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An efficient and rapid intramolecular aza-Michael addition of 2′-aminochalcones using ionic liquids as recyclable reaction media

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ABSTRACT

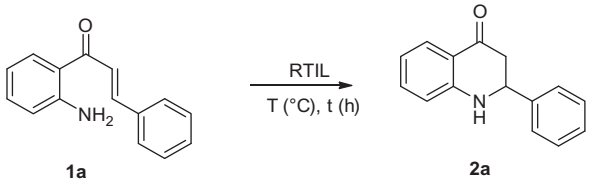
A new, convenient, and efficient method for the intramolecular aza-Michael addition reaction of 2′-aminochalcones is developed using 1-*n*-butyl-3-methylimidazolium tetrafluoroborate as the solvent and catalyst. The ionic liquid is successfully regenerated and reused.

2,3-Dihydro-2-aryl-4(1*H*)-quinolinones, which can be considered as aza-analogs of flavanones, demonstrate a wide range of biological activities, for example, as anticancer and immunosuppressive agents.[1] They also serve as valuable precursors of other medicinally important compounds,[2,3] which are often not readily accessible by other means.[3a,4] The formation of 2,3-dihydroquinolin-4(1*H*)-ones is generally accomplished by acid- or base-catalyzed isomerization of substituted 2′-aminochalcones.[5] Most of these procedures involve the use of corrosive reagents such as orthophosphoric acid, acetic acid, or strong alkali.

Many attempts have therefore been made to explore efficient catalysts to accelerate this reaction. Some of them are of limited synthetic scope due to low yields, long reaction times, and the need for a large amount of catalyst, specialized solvents,[6] or microwave activation.[7]

In recent years, room temperature ionic liquids (RTILs) have attracted considerable interest as new solvents within the chemistry community.[8] They present ecofriendly media owing to a number of attractive physical and chemical properties such as high thermal and chemical stabilities, negligible vapor pressure, non volatility, flame resistance, high polarity, and recyclability.[9] These unique properties of RTILs have led to their use as molecular tools in synthetic chemistry.[10–12]

RTILs have proven to be viable reaction media for numerous types of reaction, including, for example, Friedel–Crafts alkylations, Diels–Alder, Knoevenagel, 1,3-dipolar cycloadditions, and in three-component coupling reactions.[13]



1a 2a

Scheme 1. Model reaction for exploring the use of RTILs for the synthesis of 2-aryl-2,3-dihydroquinolin-4(1*H*)-ones.

However, the ability of RTILs to serve both as catalysts[14] and reagents has not been explored to any great extent.[15]

Some examples of the use of ammonium ionic liquids as a medium for the hetero-Michael addition of thiols[16] and aliphatic amines[17] have been reported.

As a part of a program directed toward the synthesis of new suitably functionalized heterocyclic compounds of potential biological activity,[18] we report herein the use of [bmim]BF_4 as a recyclable reaction medium and an efficient catalyst for the intramolecular hetero-Michael reaction of 2′-aminochalcone.

First, the catalytic ability of the RTILs was tested using 1-*n*-butylpyridinium tetrafluoroborate [bpy]BF_4 as a representative ionic liquid and the cyclization reaction of **1a** as a model system (Scheme 1). The results showed that no reaction took place at room temperature. However, after 1.5 h at 150 °C, the starting material had been consumed (TLC) (entries 1 and 2, Table 1). The adduct

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Table 1
Influence of the IL on the conversion and time required for the cyclization of 2′-aminochalcone into the corresponding dihydroquinolin-4-one[a]

Entry	Solvent	T (°C)/T (h)	Conv. (%)[b]/isolated yield
1	[bpy]BF_4	rt/4	0
2	[bpy]BF_4	150/3.5	100/67
3	[bmim]BF_4	150/2.5	100/83
4	[bmim]PF_6	150/1.5	100/75[c]

[a] Reaction conditions: ionic liquid (1 g), 2′-aminochalcone (100 mg).
[b] Conversion determined by ^{1}H NMR spectroscopy without isolation.
[c] Yield of pure product.

was extracted with diethyl ether and purified by flash chromatography. The structure of product **2a** was confirmed by IR, ^{1}H, and ^{13}C NMR spectroscopy.[19]

Single crystals of **2a** were grown by evaporation of an EtOAc solution and X-ray crystallographic analysis confirmed the structural assignment (Fig. 1).[20]

Next, we extended our investigations to two other ionic liquids; 1-*n*-butyl-3-methylimidazolium tetrafluoroborate ([bmim]BF_4) and 1-*n*-butyl-3-methylimidazolium hexafluorophosphate ([bmim]PF_6), as solvents (Table 1, entries 3 and 4). The best result was obtained using ([bmim]BF_4) at 150 °C for 2.5 h.

Having determined [bmim]BF_4 as an efficient catalyst for our purpose, we next studied its recycling. As demonstrated in Table 2, the room temperature ionic liquid ([bmim]BF_4) could be recycled and reused with only a slight decrease in catalytic activity. The crude product was easily separated from the IL by simple extraction with diethyl ether and the [bmim]BF_4 could be reused up to three times.

To demonstrate the efficiency and the scope of the present method, we performed the intramolecular Michael addition reaction using various substituted 2′-aminochalcones **1**. As shown in Table 3, substrates containing aromatic rings with electron-withdrawing groups (such as halide, nitro) or electron-donating groups (such as alkoxy or alkyl), gave the corresponding products **2** in good to high yields under the same reaction conditions. No obvious effects resulting from the electronic or steric nature of the aromatic ring substituents were observed.

In conclusion, we have developed a procedure using [bmim]BF_4 as a green solvent to provide an efficient and convenient protocol for the synthesis of 2,3-dihydroquinolin-4(1*H*)-ones from 2′-aminochalcones without the requirement for an additional catalyst. The reactions were carried out at 150 °C to afford the desired products

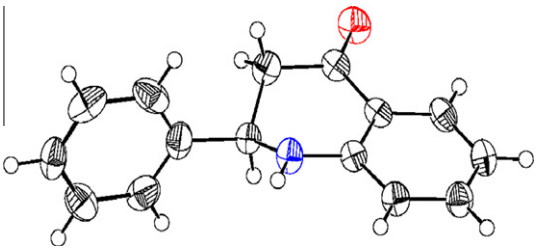
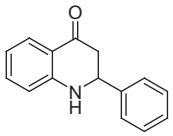
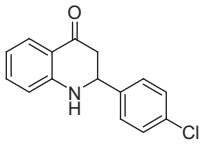
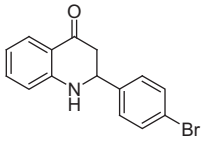
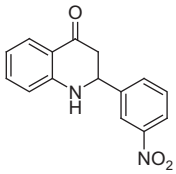
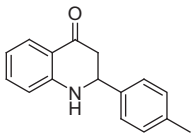
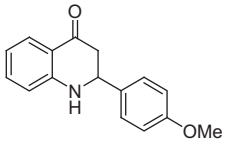
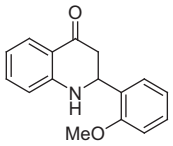
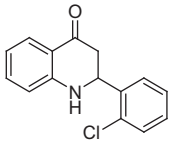


Figure 1. ORTEP plot of the X-ray crystal structure of **2a**. Displacement ellipsoids are drawn at the 50% probability level.[20]

Table 2
Isomerisation reaction of 2′-aminochalcone (**1a**) into 2-aryl-2,3-dihydroquinolin-4(1*H*)-ones (**2a**) over 2.5 h in the recovered ionic liquid

Run	1	2	3
Isolated yield (%)	83	71	64

Table 3
[bmim]BF_4-mediated cyclization of 2′-aminochalcones

Entry	Product	Yield[a] (%)	Reference
1		83	22,5a,5b
2		78	22
3		75	22,5c,6b
4		89	7a
5		92	5c,6b
6		72	22,5a,5b
7		77	7a
8		70	7a

[a] Identification of the products was ascertained by ^{1}H and ^{13}C NMR spectroscopy and by comparison with available physical and spectroscopic data.

in good yields and in short reaction times. This strategy is quite general and works with a broad range of substrates. The exact role of the ionic liquid in this isomerisation reaction is not yet fully understood and requires further investigation.

Representative procedure

In a typical reaction 2′-aminochalcone[21] (**1a**) (100 mg, 0.448 mmol) and [bmim]BF_4 (1 g) were placed in a 25 mL round-bottomed flask fitted with a condenser and a magnetic stir bar. A homogeneous solution was obtained on heating at 150 °C which was stirred at this temperature for 2.5 h. The crude product was isolated by repeated extraction with diethyl ether (7 × 10 mL) followed by evaporation. Filtration of the residue through a silica plug using CH_2Cl_2 as the eluent gave 2-phenyl-2,3-dihydroquinolin-4(1*H*)-one (**2a**).

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.05.097. These data include MOL files and InChiKeys of the most important compounds described in this article.

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19. *Selected data for 2-phenyl-2,3-dihydroquinolin-4(1H)-one* (***2a***): ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.90 (dd, J = 7.9, 1.5 Hz, 1H), 7.51–7.34 (m, 5H), 6.82 (td, J = 7.0, 1.0 Hz, 1H), 6.75 (d, J = 7.9 Hz, 1H), 4.78 (dd, J = 13.2, 4.3 Hz, 1H), 4.57 (s, 1H), 2.92–2.81 (m, 2H). ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 193.3, 151.6, 140.9, 135.4, 128.9, 128.4, 127.5, 126.6, 118.9, 118.3, 115.9, 62.5, 46.4.
20. *Crystal structure analysis for* ***2a***: $C_{15}H_{13}NO$, Mr = 223.26 g mol^{-1}, mp 149 °C, orthorhombic, space group P $2_12_12_1$, a = 5.6799(13) Å, b = 13.596(3) Å, c = 15.013(4) Å, $\alpha = \beta = \gamma = 90$, V = 1159.4(5) Å^3, Z = 4, ρc = 1.279 cm^3, $F(000)$ = 472, crystal size: 0.37 × 0.22 × 0.16 mm. Crystallographic data (excluding structure factors) for compound **2a** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 827683. This data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
21. The synthesis of 2′-aminochalcone (**1a**) is representative of the general procedure employed. To a solution of 10% NaOH (60 mg, 1.5 mmol) and EtOH (10 mL) was added 106 mg (1 mmol) of benzaldehyde and 2′-aminoacetophenone (1 mmol, 135 mg). The mixture was stirred at 25 °C for 24 h. The contents were then cooled and poured into cold H_2O. The solid obtained was filtered, washed, and dried to afford the chalcone **1a** in 82% of yield.
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