Tetrahedron 66 (2010) 5637–5641

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

DBU: a highly efficient catalyst for one-pot synthesis of substituted 3,4-dihydropyrano[3,2-*c*]chromenes, dihydropyrano[4,3-*b*]pyranes, 2-amino-4*H*-benzo[*h*]chromenes and 2-amino-4*H* benzo[*g*]chromenes in aqueous medium

Jitender M. Khurana *, Bhaskara Nand, Pooja Saluja

Department of Chemistry, University of Delhi, Delhi 110007, India

ARTICLE INFO

Article history:
Received 27 April 2010
Received in revised form
19 May 2010
Accepted 21 May 2010
Available online 26 May 2010

Keywords:
1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU)
Chromenes
Synthesis in water
Multi-component reaction
Aldehydes

ABSTRACT

We have reported DBU catalyzed one-pot synthesis of 3,4-dihydropyrano[3,2-*c*]chromenes, dihydropyrano[4,3-*b*]pyranes, 2-amino-4*H*-benzo[*h*]chromenes and 2-amino-4*H*-benzo[*g*]chromenes from aldehydes, active methylene compounds malononitrile/ethyl cyanocacetate, and 4-hydroxycoumarin/4-hydroxy-6-methylpyrone/1-naphthol/2-hydroxynaphthalene-1,4-dione in water under reflux. The attractive features of this process are mild reaction conditions, reusability of the reaction media, short reaction times, easy isolation of products, and excellent yields.

1. Introduction

The development of multi-component reactions (MCRs) designed to produce elaborate biologically active compounds has become an important area of research in organic, combinatorial, and medicinal chemistry.[1] One-pot multi-component reaction strategies offer significant advantages over conventional linear-type syntheses by virtue of their convergence, productivity, facile execution and high yields.[2] Developing MCR protocols in water or aqueous medium is an active area of research in this direction. It constitutes an attractive synthetic strategy in drug discovery research, since they provide easy and rapid access to large libraries of organic compounds with diverse substitution patterns.[3] The network of hydrogen bonds in water influences the reactivity of the substrates, which makes it an ideal solvent.[4] It is also proposed that the reactions with negative activation volume might be facilitated by water.[5] MCRs are believed to exhibit negative activation volumes owing to the condensation of several molecules into a single reactive intermediate and product.[6]

Dihydropyrano[3,2-*c*]chromenes and their derivatives are of considerable interest as they possess a wide range of biological properties,[7,8] such as spasmolytic, diuretic, *anti*-coagulant, *anti*-cancer, and *anti*-anaphylactic activity.[9] Benzo[*h*]chromenes are widely employed as cosmetics, pigments,[10] and potential biodegradable agrochemicals[11] and exhibits a wide spectrum of biological activities.[12] Benzo[*g*]chromenes also show a variety of biological activities, including anticancer,[13] *anti*-inflammatory,[14] antimalarial,[15] and pesticides activities.[16] This moiety also occurs in different natural products.[17]

A number of methods have been reported for the syntheses of 2-amino-4*H*-benzo[*h*]chromenes.[18] However, comparatively fewer methods have been described for the synthesis of dihydropyrano [3,2-*c*]chromenes[19] and 2-amino-4*H*-benzo[*g*] chromenes.[20] Some of these procedures require the use of toxic organic solvents, expensive catalysts and tedious workup. Thus, in view of the importance of chromenes for diverse therapeutic activity and in continuation to our endeavor of developing methodologies aimed at synthesis of polyfunctionalized heterocyclic moieties,[21] we considered it necessary to develop a general rapid, high yielding, environmentally benign and easy synthetic protocol for a variety of chromene derivatives.

2. Results and discussion

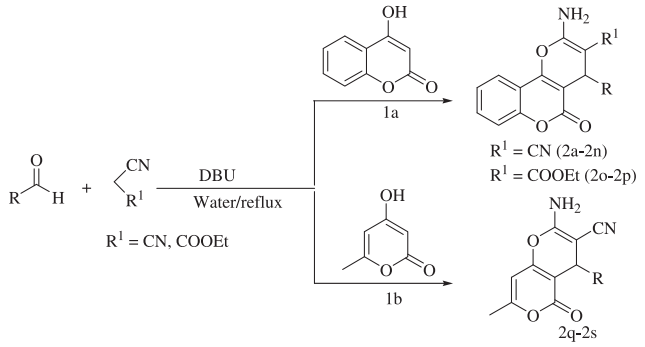
We report in this paper, highly efficient one-pot synthesis of a variety of chromene derivatives namely substituted 3,4-dihydropyrano[3,2-*c*]chromenes (**2a**–**p**), dihydropyrano[4,3-*b*]pyranes (**2q**–**s**), 2-amino-4*H*-benzo[*h*]chromenes (**3a**–**l**) and 2-amino-4

* Corresponding author. Tel.: +91 11 27667725 1384; fax: +91 11 27666605; e-mail address: jmkhurana@chemistry.du.ac.in (J.M. Khurana).

0040-4020/$ – see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2010.05.082

H-benzo[*g*]chromenes (**4a**–**l**) catalyzed by 1,8-diazabicyclo[5.4.0] undec-7-ene (DBU) in water under reflux. Reactions were complete in 5–180 min and high yields of the products were obtained by a simple workup. Careful literature analysis revealed that a variety of bases with p*K*a ranges from 4 to 11 have been used for some multi-component reactions. We speculated that use of neutral organic bases that have high basicity, and can form a stable protonated species, may suppress the formation of enaminonitrile and other side products. 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) fulfills these requirements, and has been used in many organic transformations in recent years.[22] It is a sterically hindered amidine base and especially useful where side reactions due to the inherent nucleophilicity of a basic nitrogen are a problem.[23] DBU is one of the strongest organic neutral base (p*K*a=12) and the +M effect of the adjacent nitrogen stabilizes the protonated species.

Inspired with the catalytic potential of DBU, we examined first the catalytic role of DBU in the synthesis of 3,4-dihydropyrano[3,2-*c*] chromenes via three-component condensation of aldehydes, malononitrile or ethyl cyanoacetate and α-hydroxy C–H acid, i.e., 4-hydroxycoumarin (**1a**). The reaction of 4-chlorobenzaldehyde (1 mmol), malononitrile (1.5 mmol), and 4-hydroxycoumarin (1 mmol) was carried out in the presence of varying amounts of DBU under reflux. It was observed that the use of 10 mol % DBU as a catalyst in aqueous medium yielded the desired product, to afford 2-amino-4-(4-chlorophenyl)-5-oxo-4*H*,5*H*-pyrano[3,2-*c*]chromene-3-carbonitrile, in 93% yield in 5 min (Scheme 1, Table 1, entry **2a**). When this reaction was repeated at room temperature, no desired product formation was observed. However, the product formation was also observed when the reaction was carried out in water/ethanol (1:1, v/v) at room temperature using 10 mol % of DBU. The yield was however inferior (76%) and the reaction was not completed even after 30 min. Thus refluxing all the components in presence of 10 mol % of DBU in water proved to be the optimum conditions for this reaction.



Scheme 1.

Therefore reactions of diversely substituted aromatic, heteroaromatic, and aliphatic aldehydes were attempted with malononitrile and 4-hydroxycoumarin in water under reflux in the presence of 10 mol % of DBU. All the reactions yielded corresponding dihydropyrano[3,2-*c*]chromenes (Table 1, entries **2a**–**n**) in excellent yields. All the utilized functionalities were found to be compatible under the reaction conditions. In order to broaden the scope of the present method, the replacement of malononitrile with ethyl cyanoacetate was examined. To our delight, the reaction underwent successful condensation under similar reaction conditions, to afford the corresponding chromene derivatives in high yields (Table 1, entries **2o**–**p**). Reactions were also attempted by replacing 4-hydroxycoumarin with 4-hydroxy-6-methylpyrone (**1b**). The components underwent successful condensation to give dihydropyrano[4,3-*b*]pyranes (Table 1, entries **2q**–**s**) in nearly quantitative yields (Scheme 1).

Encouraged by these results, we attempted the present protocol for condensation of aldehydes, malononitrile, and 1-naphthol. During our exploratory experiments, we observed that 4-chlorobenzaldehyde underwent the three-component condensation smoothly in the presence of 10 mol % of DBU under reflux to afford 95% of 2-amino-4-(4-chlorophenyl)-4*H*-benzo[*h*]chromene-3-carbnitrile in 5 min (Table 2, entry **3a**). Thereafter, a series of differently substituted 2-amino-4-aryl-4*H*-benzo[*h*]chromene derivatives were prepared from different aromatic aldehydes bearing electron-withdrawing and electron-donating groups using 10 mol % of DBU in aqueous medium under reflux in high yields (Scheme 2, Table 2, entries **3a**–**k**).

It was observed that with ethyl cyanoacetate a slightly longer reaction time was needed to give reasonably high yields (Table 2, entry **3l**). These results clearly indicate that reactions can tolerate a wide range of differently substituted aromatic aldehydes. However aliphatic aldehydes did not undergo condensation even using higher amount of the catalyst.

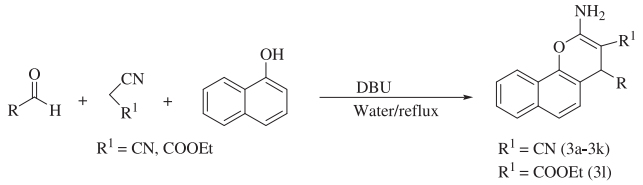
Further to realize the generality and versatility of the catalyst, this novel protocol was extended for the synthesis of 2-amino-4*H*-benzo[*g*]chromenes (**4a**–**l**) by one-pot condensation of aromatic aldehydes (1 mmol), malononitrile or ethyl cyanoacetate (1.5 mmol), and 2-hydroxynaphthalene-1,4-dione (1 mmol) in aqueous media under reflux in the presence of 10 mol % of DBU (Scheme 3).

Table 1
DBU catalyzed three-component synthesis of substituted dihydropyrano[3,2-*c*]chromene and dihydropyrano[4,3-*b*]pyranes (Scheme 1)

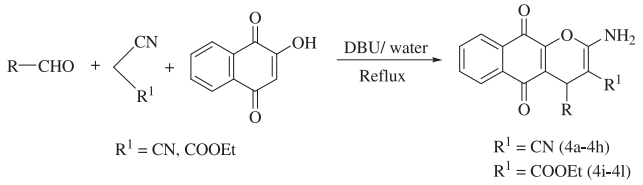
Product	R	R^1	Time (min)	Activated C–H acid	Yield (%)	Mp (°C) (obsd)	Mp (°C) (lit.)[19]
2a	4-ClC_6H_4	CN	5	**1a**	94	260–262	263–265
2b	C_6H_5	CN	7	**1a**	92	256–258	258–260
2c	4-BrC_6H_4	CN	5	**1a**	94	252–254	254–256
2d	4-$CH_3C_6H_4$	CN	8	**1a**	88	253–255	254–255
2e	4-$CH_3OC_6H_4$	CN	10	**1a**	86	248–250	247–249
2f	4-O_2NC6H_4	CN	5	**1a**	91	256–258	258–260
2g	4-HOC_6H_4	CN	12	**1a**	84	266–267	265–266
2h	4-FC_6H_4	CN	5	**1a**	89	262–263	259–261
2i	3-ClC_6H_4	CN	8	**1a**	88	242–243	240–242
2j	2,4-$Cl_2C_6H_3$	CN	12	**1a**	86	258–259	257–259
2k	4-$(CH_3)_2N$ C_6H_4	CN	12	**1a**	85	224–225	223–225
2l	2-Furanyl	CN	12	**1a**	87	250–252	252–253
2m	$(CH_3)_2$ CH	CN	15	**1a**	83	250–252	250–252
2n	$CH_3(CH_2)_2$	CN	15	**1a**	81	243–245	242–245
2o	4-ClC_6H_4	$COOC_2H_5$	20	**1a**	89	192–194	191–193
2p	4-$NO_2C_6H_4$	$COOC_2H_5$	15	**1a**	91	241–243	240–242
2q	C_6H_5	CN	12	**1b**	88	221–223	223–225
2r	4-$CH_3OC_6H_4$	CN	15	**1b**	86	200–201	200–202
2s	4-$O_2NC_6H_4$	CN	10	**1b**	90	210–212	211–213

Table 2
DBU catalyzed three-component synthesis of substituted 2-amino-4*H*-benzo[*h*]chromenes (Scheme 2)

Product	R	R^1	Time (min)	Yield (%)	Mp (°C) (Obsd)	Mp (°C) (lit.)[18]
3a	4-ClC_6H_4	CN	5	95	232–234	232–233
3b	C_6H_5	CN	6	94	218–219	217–219
3c	4-BrC_6H_4	CN	5	96	239–241	241–243
3d	4-$CH_3C_6H_4$	CN	10	88	205–206	204–206
3e	4-$O_2NC_6H_4$	CN	5	95	237–238	238–239
3f	4-HOC_6H_4	CN	10	86	246–248	247–249
3g	4-FC_6H_4	CN	5	91	236–237	235–237
3h	2,4-$Cl_2C_6H_3$	CN	7	86	214–215	214–216
3i	3-$O_2NC_6H_4$	CN	8	89	214–216	215–216
3j	3,4,5-$(CH_3O)_3C_6H_2$	CN	10	80	184–186	180–189
3k	3,4-$(CH_3O)_2C_6H_3$	CN	10	81	209–210	209–211
3l	2-ClC_6H_4	$COOC_2H_5$	15	82	162–164	161–163



Scheme 2.



Scheme 3.

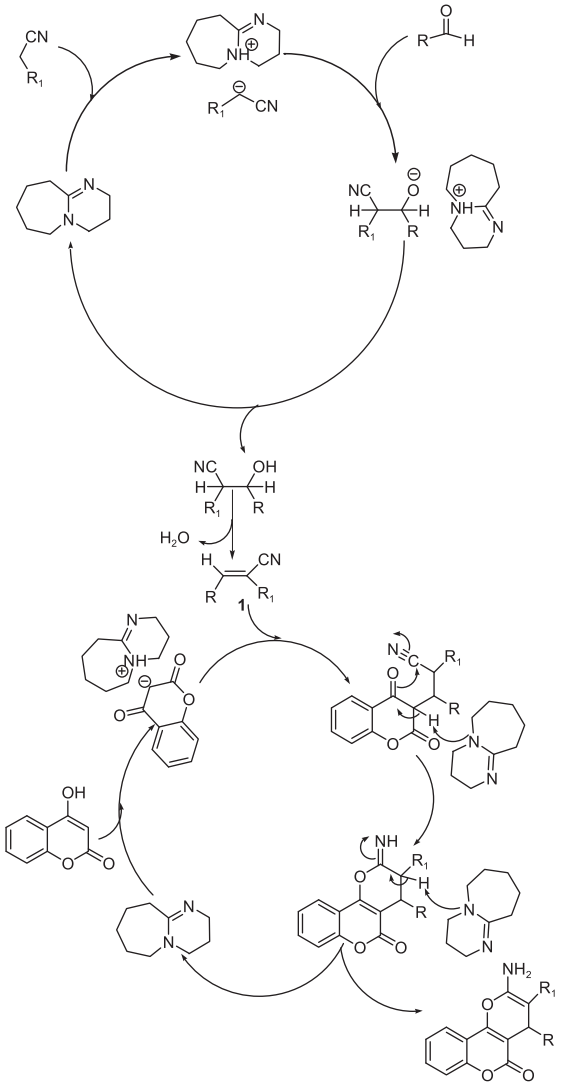
Diversely substituted aromatic aldehydes underwent this three-component *cyclo*-condensation reaction with malononitrile and 2-hydroxynaphthalene-1,4-dione to produce 2-amino-4-aryl-5,10-dioxo-5,10-dihydro-4*H*-benzo[*g*]chromene-3-carbonitriles in excellent yields (Table 3, entries **4a**–**h**). Reaction of aromatic aldehydes and 2-hydroxynaphthalene-1,4-dione, with ethyl cyanoacetate in place of malononitrile also underwent successful condensation under similar conditions, to afford a series of ethyl-2-amino-4-aryl-5,10-dioxo-5,10-dihydro-4*H*-benzo[*g*]chromene-3-carboxylate derivatives in high yields (Table 3, entries **4i**–**l**). The reactions were remarkably clean, and no chromatographic separation was required.

Table 3
DBU catalyzed three-component synthesis of substituted 2-amino-4*H*-benzo[*g*]chromenes (Scheme 3)

Product	R	R^1	Time (min)	Yield (%)	Mp (°C) (obsd)	Mp (°C) (lit.)[20]
4a	4-$O_2NC_6H_4$	CN	40	90	238–240	234–235
4b	C_6H_5	CN	60	87	260–262	261–262
4c	4-$CH_3C_6H_4$	CN	90	85	242–244	242–244
4d	2,4-$Cl_2C_6H_3$	CN	90	90	250–254	293–295
4e	4-BrC_6H_4	CN	90	89	244–246	253–255
4f	2-ClC_6H_4	CN	90	87	240	>300
4g	4-FC_6H_4	CN	90	86	240–242	286–288
4h	3,4,5-$(CH_3O)_3C_6H_2$	CN	150	85	276–278	286–288
4i	4-$O_2NC_6H_4$	$COOC_2H_5$	120	90	170–172	194–196
4j	4-FC_6H_4	$COOC_2H_5$	180	88	214–216	203–205
4k	2-$O_2NC_6H_4$	$COOC_2H_5$	120	86	184–186	223–224
4l	3-BrC_6H_4	$COOC_2H_5$	120	85	154–156	194–196

According to the proposed mechanisms, the first step of this reaction is the formation of Knoevenagel product by the condensation of an aldehyde with malononitrile.[18–20] During such base catalyzed three-component reaction, formation of many side products such as enaminonitrile, higher adducts, reduced products, and malononitrile self addition products have been noticed.[24] We believe that higher basicity, and stability of DBU–H^+ species generated in this reaction suppresses the formation of these side products and hence yield of the product increases.

The α-cyanocinnamonitrile or α-carbethoxycinnamonitrile formed initially by Knoevenagel condensation in the presence of DBU undergo subsequent reactions with α-hydroxy C–H acids, e.g., 4-hydroxycoumarin, 4-hydroxy-6-methylpyrone, 1-naphthol or 2-hydroxynaphthalene-1,4-dione in the presence of DBU to give the desired products (Scheme 4). This has been confirmed by independent reactions of α-cyano-4-chlorocinnamonitrile and α-carbethoxy-4-chlorocinnamonitrile with 4-hydroxycoumarin in the presence of DBU, which gave the desired products in 95% and 92%, respectively. The three-component reactions in the absence of DBU showed the formation of α-cyanocinnamonitrile or α-carbethoxycinnamonitriles only. The reaction media can be reused for further reactions. For example, after completion of the reaction, the solid product was collected by filtration (entry **2a**). To the filtrate, 4-chlorobenzaldehyde, malononitrile, and 4-hydroxycoumarin were added in the same molar ratio without



Scheme 4.

additional load of DBU. The reaction mixture was refluxed for specified time, marginal loss of the yield was observed in first three runs (94%, 92%, and 85%), while in fourth and fifth run the yield dropped to 75% and 65%, respectively.

3. Conclusion

In summary, we have developed a novel synthetic methodology for the synthesis of pyran annulated heterocyclic systems using 10 mol % DBU as a catalyst and moreover reusability of the reaction media without significant loss of activity was an added advantage.

4. Experimental

4.1. General

All of the chemicals used were purchased from Sigma–Aldrich and used as received. All the synthesized compounds are reportedly known, and were identified by comparison of spectral and physical data with the literature. Thin layer chromatography was used to monitor reaction progress. Compounds were purified by crystallization through hot ethanol. Melting points were determined on a melting point apparatus and are uncorrected. IR (KBr) spectra were recorded on Perkin–Elmer FTIR spectrophotometer and the values are expressed as ν_{max} cm^{-1} Mass spectral data were recorded on a Waters micromass LCT Mass Spectrometer and on JEOL-AccuTOF JMS-T100 mass spectrometer having a DART source. The ^1H NMR and ^{13}C NMR spectra were recorded on Bruker Spectrospin spectrometer and Jeol JNM ECX-400P at 300 MHz and 400 MHz, respectively using TMS as an internal standard. The chemical shift values are recorded on δ scale and the coupling constants (J) are in hertz.

4.2. General procedure for the synthesis of chromene derivatives

Aldehyde (2.5 mmol), malononitrile (or ethyl cyanoacetate) (3.75 mmol), and 10 mL of water were placed in a 50 mL round-bottomed flask mounted over a magnetic stirrer. DBU (10 mol %, 0.25 mmol) was added to the mixture and the contents were stirred. To this stirred mixture, 4-hydroxycoumarin (or 4-hydroxy-6-methylpyrone or 1-naphthol or 2-hydroxynaphthalene-1,4-dione) (2.5 mmol) was added. The reaction mixture was refluxed for an appropriate time as mentioned in Table 1 or Table 2 or Table 3. The progress of the reaction was monitored by TLC, for disappearance of aldehyde. After completion of the reaction, the reaction mixture was allowed to cool at room temperature and water was decanted. 3 mL of Ethanol was added to the mixture and it was stirred. The solid was collected by filtration at pump, washed with ethanol, and crystallized from hot ethanol to obtain pure products. The aqueous filtrate containing DBU was used as such for investigating the recyclability of the catalyst.

*4.2.1. Spectral data of some representative products given below: 2-amino-4-(4-chlorophenyl)-5-oxo-4H,5H-pyrano[3,2-c]chromene-3-carbonitrile (**2a**).* ν_{max} (KBr) 3383, 2143, 1714, 1676, 1608, 1378, 1061, 760 cm^{-1}; δ_H (300 MHz, DMSO-d_6) 4.46 (s, 1H, CH), 7.27–7.36 (m, 4H, Ar), 7.44 (br s, 2H, NH_2), 7.49 (br s, 2H, Ar), 7.70 (t, J=7.5 Hz, 1H, Ar), 7.88 (d, J=7.5 Hz, 1H, Ar); δ_C (300 MHz, DMSO-d_6) 36.4, 58.7, 104.4, 113.8, 117.3, 119.3, 123.3, 129.2, 130.4, 132.6, 133.7, 143.1, 153.0, 154.4, 158.9, 160.3; m/z 350.0458 [M^+].

*4.2.2. 2-Amino-4-(4-chlorophenyl)-4H-benzo[h]chromene-3-carbonitrile (**3a**).* ν_{max} (KBr) 3454, 3335, 2192, 1669, 1600, 1572, 1412, 1378, 1100 cm^{-1}; δ_H (300 MHz, $CDCl_3$): 4.79 (br s, 2H, NH_2), 4.88 (s, 1H, CH), 7.01 (d, J=8.7 Hz, 1H, Ar), 7.17–7.32 (m, 5H, Ar), 7.52–7.63 (m, 2H, Ar), 7.83 (d, J=7.2 Hz, 1H, Ar); 8.20 (d, J=8.1 Hz, 1H); m/z 332.0716 [M^+].

*4.2.3. 2-Amino-4-(4-nitrophenyl)-5,10-dioxo-5,10-dihydro-4H-benzo[g]chromene-3-carbonitrile (**4a**).* ν_{max} (KBr) 3458, 3354, 3190, 2925, 2199, 1664, 1594, 1516 cm^{-1}; δ_H (300 MHz, $CDCl_3$+DMSO-d_6) 7.54–8.36 (m, 8H, Ar), 6.55 (s, 2H, NH_2), 4.90 (s, 1H, CH); δ_C (300 MHz, $CDCl_3$+DMSO-d_6) 87.23, 181.67, 163.81,154.68, 153.61, 151.81, 139.56, 138.98, 135.93, 135.15, 133.85, 131.33, 131.29, 128.73, 126.83, 123.57, 62.09, 41.54; m/z 374 [MH]$^+$.

Acknowledgements

B.N. thanks C.S.I.R., New Delhi, India for the grant of Junior and Senior Research Fellowships.

Supplementary data

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.tet.2010.05.082.

References and notes

1. (a) Orru, R. V. A.; de Greef, M. *Synthesis* **2003**, 1471; (b) Balme, G.; Bossharth, E.; Monteiro, N. *Eur. J. Org. Chem.* **2003**, 4101; (c) Brase, S.; Gil, C.; Knepper, K. *Bioorg. Med. Chem.* **2002**, *10*, 2415; (d) Domling, A.; Ugi, I. *Angew. Chem., Int. Ed.* **2000**, *39*, 3168.
2. (a) Weber, L. *Drug Discovery. Today* **2002**, *7*, 143; (b) Domling, A. *Curr. Opin. Chem. Biol.* **2002**, *6*, 306.
3. (a) Weber, L. In *Multicomponent Reactions*; Zhu, J., Bienayme, H., Eds.; WILLEY-VCH GmbH: KGaA: Weinheim, 2005; (b) Hulme, C.; Gore, V. *Curr. Med. Chem.* **2003**, *10*, 51.
4. (a) Head-Gordon, T. *Chem. Rev.* **2002**, *102*, 2651; (b) Bellissent-Funnel, M. C.; Done, J. C. *Hydrogen Bond Networks*; Kluwer Academic Publications: Boston, MA, 1994; (c) *Organic Reaction in Water: Principles, Strategies and applications*; Lindstrom, U. M., Ed.; Blackwell Publishing: Oxford, UK, 2007.
5. (a) Costantino, U.; Fringuelli, F.; Orru, M.; Nocchetti, M.; Piermatti, O.; Pizzo, F. *Eur. J. Org. Chem.* **2009**, 1214; (b) Girotti, R.; Marrocchi, A.; Minuti, L.; Piermatti, O.; Pizzo, F.; Vaccaro, L. *J. Org. Chem.* **2006**, *71*, 70; (c) Amantini, D.; Fringuelli, F.; Piermatti, O.; Pizzo, F.; Vaccaro, L. *J. Org. Chem.* **2003**, *68*, 9263; (d) Amantini, D.; Fringuelli, F.; Piermatti, O.; Pizzo, F.; Vaccaro, L. *Green Chem.* **2001**, *3*, 229; (e) Fringuelli, F.; Piermatti, O.; Pizzo, F. *Synthesis* **2003**, *15*, 2331; (f) Kljin, J. E.; Engberts, J. B. N. *Nature* **2005**, *435*, 746.
6. (a) Pirrung, M. C.; Das Sharma, K. *Tetrahedron* **2005**, *61*, 11456; (b) Hailes, H. C. *Org. Process Res. Dev.* **2007**, *11*, 114.
7. Green, G. R.; Evans, J. M.; Vong, A. K. In *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; Pergamon: Oxford, 1995; Vol. 5; p 469.
8. Konkoy, C.S.; Fick, D.B.; Cai, S.X.; Lan, N.C.; Keana, J.F.W. PCT Int. Appl. WO 0075123, 2000. *Chem. Abstr.* **2001**, *134*, 29313a.
9. (a) Foye, W. O. *Principi Di Chimica Farmaceutica*; Piccin: Padova, Italy, 1991; p 416; (b) Andreani, L. L.; Lapi, E. *Bull. Chim. Farm.* **1960**, *99*, 583; (c) Zhang, Y. L.; Chen, B. Z.; Zheng, K. Q.; Xu, M. L.; Lei, X. H. *Yao Xue Bao* **1982**, *17*, 17; *Chem. Abstr.* **1982**, *96*, 135383e; (d) Bonsignore, L.; Loy, G.; Secci, D.; Calignano, A. *Eur. J. Med. Chem.* **1993**, *28*, 517; (e) Witte, E.C.; Neubert, P.; Roesch, A. Ger. Offen DE., 3427985, 1986; *Chem. Abstr.* **1986**, *104*, 224915f.
10. Ellis, G. P. In *The Chemistry of Heterocyclic Compounds Chromenes, Chromanes and Chromones*; In Weissberger, A., Taylor, E. C., Eds.; John Wiley: New York, NY, 1977; Chapter II, pp 11–139.
11. Hafez, E. A.; Elnagdi, M. H.; Elagemey, A. G. A.; El-Taweel, F. M. A. A. *Heterocycles* **1987**, *26*, 903.
12. (a) Khafagy, M. M.; El-Wahas, A. H. F. A.; Eid, F. A.; El-Agrody, A. M. *Farmaco* **2002**, *57*, 715; (b) Smith, W. P.; Sollis, L. S.; Howes, D. P.; Cherry, C. P.; Starkey, D. I.; Cobley, N. K. *J. Med. Chem.* **1998**, *41*, 787; (c) Martinez, A. G.; Marco, L. *J. Bioorg. Med. Chem. Lett.* **1997**, *7*, 3165; (d) Hiramoto, K.; Nasuhara, A.; Michiloshi, K.; Kato, T.; Kikugawa, K. *Mutat. Res.* **1997**, *395*, 47; (e) Dell, C.P.; Smith, C.W. European Patent Appl. EP 537949. *Chem. Abstr.* **1993**, *119*, 139102d; (f) Bianchi, G.; Tava, A. *Agric. Biol. Chem.* **1987**, *51*, 2001; (g) Mohr, S. J.; Chirigos, M. A.; Fuhrman, F. S.; Pryor, J. W. *Cancer Res.* **1975**, *35*, 3750; (h) Eiden, F.; Denk, F. *Arch. Pharm. Weinheim Ger. (Arch. Pharm.)* **1991**, *324*, 353.
13. (a) Li, C.J.; Li, Y.L.; U.S. Patent Appl. Publ. U.S. 2005222246 A1 20,051,006, 2005. (b) Ough, M.; Lewis, A.; Bey, E. A.; Gao, J.; Ritchie, J. M.; Bornmann, W.; Boothman, D. A.; Oberley, L. W.; Cullen, J. *J. Cancer Biol. Ther.* **2005**, *4*, 95.
14. Moon, D. O.; Choi, Y. H.; Kim, N. D.; Park, Y. M.; Kim, G. Y. *Int. Immunopharmacol.* **2007**, *7*, 506.
15. (a) De Andrade-Neto, V. F.; Goulart, M. O. F.; Da Silva Filho, J. F.; Da Silva, M. J.; Pinto, M. D. C. F. R.; Pinto, A. V.; Zalis, M. G.; Carvalho, L. H.; Krettli, A. U. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 1145; (b) Elisa, P. S.; Ana, E. B.; Ravelo, A. G.; Yapu, D. J.; Turba, A. G. *Chem. Biodivers.* **2005**, *2*, 264.

16. Shestopalov, A. M.; Emelianova, Y. M.; Nesterov, V. N. *Russ. Chem. Bull.* **2003**, *52*, 1164.
17. (a) Da Silva, A. J. M.; Buarque, C. D.; Brito, F. V.; Aurelian, L.; Macedo, L. F.; Malkas, L. H.; Hickey, R. J.; Lopes, D. V. S.; Noel, F.; Murakami, Y. L. B.; Silva, N. M. V.; Melo, P. A.; Caruso, R. R. B.; Castro, N. G.; Costa, P. R. R. *Bioorg. Med. Chem.* **2002**, *10*, 2731; (b) Qabaja, G.; Jones, G. B. *J. Org. Chem.* **2000**, *65*, 7187; (c) Rueping, M.; Sugiono, E.; Merino, E. *Angew. Chem., Int. Ed.* **2008**, *47*, 3046; (d) Brown, P. M.; Krishnamoorthy, V.; Mathieson, J. W.; Thomson, R. H. *J. Chem. Soc. C* **1970**, *10*, 9; (e) Armstrong, J. J.; Turner, W. B. *J. Chem. Soc.* **1965**, 5927; (f) Keniry, M. A.; Poulton, G. A. *Magn. Reson. Chem.* **1991**, *29*, 46.
18. (a) Bloxham, J.; Dell, C. P.; Smith, C. W. *Heterocycles* **1994**, *38*, 399; (b) Elagamey, A. G. A.; El-Taweel, F. M. A. A.; Khodeir, M. N. M.; Elnagdi, M. H. *Bull. Chem. Soc. Jpn.* **1993**, *66*, 464; (c) Kumar, D.; Reddy, V. B.; Mishra, B. G.; Rana, R. K.; Nadagoudac, M. N.; Varma, R. S. *Tetrahedron* **2007**, *63*, 3093; (d) Balalaie, S.; Ramezanpour, S.; Bararjanian, M.; Gross, J. H. *Synth. Commun.* **2008**, *38*, 1078; (e) Ballini, R.; Bosica, G.; Conforti, M. L.; Maggi, R.; Mazzacani, A.; Righi, P.; Sartori, G. *Tetrahedron* **2001**, *57*, 1395; (f) Maggi, R.; Ballini, R.; Sartori, G.; Sartorio, R. *Tetrahedron Lett.* **2004**, *45*, 2297; (g) Ren, Y.-M.; Cai, C. *Catal. Commun.* **2008**, *9*, 1017; (h) Wang, X.; ShiShi, D.; Yu, H.; Wang, G.; Tu, S. *Synth. Commun.* **2004**, *34*, 509; (i) Patra, A.; Tanusri, M. *J. Chem. Res.* **2008**, *7*, 405.
19. (a) Shaker, R. M. *Pharmazie* **1996**, *51*, 148; (b) Abdolmohammadi, S.; Balalaie, S. *Tetrahedron Lett.* **2007**, *48*, 3299; (c) Khurana, J. M.; Kumar, S. *Tetrahedron Lett.* **2009**, *50*, 4125; (d) Heravi, M. M.; Sadjadi, S.; Haj, N. M.; Oskooie, H. A.; Bamoharram, F. F. *Catal. Commun.* **2009**, *10*, 1643.
20. (a) Goujon, J. Y.; Zammattio, F.; Pagnoncelli, S.; Boursereau, Y.; Kirschleger, B. *Synlett* **2002**, 322; (b) Kabalka, G. W.; Venkataiah, B.; Das, B. C. *Synlett* **2004**, 2194; (c) Kesteleyn, B.; De Kimpe, N.; Van Puyvelde, L. *J. Org. Chem.* **1999**, *64*, 1173; (d) Shaabani, A.; Ghadari, R.; Ghasemi, S.; Pedarpour, M.; Rezayan, A. H.; Sarvary, A.; Weng Ng, S. *J. Comb. Chem.* **2009**, *11*, 956; (e) Changsheng, Y.; Chenxia, Y.; Tuanjiea, L.; Shujiang, T. *Chin. J. Chem.* **2009**, *27*, 1989.
21. (a) Khurana, J. M.; Kukreja, G.; Bansal, G. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2520; (b) Khurana, J. M.; Kukreja, G. *J. Heterocycl. Chem.* **2003**, *40*, 677; (c) Khurana, J. M.; Agarwal, A.; Kukreja, G. *Heterocycles* **2006**, *68*, 1885; (d) Khurana, J. M.; Arora, R.; Satija, S. *Heterocycles* **2007**, *71*, 2709; (e) Khurana, J. M.; Sharma, V. *Chem. Heterocycl. Compd.* **2008**, 404; (f) Khurana, J. M.; Magoo, D. *Tetrahedron Lett.* **2009**, *50*, 4777; (g) Khurana, J. M.; Magoo, D. *Tetrahedron Lett.* **2009**, *50*, 7300.
22. (a) Reed, R.; Reau, R.; Dahan, F.; Bertrand, G. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 399; (b) Ghosh, N. *Synlett* **2004**, 574; (c) Baidya, M.; Mayr, H. *Chem. Commun.* **2008**, 1792; (d) Aggarwal, V. K.; Mereu, A. *Chem. Commun.* **1999**, 2311; (e) Ying, A.-G.; Liu, L.; Wua, G.-F.; Chen, G.; Chen, X.-Z.; Ye, W.-D. *Tetrahedron Lett.* **2009**, *50*, 1653.
23. (a) Oediger, H.; Moller, F.; Eiter, K. *Synthesis* **1972**, 591; (b) Yeom, C.-E.; Kim, M. J.; Kim, B. M. *Tetrahedron* **2007**, *63*, 904; (c) Sutherland, J. K. *Chem. Commun.* **1997**, 325; (d) Shiel, W.-C.; Dell, S.; Repic, O. *J. Org. Chem.* **2002**, *67*, 2188; (e) Im, Y. J.; Gong, J. H.; Kim, H. J.; Kim, J. N. *Bull. Korean Chem. Soc.* **2001**, *22*, 1053.
24. (a) Costa, M.; Areias, F.; Abrunhosa, L.; Venancio, A.; Proencua, F. *J. Org. Chem.* **2008**, *73*, 1954; (b) Evdokimov, N. M.; Kireev, A. S.; Yakovenko, A. A.; Antipin, M. Y.; Magedov, I. V.; Kornienko, A. *J. Org. Chem.* **2007**, *72*, 3443.