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PAPER

Catalyst-free synthesis of quinazoline derivatives using low melting sugar–urea–salt mixture as a solvent†

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Low melting mixture of maltose–dimethylurea (DMU)–NH_4Cl was found to be an inexpensive, non-toxic, easily biodegradable and effective reaction medium in the catalyst-free synthesis of quinazoline derivatives. This simple and efficient method furnished the corresponding quinazolines in high yields *via* one-pot three-component reaction of 2-aminoaryl ketones, aldehyde, and ammonium acetate under aerobic oxidation conditions.

Introduction

Solvent choice is a crucial step in organic synthesis. Despite a small number of organic reactions which can be performed in the solid state or solvent-free conditions, these approaches are restricted due to the easy formation of undesired side products and the difficult heat flow control.[1] In the last decade, many promising media have appeared as innocuous solvents, such as water,[2] ionic liquids,[3] supercritical fluids,[4] polyethylene glycol,[5] glycerol,[6] and perfluorinated solvents.[7] However, the use of these solvents is still limited by many problems: some compounds, substrates, or reagents have a poor solubility or stability in water; some ionic liquids lack of toxicity and biocompatibility data with high prices; sophisticated equipment is usually required when perfluorinated solvents are employed.

In recent years, low melting mixtures consisting of carbohydrates, urea and inorganic salts have been introduced as new alternative sustainable solvents for organic transformations.[8] These solvents have been applied to Stille,[9] Diels–Alder,[10] Heck, and cycloaddition reactions.[11] The synthesis of 5-hydroxymethylfurfural,[12] glycosyl ureas,[13] and 3,4-dihydropyrimidin-2-ones,[14] have been reported by using of low melting mixture of carbohydrates, urea and inorganic salts as solvents. The peculiar physical and chemical properties of low melting mixtures, such as polarity, low toxicity, non-volatility, biodegradability, low cost, thermal stability, and ready availability from bulk renewable resources without any further modification, prompted us to extend their use as green solvents in organic synthesis.

Quinazoline is one of the most important nitrogen heterocycles commonly found in a wide variety of natural products, pharmaceutical molecules, and functional materials. Quinazoline derivatives have been reported to possess diverse biological and therapeutic properties such as antibacterial,[15] anti-inflammatory,[16] antiplasmodial,[17] antitumor,[18] antimicrobial and antioxidant.[19] In addition, they have also been used as photochemotherapeutic agents,[20] DNA-gyrase, JAK2, PDE5, and EGFR tyrosine kinase inhibitors,[21] as well as CB2 receptor agonists.[22] Consequently, wide demands of diverse quinazoline derivatives in various fields have promoted the development of practical and diversified synthetic methods. A variety of procedures have been reported, such as (i) copper-catalyzed cascade coupling of 2-bromobenzaldehyde with acetamidine hydrochloride;[23] (ii) cyclization of substituted [2-(methyleneamino) phenyl] methanoneoximes by photochemical methods;[24] (iii) the reaction of *N*-imidoyliminophosphorane and aldehyde using conventional microwave oven;[25] (iv) copper-catalyzed alkynylation and cyclization of *N*-phenylbenzamidines;[26] (v) tandem reaction from 2-aminobenzophenones and benzylic amines followed by sp^3 C–H functionalization;[27] (vi) the condensation of aldehydes with 2-aminobenzylamine using sodium hypochlorite[28] or MnO_2 [29] as oxidant; (vii) copper-catalyzed Ullmann *N*-arylation coupling process;[30] (viii) microwave irradiations of 2-(aminoaryl)alkanone *O*-phenyl oximes and carbonyl compounds;[31] Nevertheless, those methods suffer from limitations of substrate generality, the availability of starting materials, multistep synthesis, use of expensive catalyst, ligand or additives, lower product yields, and harsh conditions. Therefore, the design of improved and environmentally benign approaches that allow for the rapid, cost-effective synthesis of quinazolines from readily available precursors would be highly desired.

One such way is to use multicomponent reactions (MCRs) that can construct complex molecules from common starting materials in an one-pot manner, which provide significant advantages over conventional linear-type syntheses due to their flexible, convergent and atom efficient nature. These reactions can avoid time-consuming and costly processes for purification of the intermediates and tedious steps of protection and deprotection of functional groups, thereby enhancing the greenness of transformations. Thus, MCRs have become an important area of research in organic, medicinal and combinatorial chemistry for

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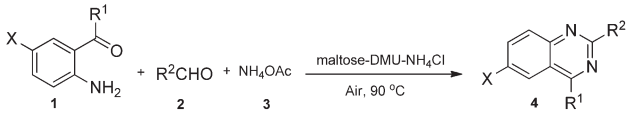


Scheme 1 Synthesis of quinazoline derivatives in maltose–DMU–NH_4Cl.

assembling compounds and lead to the identification of bioactive ones.[32] If such reactions could be run in innocuous solvents, they would comply with most of the green chemistry principles.[33]

As part of our continuing interest in developing efficient and environmental benign synthetic methodologies,[34] herein, we describe the use of low melting mixtures of maltose–dimethylurea (DMU)–NH_4Cl as a green solvent for the synthesis of quinazoline derivatives *via* a one-pot three-component reaction of 2-aminoaryl ketones, aldehydes, and ammonium acetate under aerobic oxidation conditions (Scheme 1).

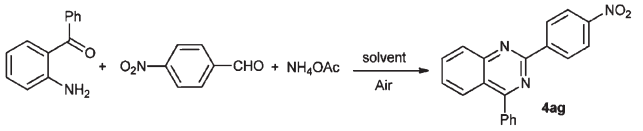
Results and discussion

The initial attempt was guided by the model reaction of 2-aminobenzophenone with 4-nitrobenzaldehyde and ammonium acetate in different solvents under aerobic oxidation conditions, and the results are summarised in Table 1. Only a trace amount of quinazoline (**4ag**) was detected when the reactions were carried out in EtOH or H_2O. Poor to low yields were observed when the reaction proceeded in CH_3CN, DMF, DMSO, toluene or in neat conditions (Table 1, entries 3–7). From an environmental point of view, these procedures do not meet the requirement of green chemistry, although a good result was obtained in refluxing acetic acid, where a mixture of dihydroquinazoline and quinazoline was formed.[35] Considering the fact that sugar–urea–salt mixtures are high polar, have low melting temperatures (65–90 °C), and have small vapour pressures, like ionic liquids, they can be used as an alternative green solvent. The model reaction was carried out in various melt mixtures, including citric acid–DMU, D-(−)-fructose–DMU, L-(+)-tartaric acid–DMU, L-(+)-tartaric acid–choline chloride, mannose–DMU–NH_4Cl, lactose–DMU–NH_4Cl, and maltose–DMU–NH_4Cl at their minimal melting temperature. As expected, the reaction proceeded in these melt mixtures, and the corresponding product was obtained in 75–92% yields (Table 1, entries 9–15). Further investigation of this reaction was achieved by using these melt mixtures at 90 °C. Maltose–DMU–NH_4Cl was found to be superior to other melts, which gave 93% yield of the product. In addition, other eutectic mixture such as choline chloride–urea was also examined and an 85% yield of the desired product was obtained (Table 1, entry 22).

We also tried our methodology by employing other ammonia sources such as NH_4F, $(NH_4)_2SO_4$, $(NH_4)_2CO_3$, and urea in place of ammonium acetate under identical reaction conditions. The yield of the reaction was decreased when these ammonia sources were used (Table 1, entries 23–26). Noteworthy, when maltose–DMU–NH_4Cl was used in the absence of ammonium acetate, the reaction can be proceeded, albeit affording the desired product with diminished yield (55%, Table 1, entry 27). In this case NH_4Cl itself acts as an ammonia source in the formation of quinazoline.

Importantly, the isolation and purification steps of this procedure are very simple. After completion of the reaction, water was added. The components of the melt dissolved in water, and products precipitated amorphously. The solid was isolated by

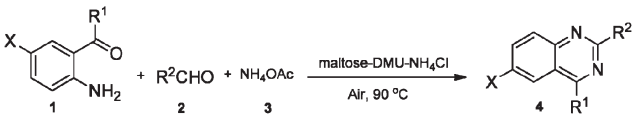
Table 1 Three-component reaction of 2-amino-benzophenone, 4-nitrobenzaldehyde and ammonium acetate in various solvents[a]



Entry	Solvent	Temp (°C)	Time (min)	Yield (%)
1	EtOH	Reflux	180	Trace
2	H_2O	Reflux	180	Trace
3	No	90	180	10
4	CH_3CN	Reflux	180	19
5	DMSO	Reflux	180	20
6	DMF	Reflux	180	13
7	Toluene	Reflux	180	18
8	CH_3COOH[b]	Reflux	600	50[35]
9	Citric acid–DMU (40 : 60)	65	200	85
10	D-(−)-Fructose–DMU (70 : 30)	71	300	75
11	L-(+)-Tartaric acid–DMU (30 : 70)	70	300	82
12	L-(+)-Tartaric acid–choline chloride (50 : 50)	90	250	89
13	Mannose–DMU–NH_4Cl (50 : 40 : 10)	89	250	82
14	Lactose–DMU–NH_4Cl (50 : 40 : 10)	88	250	86
15	Maltose–DMU–NH_4Cl (50 : 40 : 10)	84	150	92
16	Citric acid–DMU (40 : 60)	90	150	90
17	D-(−)-Fructose–DMU (70 : 30)	90	150	80
18	L-(+)-Tartaric acid–DMU (30 : 70)	90	150	85
19	Mannose–DMU–NH_4Cl (50 : 40 : 10)	90	150	86
20	Lactose–DMU–NH_4Cl (50 : 40 : 10)	90	150	88
21	Maltose–DMU–NH_4Cl (50 : 40 : 10)	90	150	93
22	Choline chloride–urea (54.1 : 45.9)	90	150	85
23	Maltose–DMU–NH_4Cl (50 : 40 : 10)	90	150	64[c]
24	Maltose–DMU–NH_4Cl (50 : 40 : 10)	90	150	70[d]
25	Maltose–DMU–NH_4Cl (50 : 40 : 10)	90	150	65[e]
26	Maltose–DMU–NH_4Cl (50 : 40 : 10)	90	150	78[f]
27	Maltose–DMU–NH_4Cl (50 : 40 : 10)	90	150	55[g]
28	Maltose–DMU–NH_4Cl (50 : 40 : 10)	84	180	90[h]

[a] Reaction conditions: 2-aminobenzophenone (1 mmol), 4-nitrobenzaldehyde (1 mmol), ammonium acetate (1 mmol), solvent (1.5 g). [b] The reaction of 2-aminobenzophenone, benzaldehyde and ammonium acetate in refluxing acetic acid gave dihydroquinazoline and quinazoline in a combined yield of 50%. [c] NH_4F was used. [d] $(NH_4)_2SO_4$ was used. [e] $(NH_4)_2CO_3$ was used. [f] Urea was used. [g] The reaction was carried out in the absence of ammonium acetate. [h] 50 mmol scale.

Table 2 Synthesis of quinazoline derivatives in maltose–DMU–NH_4Cl melt[a]



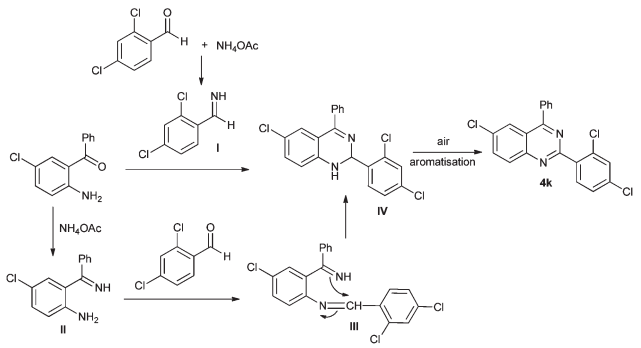
Entry	X	R^1	R^2	Product	Time (min)	Yield[b] (%)	m.p. (°C) Found	m.p. (°C) Reported
1	Cl	Ph	C_6H_5	**4a**	180	86	185–186	185[36]
2	Cl	Ph	4-$CH_3C_6H_5$	**4b**	170	88	216–218	
3	Cl	Ph	4-$OCH_3C_6H_5$	**4c**	150	91	208–210	210–215[27d]
4	Cl	Ph	3,4-$(OMe)_2C_6H_3$	**4d**	90	93	180–181	
5	Cl	Ph	2-OHC_6H_4	**4e**	150	88	213–214	214–215[37]
6	Cl	Ph	3-FC_6H_4	**4f**	180	89	174–175	173[36]
7	Cl	Ph	4-FC_6H_4	**4g**	180	90	172–174	175–180[27d]
8	Cl	Ph	2-ClC_6H_4	**4h**	180	88	95–96	
9	Cl	Ph	3-ClC_6H_4	**4i**	180	90	187–188	
10	Cl	Ph	4-ClC_6H_4	**4j**	200	86	186–187	185–187[27d]
11	Cl	Ph	2,4-$Cl_2C_6H_3$	**4k**	240	84	163–164	162[36]
12	Cl	Ph	3-BrC_6H_4	**4l**	220	87	177–179	178[36]
13	Cl	Ph	4-BrC_6H_4	**4m**	210	91	194–195	
14	Cl	Ph	2-$NO_2C_6H_4$	**4n**	270	81	126–127	128[36]
15	Cl	Ph	4-$NO_2C_6H_4$	**4o**	200	91	220–223	222–224[37]
16	Cl	Ph	3-$CF_3C_6H_4$	**4p**	200	91	160–161	
17	Cl	Ph	4-$CF_3C_6H_4$	**4q**	140	93	161–162	160[39]
18	Cl	Ph	3-Pyridyl	**4r**	200	86	172–173	173[36]
19	Cl	Ph	4-Pyridyl	**4s**	200	87	190–192	192[38]
20	Cl	Ph	2-Thienyl	**4t**	170	91	225–226	220–223[37]
21	Cl	Ph	CH_3CH_2	**4u**	180	89	108–109	110[38]
22	Cl	Ph	$CH_3(CH_2)_7$	**4v**	160	91	46–47	
23	H	Ph	C_6H_5	**4w**	200	87	120–121	118–120[27d]
24	H	Ph	4-$CH_3C_6H_5$	**4x**	180	90	165–166	167–170[27d]
25	H	Ph	4-$OCH_3C_6H_5$	**4y**	200	88	155–156	159–162[27d]
26	H	Ph	4-OHC_6H_4	**4z**	150	90	185–186	
27	H	Ph	3-ClC_6H_4	**4aa**	200	85	115–117	116–118[38]
28	H	Ph	4-ClC_6H_4	**4ab**	200	86	172–174	193–196[27d]
29	H	Ph	3-BrC_6H_3	**4ac**	250	83	98–99	97[37]
30	H	Ph	4-BrC_6H_4	**4ad**	250	85	140–143	140–145[27d]
31	H	Ph	2-$NO_2C_6H_4$	**4ae**	190	85	159–161	
32	H	Ph	3-$NO_2C_6H_4$	**4af**	180	88	182–183	181–183[38]
33	H	Ph	4-$NO_2C_6H_4$	**4ag**	150	93	194–195	195[37]
34	H	Ph	3-$CF_3C_6H_4$	**4ah**	200	88	152–153	
35	H	Ph	4-$CF_3C_6H_4$	**4ai**	175	90	124–125	126–129[27d]
36	H	Ph	3-Pyridyl	**4aj**	200	86	143–144	142[36]
37	H	Ph	2-Thienyl	**4ak**	200	82	146–147	145[36]
38	NO_2	Ph	3-FC_6H_4	**4al**	250	79	204–206	
39	NO_2	Ph	3-ClC_6H_4	**4am**	250	80	215–217	
40	NO_2	Ph	3-$CF_3C_6H_4$	**4an**	200	82	198–199	
41	Cl	2-ClC_6H_4	3-$CF_3C_6H_4$	**4ao**	240	90	178–179	
42	Cl	2-ClC_6H_4	2-Thienyl	**4ap**	300	86	195–196	
43	H	Me	3-ClC_6H_4	**4aq**	180	86	87–88	
44	H	Me	3-$NO_2C_6H_4$	**4ar**	170	89	138–139	
45	H	Me	3-Pyridyl	**4as**	200	88	104–105	105–106[10]

[a] Reaction conditions: 2-aminoaryl ketone (1 mmol), aldehyde (1 mmol), ammonium acetate (1 mmol) in maltose–DMU–NH_4Cl melt (1.5 g) at 90 °C. [b] Isolated yield.

filtration, and pure product was obtained by crystallization from ethanol. Alternatively, after completion of the reaction, the reaction mixture was cooled to room temperature, the product was extracted with ethyl acetate. The melt mixture was dried under vacuum and was directly reused for the next round without further purification. The melt mixture maintained high efficiency even after being reused three times. The product **4ag** was obtained in 92%, 90%, and 89% yields after successive cycles. Furthermore, the ^1H and ^{13}C NMR spectra of the reaction media after the reaction did not show any significant change, which proved its stability under the reaction conditions.

Moreover, this simple procedure allowed easy scale-up of the reaction, and as shown in Table 1, 90% yield was obtained in the 50 mmol scale reaction (Table 1, entry 28), indicating the practicability of our protocol.

To evaluate the substrate scope and limitations of this methodology, we extended our studies with a wide range of substrate combinations. As shown in Table 2, this three-component



Scheme 2 A proposed mechanism for the synthesis of product **4k**.

reaction was performed well for most of the substrates. Both aromatic aldehydes and aliphatic aldehydes, were applicable in this system. It was found that there was no remarkable electron and position effects from the aromatic aldehydes for this reaction, as evidenced by benzaldehydes with either an *o*-, *m*- or *p*-Cl substituent (Table 2, entries 8–10), which resulted in the corresponding products (86–90%). Both 4-methoxybenzaldehyde (Table 2, entry 3) and 4-nitrobenzaldehyde (Table 2, entry 15) were suitable substrates in this reaction. Of particular note, acid-sensitive aldehydes such as thiophene-2-carbaldehyde and pyridin-2-aldehyde also worked well for this reaction. The reaction was well tolerated with many other functional groups such as nitro, halides, hydroxy, methoxy, and trifluoromethyl group on the substrates. Nevertheless, a limitation was found in the reaction of anthracene-9-carbaldehyde, which is less reactive in this system and only a trace amount of desired product was detected. This may indicate that the steric effect is serious enough to prevent the reaction from taking place.

Different substituents on the ketone moiety were also examined. It was found that the performance of this three-component reaction strongly depends on the electronic property of the substituents on the aniline ring of 2-aminobenzophenone. In general, electron-withdrawing groups worked well, affording good-to-excellent yields in all cases. Unexpectedly, when 2-aminobenzophenone with an electron-donating group, such as 2-amino-5-methylbenzophenone, was used as the substrate, the corresponding product failed to generate, even after prolonging reaction time. Expediently, when 2-amino-benzophenone was replaced by 1-(2-aminophenyl)ethanone, the reaction also led to the formation of the desired quinazolines in high yields (Table 2, entries 43–45).

Although the detailed mechanism for this three-component reaction has not been established, according to the suggestions from Sarma and Prajapati,[35] product **4k** could be formed *via* two possible pathways (Scheme 2). To elucidate the reaction mechanism, the reaction of (2-amino-5-chlorophenyl)(phenyl)methanone with 2,4-dichlorobenzaldehyde and ammonium acetate was quenched at 40 min. It was found that 6-chloro-2-(2,4-dichlorophenyl)-4-phenyl-1,2-dihydroquinazoline (intermediate **IV**) was formed. Furthermore, only a trace amount of product **4k** was obtained in the absence of air or under a nitrogen atmosphere. This result demonstrated that air is necessary in the process for the preparation of quinazoline derivatives. We think that the aromatisation of dihydroquinazoline is the rate determining step for this three-component reaction. The formation of aldimine (**I**) is much easier than that of ketimine (II). Therefore, it is evidently reasonable that the first mechanism is the right way to go.

Conclusion

In conclusion, we have developed a general, highly efficient, catalyst-free, step-economic, and eco-friendly method for the synthesis of quinazoline derivatives *via* the one-pot three-component coupling reaction of 2-aminoaryl ketones, aldehydes, and ammonium acetate under aerobic oxidation conditions using low melting mixtures of maltose–dimethylurea (DMU)–NH_4Cl as a novel and green reaction medium. The simple work-up, mild reaction condition and high yields make this new strategy attractive for the preparation of a wide variety of biologically relevant quinazolines.

Experimental

General

Melting points were determined by using an X-4 melting point apparatus. IR spectra were recorded on a Shimadzu FTIR-8900 spectrometer using KBr plates. The ^{1}H NMR (500 MHz) and ^{13}C NMR (125 MHz) spectra were recorded on a Bruker DRX-500 spectrometer using $CDCl_3$ as solvent and TMS as internal standard. Elemental analyses were carried out on a Vario EL III CHNOS elemental analyzer. Commercially available reagents were used without further purification.

General procedure for the synthesis of quinazoline derivatives

To a round-bottomed flask containing 1.5 g of maltose–DMU–NH_4Cl (50 : 40 : 10), was added 2-aminoaryl ketone (1.0 mmol), aldehyde (1.0 mmol) and ammonium acetate (1.0 mmol). The mixture was heated at 90 °C under stirring, while air was bubbled into the reaction. The progress of reaction was monitored by TLC. After completion of the reaction, the mixture was cooled to room temperature. Water was added, the precipitated solid was collected by filtration and washed with water. This was further purified by crystallisation from ethanol or by short column chromatography on silica gel using ethyl acetate–petroleum ether as the eluant.

Acknowledgements

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References

1 (*a*) M. A. P. Martins, C. P. Frizzo, D. N. Moreira, L. Buriol and P. Machado, *Chem. Rev.*, 2009, **109**, 4140–4182; (*b*) C. R. Strauss and D. W. Rooney, *Green Chem.*, 2010, **12**, 1340–1344; (*c*) G. Imperato, S. Hoger, D. Lenoir and B. Konig, *Green Chem.*, 2006, **8**, 1051–1055.
2 (*a*) R. N. Butler and A. G. Coyne, *Chem. Rev.*, 2010, **110**, 6302–6337; (*b*) K. Kumaravel and G. Vasuki, *Curr. Org. Chem.*, 2009, **13**, 1820–1841.

3 (*a*) A. P. Abbott, G. Frisch, J. Hartley and K. S. Ryder, *Green Chem.*, 2011, **13**, 471–481; (*b*) J. Gao, J.-Q. Wang, Q.-W. Song and L.-N. He, *Green Chem.*, 2011, **13**, 1182–1186; (*c*) X. S. Wang, J. Sheng, L. A. Lu, K. Yang and Y. L. Li, *ACS Comb. Sci.*, 2011, **13**, 196–199.

4 (*a*) T. Adschiri, Y. W. Lee, M. Goto and S. Takami, *Green Chem.*, 2011, **13**, 1380–1390; (*b*) W. Leitner and M. Poliakoff, *Green Chem.*, 2008, **10**, 730–730; (*c*) X. J. Feng, M. Yan, T. Zhang, Y. Liu and M. Bao, *Green Chem.*, 2010, **12**, 1758–1766; (*d*) R. Mello, A. Olmos, J. Parra-Carbonell, M. E. Gonzalez-Nunez and G. Asensio, *Green Chem.*, 2009, **11**, 994–999; (*e*) N. S. Kus, *Tetrahedron*, 2012, **68**, 949–958.

5 (*a*) J. Chen, S. K. Spear, J. G. Huddleston and R. D. Rogers, *Green Chem.*, 2005, **7**, 64–82; (*b*) J. Lu, Z. Z. Guan, J. W. Gao and Z. H. Zhang, *Appl. Organomet. Chem.*, 2011, **25**, 537–541; (*c*) X. N. Zhang, Y. X. Li and Z. H. Zhang, *Tetrahedron*, 2011, **67**, 7426–7430.

6 (*a*) Y. L. Gu and F. Jerome, *Green Chem.*, 2010, **12**, 1127–1138; (*b*) J. Francos and V. Cadierno, *Green Chem.*, 2010, **12**, 1552–1555; (*c*) J. I. García, H. García-Marín, J. A. Mayoral and P. Pérez, *Green Chem.*, 2010, **12**, 426–434.

7 W. Zhang, *Green Chem.*, 2009, **11**, 911–920.

8 D. Reinhardt, F. Ilgen, D. Kralisch, B. Konig and G. Kreisel, *Green Chem.*, 2008, **10**, 1170–1181.

9 G. Imperato, R. Vasold and B. Konig, *Adv. Synth. Catal.*, 2006, **348**, 2243–2247.

10 G. Imperato, E. Eibler, J. Niedermaier and B. Konig, *Chem. Commun.*, 2005, 1170–1172.

11 F. Ilgen and B. Konig, *Green Chem.*, 2009, **11**, 848–854.

12 F. Ilgen, D. Ott, D. Kralisch, C. Reil, A. Palmberger and B. Konig, *Green Chem.*, 2009, **11**, 1948–1954.

13 C. Russ, F. Ilgen, C. Reil, C. Luff, A. H. Begli and B. Konig, *Green Chem.*, 2011, **13**, 156–161.

14 S. Gore, S. Baskaran and B. Koenig, *Green Chem.*, 2011, **13**, 1009–1013.

15 R. Tiwari and G. Chhabra, *Asian J. Chem.*, 2010, **22**, 5981–5986.

16 (*a*) C. Balakumar, P. Lamba, D. P. Kishore, B. L. Narayana, K. V. Rao, K. Rajwinder, A. R. Rao, B. Shireesha and B. Narsaiah, *Eur. J. Med. Chem.*, 2010, **45**, 4904–4913; (*b*) A. M. Alafeefy, A. A. Kadi, O. A. Al-Deeb, K. E. H. El-Tahir and N. A. Al-Jaber, *Eur. J. Med. Chem.*, 2010, **45**, 4947–4952.

17 Y. Kabri, N. Azas, A. Dumetre, S. Hutter, M. Laget, P. Verhaeghe, A. Gellis and P. Vanelle, *Eur. J. Med. Chem.*, 2010, **45**, 616–622.

18 (*a*) M. N. Noolvi, H. M. Patel, V. Bhardwaj and A. Chauhan, *Eur. J. Med. Chem.*, 2011, **46**, 2327–2346; (*b*) A. S. El-Azab, M. A. Al-Omar, A. A. M. Abdel-Aziz, N. I. Abdel-Aziz, M. A. A. El-Sayed, A. M. Aleisa, M. M. Sayed-Ahmed and S. G. Abdel-Hamide, *Eur. J. Med. Chem.*, 2010, **45**, 4188–4198.

19 A. Kumar, P. Sharma, P. Kumari and B. L. Kalal, *Bioorg. Med. Chem. Lett.*, 2011, **21**, 4353–4357.

20 P. Barraja, L. Caracausi, P. Diana, A. Montalbano, A. Carbone, A. Salvador, P. Brun, I. Castagliuolo, S. Tisi, F. Dall'Acqua, D. Vedaldi and G. Cirrincione, *ChemMedChem*, 2011, **6**, 1238–1248.

21 (*a*) S. Boyapati, U. Kulandaivelu, S. Sangu and M. R. Vanga, *Arch. Pharm.*, 2010, **343**, 570–576; (*b*) S. H. Yang, D. B. Khadka, S. H. Cho, H. K. Ju, K. Y. Lee, H. J. Han, K. T. Lee and W. J. Cho, *Bioorg. Med. Chem.*, 2011, **19**, 968–977; (*c*) Y. H. Kim, H. Choi, J. Lee, I. C. Hwang, S. K. Moon, S. J. Kim, H. W. Lee, D. S. Im, S. S. Lee, S. K. Ahn, S. W. Kim, C. K. Han, J. H. Yoon, K. J. Lee and N. S. Choi, *Bioorg. Med. Chem. Lett.*, 2008, **18**, 6279–6282; (*d*) O. Cruz-Lopez, A. Conejo-Garcia, M. C. Nunez, M. Kimatrai, M. E. Garcia-Rubino, F. Morales, V. Gomez-Perez and J. M. Campos, *Curr. Med. Chem.*, 2011, **18**, 943–963.

22 R. Saari, J.-C. Törmä and T. Nevalainen, *Bioorg. Med. Chem.*, 2011, **19**, 939–950.

23 C. Huang, Y. Fu, H. Fu, Y. Y. Jiang and Y. F. Zhao, *Chem. Commun.*, 2008, 6333–6335.

24 R. Alonso, A. Caballero, P. J. Campos, D. Sampedro and M. A. Rodriguez, *Tetrahedron*, 2010, **66**, 4469–4473.

25 V. Kumar, C. Mohan, M. Gupta and M. P. Mahajan, *Tetrahedron*, 2005, **61**, 3533–3538.

26 Y. Ohta, Y. Tokimizu, S. Oishi, N. Fujii and H. Ohno, *Org. Lett.*, 2010, **12**, 3963–3965.

27 (*a*) J. T. Zhang, D. P. Zhu, C. M. Yu, C. F. Wan and Z. Y. Wang, *Org. Lett.*, 2010, **12**, 2841–2843; (*b*) B. Han, C. Wang, R. F. Han, W. Yu, X. Y. Duan, R. Fang and X. L. Yang, *Chem. Commun.*, 2011, **47**, 7818–7820; (*c*) J. T. Zhang, C. M. Yu, S. J. Wang, C. F. Wan and Z. Y. Wang, *Chem. Commun.*, 2010, **46**, 5244–5246; (*d*) K. Karnakar, J. Shankar, S. N. Murthy, K. Ramesh and Y. V. D. Nageswar, *Synlett*, 2011, 1089–1096.

28 C. U. Maheswari, G. S. Kumar, M. Venkateshwar, R. A. Kumar, M. L. Kantam and K. R. Reddy, *Adv. Synth. Catal.*, 2010, **352**, 341–346.

29 Y. Y. Peng, Y. Y. Zeng, G. Y. S. Qiu, L. S. Cai and V. W. Pike, *J. Heterocycl. Chem.*, 2010, **47**, 1240–1245.

30 (*a*) V. L. Truong and M. Morrow, *Tetrahedron Lett.*, 2010, **51**, 758–760; (*b*) D. Qiu, F. Y. Mo, Z. T. Zheng, Y. Zhang and J. B. Wang, *Org. Lett.*, 2010, **12**, 5474–5477.

31 (*a*) F. Portela-Cubillo, J. S. Scott and J. C. Walton, *Chem. Commun.*, 2008, 2935–2937; (*b*) F. Portela-Cubillo, J. S. Scott and J. C. Walton, *J. Org. Chem.*, 2009, **74**, 4934–4942.

32 (*a*) B. Jiang, T. Rajale, W. Wever, S. J. Tu and G. G. Li, *Chem.–Asian J.*, 2010, **5**, 2318–2335; (*b*) N. Isambert, M. D. S. Duque, J. C. Plaquevent, Y. Genisson, J. Rodriguez and T. Constantieux, *Chem. Soc. Rev.*, 2011, **40**, 1347–1357; (*c*) E. Ruijter, R. Scheffelaar and R. V. A. Orru, *Angew. Chem., Int. Ed.*, 2011, **50**, 6234–6246; (*d*) P. J. Tambade, Y. P. Patil and B. M. Bhanage, *Curr. Org. Chem.*, 2009, **13**, 1805–1819; (*e*) H. F. Jiang, J. H. Li and Z. W. Chen, *Tetrahedron*, 2010, **66**, 9721–9728; (*f*) M. J. Aliaga, D. J. Ramón and M. Yus, *Org. Biomol. Chem.*, 2010, **8**, 43–46.

33 (*a*) N. Asfaw, Y. Chebude, A. Ejigu, B. B. Hurisso, P. Licence, R. L. Smith, S. L. Y. Tang and M. Poliakoff, *Green Chem.*, 2011, **13**, 1059–1060; (*b*) M. Avalos, R. Babiano, P. Cintas, J. L. Jimenez and J. C. Palacios, *Angew. Chem., Int. Ed.*, 2006, **45**, 3904–3908; (*c*) P. G. Jessop, *Green Chem.*, 2011, **13**, 1391–1398.

34 (*a*) Y. H. Liu, Q. S. Liu and Z. H. Zhang, *J. Mol. Catal. A: Chem.*, 2008, **296**, 42–46; (*b*) Y. H. Liu, Z.H. Zhang and T. S. Li, *Synthesis*, 2008, 3314–3318; (*c*) Y. H. Liu, Q. S. Liu and Z. H. Zhang, *Tetrahedron Lett.*, 2009, **50**, 916–921; (*d*) Z. H. Zhang, H. Y. Lü, S. H. Yang and J. W. Gao, *J. Comb. Chem.*, 2010, **12**, 643–646; (*e*) H. J. Wang, L. P. Mo and Z. H. Zhang, *ACS Comb. Sci.*, 2011, **13**, 181–185; (*f*) J. Deng, L. P. Mo, F. Y. Zhao, L. L. Hou, L. Yang and Z. H. Zhang, *Green Chem.*, 2011, **13**, 2576–2584; (*g*) Y. H. Liu, J. Deng, J. W. Gao and Z. H. Zhang, *Adv. Synth. Catal.*, 2012, **354**, 441–447.

35 R. Sarma and D. Prajapati, *Green Chem.*, 2011, **13**, 718–722.

36 M. Dabiri, P. Salehi and M. Bahramnejad, *Synth. Commun.*, 2010, **40**, 3214–3225.

37 G. Kempter, H. U. Lehm, M. Plesse and A. Barth, *J. Prakt. Chem.*, 1982, **324**, 841–846.

38 W. Szczepankiewicz, P. Wagner, M. Danicki and J. Suwinski, *Tetrahedron Lett.*, 2003, **44**, 2015–2017.

39 H. Kohl, N. J. de Souza and P. D. Desai, *J. Med. Chem.*, 1973, **16**, 1045–1047.

