1]. The preliminary pharmacological tests of these heterocycles showed promising biological activity [2].

Apart from continual interest in the development new synthetic methods, our research group has been studying new protocols to improve the synthesis of intermediates to be used in heterocyclic chemistry. A review of the literature has show that, *room temperature ionic liquids* (RTILs) are attracting much attention as promising 'green' solvents and alternatives to the hazardous traditional organic solvents [5], due to properties such as non-flammability, negligible vapor pressure, high thermal stability, solvating ability and easy recyclability [6]. Many studies have recently shown that RTILs can promote and cat-

alyze important organic transformations without the need for any added catalyst or ligand [7]. The ionic liquids based on imidazolium salts are the most used RTILs and they are finding increasing applications in organic synthesis and the industry [8]. Ionic liquids have been investigated as reaction media in many organic and organometallic syntheses such as Heck reactions [5], Friedel–Crafts reactions [5], alkylation [5], hydrogenation [9], hydroformylation [9], dimerization [10], condensation [11], acylative cleavage of cyclic and acyclic ethers [12], polymerization [13], Diels Alder reactions [14], epoxydations [15] and Michael additions [16]. Although there are several papers reporting the Friedel–Crafts reactions [5], there are very few reports in the literature of other types of acylation reactions in ionic liquid. The acylation of vinyl ethers requires strong activation from acylating agents. The employment of Friedel–Crafts catalysts is naturally limited to enol ethers with a negligible polymerization tendency [3]. Electronegative substituents such as the trifluoro or trichloro methyl groups attached to the carbonyl carbon increase the reactivity of the acyl component furnishing β-trihaloacyl-substituted vinyl ethers in quantitative yields. Effenberger and Maier [3] have already demonstrated how the course of the reaction depends on the electrophilic potential of the acyl function. Thus, the classical method used in the acylation reaction of enol ethers with trihaloacetyl acylants to obtain 1,1,1-trihalo-3-alken-2-ones is performed in presence of pyridine and an anhydrous atmosphere, with dichloromethane or

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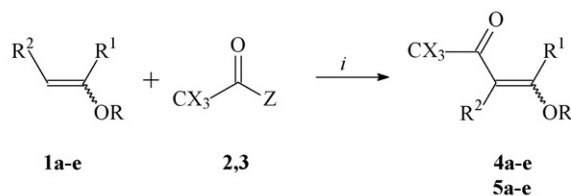*URL:* http://www.ufsm.br/nuquimhe (M.A.P. Martins).

ethyl ether as solvent. This procedure is tedious and the reaction time is relatively long (16–48 h) [3,4]. Thus, the aim of this work is to investigate the use of the ionic liquids based on imidazolium salts as a media for the synthesis of 1,1,1-trihalo-3-alken-2-ones from the acylation reaction of enol ethers with trihaloacetyl acylants. In addition, correlated reaction times and yields were correlated with the classical method.

2. Results and discussion

The acylation reaction of enol ethers (**1**) with trichloroacetyl chloride (**2**) or trifluoroacetic anhydride (**3**) was carried out with 1-butyl-3-methylimidazolium tetrafluoroborate ([BMIM]·BF_4) in pyridine, at a molar ratio of 1.0:1.0:0.1:1.0, respectively. The same reaction conditions were used for the hexafluorophosphate ([BMIM]·PF_6) as the catalyst. The mixture of enol ethers (**1**), RTIL and pyridine was slowly added (drop-by-drop) to the acylant (**2,3**) under ice bath conditions, and then the ice bath was removed and the mixture was stirred for 1.5 h at room temperature. The products 1,1,1-trihalo-3-alken-2-ones (**4a–e** and **5a–e**) were isolated from the extraction with diethyl ether (Scheme 1). The isolated yields of products **4**, **5** with the different ionic liquid used are summarized in Table 1. The structure of compounds **4**, **5** were confirmed by ^1H and ^{13}C NMR (Table 2) and compared with literature data [4].

These results showed that RTILs improved the synthesis of 1,1,1-trihalo-3-aken-2-ones and that most product yields obtained were similar to those obtained by the conventional method (Table 1). It can be observed that, less than an equimolar proportion of the ionic liquid is sufficient to obtain optimum results beyond which there is no further increase of conversion.

We have not attempted to study the mechanism of this acylation in ionic liquid. Moreover, '*the manner in which RTILs act in the organic reactions*' is not clear and there has been and continues to be much controversy over this. There are many data on dielectric constants, polarity, etc., for RTILs, obtained from different methods. Each author argues that his method to determine some properties for a particular substrate or solvent is better. Nevertheless, the authors agree that "the data on these properties (dielectric constants, polarity, etc.) are

Table 1
Yields of products **4,5** with different ionic liquids used

Compound	Yield (%)[a]		
	[BMIM]·BF_4	[BMIM]·PF_6	Literature[b]
4a	80	81	79
4b	95	95	94
4c	91	88	79
4d	81	79	83
4e	78	74	80
5a	80	85	79
5b	91	90	82
5c	76	75	64
5d	80	78	84
5e	85	80	78

[a] Yield of isolated product.
[b] Ref. [3].

not sufficient to explain the solvent/catalyst effect of RTILs in organic transformations. For example, some studies indicate that RTILs have polarities similar to those of short-chain alcohols and other polar, aprotic solvents (DMSO or DMF) and their polarity is intermediate between water and chlorinated organic solvents, varying in accordance with the nature of the RTIL components [18,19]; others report that they exhibit solvent strengths as great as or greater than the most polar aprotic solvent (acetonitrile) [20]; they have additionally been classified as solvents of moderate polarity [21]. Moreover, attempts have been made to develop empirical solvent polarity scales as a means to help explain differences in solvent-mediated reaction pathways, reaction yields, synthesis product ratios, chromatographic retention, and extraction coefficients. Clearly, a single parameter of "polarity"/"solvent strength"/"interaction" is not sufficient to explain the variation in experimental results in many solvent-mediated processes. Most simple molecular solvents (hexane, for example) are limited in the number and types of solvation interactions possible with dissolved molecules. More complex solvents with additional functional groups can produce additional interactions with dissolved molecules. RTILs are among the most complex solvents. Given their structure and diversity of functionality, they are capable of most type of interactions (*e.g.*, dispersive, π–π, n–π, hydrogen bonding, dipolar, ionic/charge–charge). In every solution, there may be a number of differences (in terms of type and strength) and often simultaneous solute–solvent interactions. The various single parameter polarity scales are essentially weighted averages of all-possible solute–solvent interactions. Thus, it is not surprising that these averages are similar for any class of solvents and that they do not adequately explain many experimental observations. Since RTILs are much more complex solvent systems capable of undergoing many types of interactions, characterizing them with a single polarity term fails to encompass the broad spectrum of types and the magnitude of individual interactions that make each RTIL unique. RTILs exhibit multiple behaviors, which explains why many RTILs act as polar solvents in organic reactions containing polar molecules and as less polar solvents in the presence of less polar molecules [23]. Also, the well-established scenarios for describing dipolar interactions in molecular liq-

i: Pyridine (1 equiv), [BMIM]•BF_4 or [BMIM]•PF_6 (0.1 equiv), 0° to r.t., 1.5h

1,4,5	R^1	R^2	R		2,4	3,5
a	H	H	Et	X	Cl	F
b	Me	H	Me			
c	H	Me	Et			
d	H	-(CH_2)_2-			2	3
e	H	-(CH_2)_3-		Z	Cl	OC(O)CF_3

Scheme 1.

Table 2
Selected physical and spectral data of compounds **4,5**

Product	Molecular formula (M.w.)	^{1}H NMR[a] δ, J (Hz)	^{13}C NMR[a] δ	Product	Molecular formula (M.w.)	^{1}H NMR[a] δ, J (Hz)	^{13}C NMR[a] δ
4a	$C_6H_7Cl_3O_2$ (217.47)	7.61 (d, 1H, H3) 5.34 (d, 1H, H4) 4.09 (q, 2H, H5) 1.32 (t, 3H, H6)	187.1 (C2) 160.0 (C4) 102.3 (C3) 98.0 (C1) 64.5 (C5) 17.3 (C6)	**5a**	$C_6H_7F_3O_2$ (168.11)	7.88 (d, 1H, H3) 5.84 (d, 1H, H4) 4.14 (q, 2H, H5) 1.40 (t, 3H, H6)	187.8 (C2) 169.0 (C4) 112.1 (C3) 97.8 (C1) 62.4 (C5) 19.3 (C6)
4b	$C_7H_9Cl_3O_2$ (231.50)	6.01 (s, 1H, H3) 3.81 (s, 3H, H5) 2.40 (s, 3H) 1.32 (t, 3H, H6)	186.2 (C2) 170.0 (C4) 100.0 (C3) 98.8 (C1) 52.5 (C5) 16.5 (C6)	**5b**	$C_7H_9F_3O_2$ (182.13)	5.70 (s, 1H, H3) 3.80 (s 3H, H5) 2.41 (s 3H, H6)	187.0 (C2) 184.5 (C4) 120.7 (C3) 96.9 (C1) 61.8 (C5) 26.3 (C6)
4c	$C_7H_9Cl_3O_2$ (231.50)	7.90 (s, 1H, H4) 4.17 (q, 2H, H5) 1.91 (s, 3H, H7) 1.39 (t, 3H, H6)	175.0 (C2) 158.0 (C4) 110.9 (C3) 96.8 (C1) 65.8 (C5) 15.3 (C6) 7.9 (C7)	**5c**	$C_7H_9Cl_3O_2$ (182.13)	7.55 (s, 1H, H4) 4.21 (q, 2H, H5) 1.79 (s, 3H, H7) 1.40 (t, 3H, H6)	178.0 (C2) 171.0 (C4) 109.2 (C3) 97.6 (C1) 50.8 (C5) 19.1 (C6) 8.1 (C7)
4d	$C_6H_5Cl_3O_2$ (215.46)	7.84 (s, 1H, H1) 4.65 (t, 2H, H5) 3.05 (t, 2H, H6)	170.5 (C3) 152.8 (C1) 120.9 (C2) 99.8 (C4) 60.5 (C6) 37.3 (C5)	**5d**	$C_6H_5F_3O_2$ (166.09)	7.65 (s, 1H, H4) 4.69 (t, 2H, H5) 2.97 (t, 2H, H6)	175.8 (C2) 163.9 (C4) 117.9 (C1) 114.2 (C3) 73.9 (C5) 26.7 (C6)
4e	$C_7H_7Cl_3O_2$ (229.48)	7.82 (s, 1H, H1) 4.02 (t, 2H, H5) 2.33 (t, 2H, H6) 1.95 (t, 2H, H7)	176.3 (C3) 152.5 (C1) 118.0 (C2) 98.1 (C4) 60.2 (C6) 25.3 (C6) 18.6 (C5)	**5e**	$C_7H_7F_3O_2$ (180.12)	7.80 (s, 1H, H4) 4.20 (t, 2H, H5) 2.33 (t, 2H, H7) 1.95 (m, 2H, H6)	179.0 (C2) 162.2 (C4) 118.1 (C1) 111.1 (C3) 67.7 (C5) 20.3 (C7) 17.7 (C6)

[a] Bruker DPX 400 spectrometer, ^{1}H at 400 MHz and ^{13}C at 100.6 MHz with 0.5 M solutions in $CDCl_3$/TMS.

uids are not easily transferred to RTILs because the net charges of the ions create a fundamentally different environment with partial charge-ordering and screening of dipole–dipole interactions by the sea of surrounding ions. The presence of charged species adds new degrees of freedom in the mix of interactions. In this case, the concept of polarity may even require a careful rethinking of the fundamental nature of solvation [21].

Thus, we postulate the enhanced rate of the reactions is due to the decrease of activation energy of the slow reaction step. This, probably due the general RTILs effect 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 these media [22].

A comparison of the results with literature data [4] show that this method allows a relatively short reaction time and little work up for the reaction mixture. All the reactions proceeded to completion under ambient conditions in both ionic liquids without any other catalyst. It is worth nothing that, the utilization of the RTILs and absence of solvent in this reaction is consistent with the concept of 'green chemistry'.

Finally, we investigated the reusability and efficiency of the ionic liquids [BMIM]BF$_4$ and [BMIM]PF$_6$. After the first reaction, the ionic liquid was recovered from the extraction product by filtration of the pyridine salt and since the products were not very soluble in the ionic phase, they were easily separated by simple extraction with ethyl ether followed by evaporation under vacuum. The advantage of the use of ionic liquids as novel reaction media for this acylation is that these ionic liquids can be easily recovered and reused. Successive runs were

Table 3
Results obtained using recycled ionic liquid

Compound	Yield (%)[a]			
	[BMIM]·BF$_4$		[BMIM]·PF$_6$	
	1° cycle	2° cycle	1° cycle	2° cycle
4a	80	80	81	80
4b	95	94	95	93
5a	80	79	85	86
5b	91	89	90	90

[a] Yield of isolated product.

performed with recovered ionic liquid for this same reaction. The results in Table 3 show that the ionic liquids could be recovered quantitatively without loss of activity.

3. Conclusion

In conclusion, we have developed a mild, convenient and efficient protocol for the synthesis of an important chemical intermediate via acylation reaction by the using RTILs ([BMIM]BF$_4$ and [BMIM]PF$_6$). We consider that the use of RTILs induces faster reaction times, easy work up, easier purification of products and better yields than classical methods. In addition, RTILs can be easily and quantitatively recovered and recycled without losing their activity. The experimental procedure unites the feature of simple isolation, little solvent use, efficient recovery, recycling of the ionic liquid and absence of a catalyst making it an environmentally benign methodology apt for development.

4. Experimental

4.1. Synthesis of the RTILs

The ionic liquids were synthesized according to literature [17].

4.2. Synthesis of 1,1,1-trihalo-3-alken-2-one (**4a–e**, **5a–e**)

All glassware must be dried meticulously for this procedure. A mixture of enol ether (**1**) (5 mmol), pyridine (5 mmol) and RTIL (0.5 mmol) was slowly (drop-by-drop) added to a round bottomed flask containing trichloroacetyl chloride (**2**) (5 mmol) or trifluoroacetic anhydride (**3**) (5 mmol), in an ice-bath or ice/salt mixture, under magnetic stirring. After the addition, the ice-bath was removed and the reaction was took place during 1.5 h. The reaction mixture was extracted with diethyl ether (3× 10 mL), and then the solvent was evaporated in a rotatory evaporator, and traces of solvent were removed under vacuum (10 mbar) for 1 h, and the pure product (**4**,**5**) was obtained with no further purification.

4.3. Recuperation of RTILs

After the reaction time finish, organic product was separated from ionic liquid by filtration of the pyridine salt and since the products were not very soluble in the ionic phase, they were easily separated by simple extraction with diethyl ether (2× 10 mL). The *RTILs* was completely recovered and purified under vacuum (10 mbar) for 8 h.

Acknowledgements

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