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ORIGINAL PAPER

Ionic liquid: an efficient and recyclable medium for the synthesis of octahydroquinazolinone and biscoumarin derivatives

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Abstract A facile and environmentally benign procedure for the synthesis of octahydroquinazolinone and biscoumarin derivatives in ionic liquids is reported. Octahydroquinazolinones were synthesized in the presence of trimethylsilyl chloride (TMSCl) while the synthesis of biscoumarins required no additive. The ability to reuse the ionic liquid, the high yields, and ease of purification are the important features of this process.

Keywords Octahydroquinazolinone · Biscoumarin · Trimethylsilyl chloride · Ionic liquid

Introduction

Heterocyclic systems are common structural motifs in many biologically active substances and natural products and therefore warrant the design of newer and efficient protocols for their synthesis. In view of this, multicomponent reactions (MCRs) are an important sub-class of tandem reactions which can be used to rapidly generate vast libraries of compounds [1, 2], and their highly flexible and selective nature makes MCRs a convenient tool for the construction of many heterocyclic compounds [3–6]. In recent years, green chemistry [7, 8] has emerged as a revolutionary concept and one of its tenets focuses on providing alternative reaction conditions and reaction media that are environmentally benign. In this context, ionic liquids have gained recognition as possible 'green' alternatives to more volatile organic solvents [9–12]. Their negligible vapour pressure, wide liquid range, tunable polarity and potential for recycling circumvent many of the problems associated with common organic solvents. In view of the above observations and our continuing interest in the synthesis of heterocyclic compounds [13–17], we have investigated the synthesis of octahydroquinazolinones (which have potential antibacterial activity and also act as calcium antagonists [18–20]) and biscoumarin derivatives (which have been reported to have anticoagulant [21, 22], spasmolytic [23] and antifungal activity [24]) in ionic liquids.

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Results and discussion

In this paper, we report a simple and convenient synthesis of octahydroquinazolinone and biscoumarin derivatives in ionic liquids. Our initial attempts were directed towards the synthesis of octahydroquinazolinones. In order to optimize the reaction conditions for the synthesis, a reaction using benzaldehyde (2 mmol), dimedone (2 mmol) and urea (3 mmol) was attempted in the ionic liquid 1-butyl-3-methylimidazolium bromide ([bmim]Br) at 100 °C. After 10 h, the reaction was found to be incomplete and only 30% of 4,6,7,8-tetrahydro-7,7-dimethyl-4-phenyl-1*H*,3*H*-quinazoline-2,5-dione was obtained. When this reaction was repeated in presence of TMSCl (4 mmol), the yield improved remarkably to 92% in 2.5 h. Subsequently, the effect of different ionic liquids on the rate of reaction and the yield of products was investigated. It can be inferred from Table 1 that [bmim]Br and [bmim]BF_4 were the preferred media for high yields as compared with [bmim]Cl and [bmim]PF_6. Therefore, [bmim]Br was chosen as the reaction medium for subsequent reactions.

Table 1 Effect of different ionic liquids on condensation reaction of dimedone, benzaldehyde and urea

Entry	Ionic liquid	Catalyst	Yield (%)
1	[bmim]Br	TMSCl	92
2	[bmim]Cl	TMSCl	62
3	[bmim]BF_4	TMSCl	84
4	[bmim]PF_6	TMSCl	65
5	[bmim]Br	–	30

Having established the reaction conditions for the multicomponent reaction, the scope and limitations of the reaction with different aldehydes and cyclic β-diketones was investigated. The reactions of dimedone with various aromatic aldehydes containing electron-withdrawing and electron-donating groups and urea or thiourea proceeded smoothly in presence of TMSCl and were complete in 2–4 h. The reactions were slightly faster for aromatic aldehydes bearing an electron-withdrawing group. A series of octahydroquinazolinones and octahydrothioquinazolinones were prepared (Scheme 1) and the results are listed in Table 2. Some of these reactions were also attempted under microwave irradiation [25] but these resulted in a mixture of products and were discarded.

Cyclocondensation of 1,3-cyclohexanedione with aldehydes and urea was also investigated. The reaction of benzaldehyde was performed with 1,3-cyclohexanedione and urea under the same conditions in [bmim]Br at 100 °C. Interestingly, the reaction was incomplete even after 15 h and only 55% of the product was obtained. However, when the reaction was performed in [bmim]BF_4 at 60–70 °C, 94% of 1,2,3,4,5,6,7,8-octahydro-4-phenylquinazoline-2,5-dione was obtained in 6.5 h. The generality of the condensation was confirmed by carrying out reactions of different aldehydes with 1,3-cyclohexanedione and urea (Scheme 2). These reactions were slow compared with reactions of dimedone. The results are listed in Table 3.

The scope of the present protocol was extended to another active methylene compound, 4-hydroxycoumarin, in place of dimedone or 1,3-cyclohexanedione. A pilot reaction was performed by the condensation of benzaldehyde, 4-hydroxycoumarin and urea in [bmim]BF_4, using TMSCl as catalyst. However, to our surprise, the isolated product was identified to be 3,3′-benzylidenebis-(4-hydroxycoumarin) as characterized by its melting point and spectral data, and urea was found unreacted in the reaction mixture. Subsequently, it was observed that biscoumarins could be obtained even without a catalyst by simply heating the aldehyde and 4-hydroxycoumarin in ionic liquid at 60–70 °C. Consequently, the condensation of a series of aromatic, heteroaromatic and aliphatic aldehydes was carried out with 4-hydroxycoumarin under similar conditions. All aldehydes reacted almost equally fast to afford biscoumarins in excellent yields (Scheme 3). All these results are listed in Table 4.

Table 2 Synthesis of various octahydroquinazolinone and octahydrothioquinazolinone derivatives using dimedone, aldehydes, and urea or thiourea

Entry	R	X	Product	Time (h)	Isolated yield (%)	Ref.
1	C_6H_5	O	**2a**	2.5	92, (86, 84, 72)[a]	[26]
2	4-BrC_6H_4	O	**2b**	2.0	93	[26]
3	3-ClC_6H_4	O	**2c**	2.5	84	[26]
4	4-$O_2NC_6H_4$	O	**2d**	2.5	85	[26]
5	4-$CH_3C_6H_4$	O	**2e**	3.0	81	[26]
6	2,4-$Cl_2C_6H_3$	O	**2f**	2.5	86	[26]
7	4-$(CH_3)_2NC_6H_4$	O	**2g**	3.5	77	[26]
8	$(CH_3)_2CH$	O	**2h**	3.5	85	[26]
9	C_6H_5	S	**2i**	2.5	91	[26]
10	4-BrC_6H_4	S	**2j**	2.5	89	[26]
11	3-ClC_6H_4	S	**2k**	3.0	81	[26]
12	4-$CH_3C_6H_4$	S	**2l**	3.5	82	[26]
13	4-$(CH_3)_2NC_6H_4$	S	**2m**	4.0	74	[26]

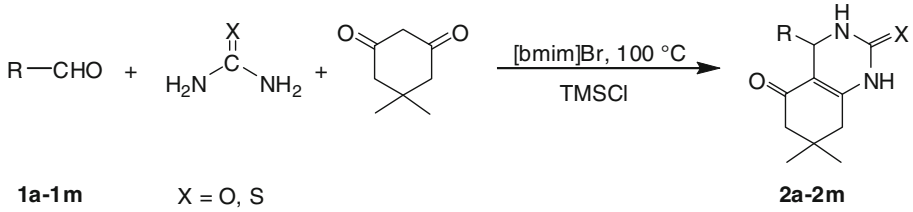
[a] Yields in parentheses are the yields obtained by using the recovered ionic liquid in successive runs

In conclusion we have reported an easy and efficient protocol for the synthesis of octahydroquinazolinones and biscoumarins in the easily accessible ionic liquids [bmim]Br and [bmim]BF_4. The method offers marked improvement with its operational simplicity, short reaction time and high isolated yield of pure products.

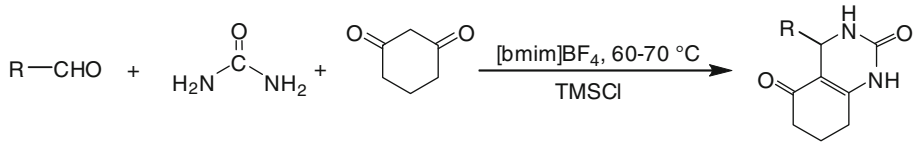
Experimental

The ionic liquids were prepared by reported procedures [31, 32]. All products were confirmed by their m.p., IR,

Scheme 1



Scheme 2



3a-3f **4a-4f**

Table 3 Synthesis of various octahydroquinazolinone derivatives using 1,3-cyclohexanedione, aldehydes and urea

Entry	R	Product	Time (h)	Yield (%)	Ref.
1	C_6H_5	**4a**	6.5	94	[19]
2	4-BrC_6H_4	**4b**	6.0	93	[19]
3	4-ClC_6H_4	**4c**	6.0	88	[19]
4	4-$NO_2C_6H_4$	**4d**	6.5	81	[19]
5	2,4-$Cl_2C_6H_3$	**4e**	7.0	82	[19]
6	4-$CH_3C_6H_4$	**4f**	8.0	78	[19]

Table 4 Synthesis of various biscoumarins by condensation of aldehydes and 4-hydroxycoumarin

Entry	R	Product	Time (h)	Yield (%)	Ref.
1	C_6H_5	**6a**	2.0	84	[27]
2	4-ClC_6H_4	**6b**	2.5	91	[27]
3	4-BrC_6H_4	**6c**	2.5	87	[27]
4	3-ClC_6H_4	**6d**	2.5	84	[28]
5	4-$NO_2C_6H_4$	**6e**	2.5	84	[27]
6	4-$CH_3C_6H_4$	**6f**	3.0	83	[29]
7	4-$CH_3OC_6H_4$	**6g**	3.0	87	[28]
8	CH=CH–C_6H_5	**6h**	3.0	82	[27]
9	$CH(CH_3)_2$	**6i**	3.0	77	[28]
10	2-Furanyl	**6j**	3.0	83	[27]
11	2-Pyridyl	**6k**	3.0	81	[30]

NMR and mass spectra and comparison with data in references [19, 26–30]. All melting points were recorded on a Tropical Labequip apparatus. IR spectra were recorded on Perkin-Elmer FTIR-1710 instrument. ^1H and ^{13}C NMR spectra were recorded on Bruker Advance Spectrospin 300 and 400 MHz spectrometer using TMS as internal standard. Mass spectra were recorded on Jeol-JMS-D300 and Jeol SX102 instruments.

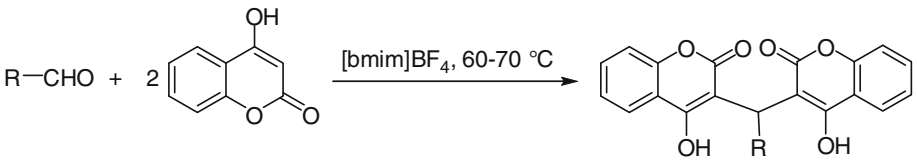
General procedure for the synthesis of octahydroquinazolinone and octahydrothioquinazolinone derivatives ***2a–2m*** *and* ***4a–4f***

In a typical experiment, in a round-bottomed flask aldehyde (n mmol), dimedone or 1,3-cyclohexanedione (n mmol), urea or thiourea (1.5n mmol), TMSCl (2n mmol) and ionic liquid (4n mmol) were heated at 100 °C under nitrogen atmosphere with vigorous stirring. After completion of the reaction as monitored by TLC, the reaction mixture was cooled to room temperature. The product was extracted in diethyl ether and washed well with water. The combined extract was dried over anhydrous $MgSO_4$ and concentrated on a rotary evaporator. The crude product was recrystallized from ethanol to give the pure desired product. The rest of the viscous ionic liquid was thoroughly washed with diethyl ether and recycled in subsequent reactions. Second and third runs using recovered ionic liquid afforded similar yields to those obtained in the first run (see Table 2). However, in the fourth and fifth runs, the yields decreased gradually.

General procedure for the synthesis of biscoumarins ***6a–6k***

In a typical experiment, an aldehyde (n mmol), 4-hydroxycoumarin (2n mmol) and [bmim]BF_4 (4n mmol) were heated in a round-bottomed flask at 60–70 °C with vigorous stirring. After completion of the reaction as monitored by TLC, the reaction mixture was cooled to room temperature. The product was extracted in diethyl ether and washed well with water. The combined extract was dried over anhydrous $MgSO_4$ and concentrated on a rotary evaporator. The crude product was recrystallized from ethanol to give the pure desired product. The rest of the viscous ionic liquid was thoroughly washed with diethyl ether and recycled in subsequent reactions.

Scheme 3



5a-5k **6a-6k**

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References

1. Kappe CO (2002) Curr Opin Chem Biol 6:314
2. Ugi I (2001) Pure Appl Chem 73:187
3. Pandey G, Singh RP, Singh VK (2005) Tetrahedron Lett 46:2137
4. Werner B, Domling A (2003) Molecules 8:53
5. Kappe CO (2000) Acc Chem Res 33:879
6. Terret NK, Gardner M, Gordon DW, Kobylecki RJ, Steele J (1995) Tetrahedron 51:8135
7. Anastas PT, Warner JC (1998) Green chemistry: theory and practice. Oxford University Press, Oxford
8. Clark JH (2001) Pure Appl Chem 73:103
9. Welton T (1999) Chem Rev 99:2071
10. Wasserscheid P, Keim W (2000) Angew Chem Int Ed 39:3773
11. Kumar A, Parwar SS (2004) J Org Chem 69:1419
12. Sheldon R (2001) Chem Commun 2399
13. Khurana JM, Kukreja G, Bansal G (2002) J Chem Soc Perkin Trans 1 2520
14. Khurana JM, Kukreja G (2003) J Heterocycl Chem 40:677
15. Khurana JM, Agrawal A, Kukreja G (2006) Heterocycles 68:1885
16. Khurana JM, Arora R, Satija S (2007) Heterocycles 71:2709
17. Khurana JM, Sharma V (2008) Chem Heterocycl Compd 44:309
18. Kidwai M, Sexana S, Khan MKR, Thukhral SS (2005) Eur J Med Chem 40:816
19. Lin H, Zhao Q, Xu B, Xi Wang (2007) J Mol Catal A Chem 268:221
20. Zorkun İ, Sarac S, Celebi S, Erol K (2006) Bioorg Med Chem Lett 14:8582
21. Nagashima R, Reilly RO, Levy G (1969) Clin Pharm Ther 1:22
22. Reilly RO, Ohms J, Motley C (1969) J Biol Chem 244:1303
23. Kostava I, Manolov I, Nicolova I, Konstantonov S, Karaivanova M (2001) Eur J Med Chem 36:339
24. Chohan ZH, Shaikh AU, Rauf A, Supuran CT (2006) J Enzym Inhib Med Chem 21:741
25. Qadir S, Dar AA, Khan KZ (2008) Synth Commun 38:3490
26. Kantevari S, Bantu R, Nagarapu L (2006) Arkivoc xvi:136
27. Kidwai M, Bansal V, Mothsra P, Saxena S, Somvanshi RK, Dey S, Singh TP (2007) J Mol Catal A Chem 268:76
28. Khan KM, Iqbal S, Lodhi MA, Maharvi GM, Ullah Z, Choudhary MI, Rehman A, Parveen S (2004) Bioorg Med Chem 12:1963
29. Manolov I, Moessmer C, Nicolova I, Danchev N (2006) Eur J Med Chem 41:882
30. Manolov I, Moessmer C, Nicolova I, Danchev N (2006) Arch Pharm Chem Life Sci 339:319
31. Bohnote P, Dias AP, Papageorgiou N, Kalyanasundaram K, Gratzel M (1996) Inorg Chem 35:1168
32. Suarez PAZ, De Souza RF, Dupont J (1996) Polyhedron 15:1217