Molecular iodine mediated one step synthesis of 3-substituted-6-(6-substituted-2-oxochromen-3-yl)-7*H*[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazines

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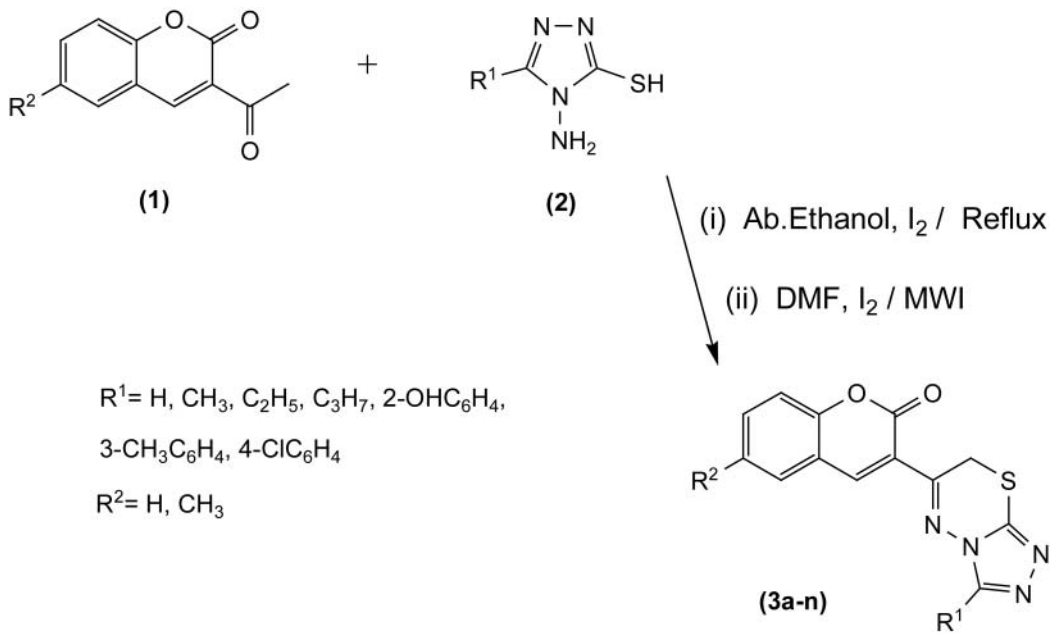
Iodine mediated condensation of 3-acetyl-6-substituted coumarin **(1)** with 3-alkyl/aryl-4-amino-5-mercapto[1,2,4]triazoles **(2)** have been found to give 3-alkyl/aryl-6-(6-substituted-2-oxochromen-3-yl)-7*H*[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazines **(3a–n)** directly in one step. The reaction has also been carried out using microwave irradiation. This protocol is an improvement on reported methods as it occurs in a single step and avoids the use of highly lachrymatory molecular bromine.

Keywords: 6-(6-substituted-2-oxochromen-3-yl)-7*H*[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazines, molecular iodine, 3-acetylcoumarin

Coumarins are a class of naturally occurring compounds that exhibit diverse pharmacological activities. Enormous number of compounds bearing coumarin system in their structure have been synthesised and these derivatives have shown a remarkably broad spectrum of pharmacological activities and they have been used as anticoagulant,[1–3] antibacterial,[4,5] antiviral,[6,7] antitumor,[8–11] bactericidal,[12] fungicidal[13] and anti-inflammatory agents.[14] Also, in recent times there are reports regarding anti-HIV activity[15–18] of coumarin derivatives. Coumarins linked with nitrogen/nitrogen and sulfur heterocyclic units at 3-position are well known to exhibit spasmolytic,[19] uricosuric,[19] anticancer[20] and antitubercular activitiy.[21]

Few reports have appeared regarding the synthesis and biological importance of variously substituted 2-oxochromen-3-yl-7*H*[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazines.[22–26] All these methods involve the conversion of 3-acetylcoumarins into 3-(2-bromoacetyl)coumarins prior to their reaction with variously substituted 4-amino-5-mercapto[1,2,4]triazoles, hence the reaction takes place in two steps. The first step involves the use of molecular bromine which is highly corrosive and the bromoacetyl derivatives formed is quite lachrymatory. We now report a highly efficient one-step synthesis of 3-alkyl/aryl-6-(6-substituted-2-oxochromen-3-yl)-7*H*[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazines by direct condensation of 3-acetylcoumarins with 4-amino-3-alkyl/aryl-5-mercapto[1,2,4]triazoles in the presence of molecular iodine. 4-Amino-5-mercapto[1,2,4]triazole **(1)** was refluxed with 3-acetylcoumarin **(2)** in absolute ethanol in the presence of molecular iodine in catalytic quantity. On working up the reaction mixture, a colourless solid, m.p. 218–220 °C, was obtained in 65% yield. Its IR spectra showed absorption at 1717 cm^{-1} due to the C=O stretching frequency of the lactone ring of coumarin, absorption at 1604 cm^{-1} due to C=N stretching present in the ring showing cyclic structure. In the ^1H NMR spectra, it showed a singlet for two protons at δ 4.20 was assigned to S–CH_2 group which further confirmed the cyclic structure. Based on the above data, the compound was assigned the structure as (2-oxochromen-3-yl)-7*H*[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazines **(3a)**. The reaction between 4-amino-5-mercapto[1,2,4]triazole **(1)** was refluxed with 3-acetylcoumarin **(2)** was also carried out using microwave irradiations in dimethylformamide (Scheme 1). The time required for the completion of the reaction was found to be much shorter (100 s) as compared to time under thermal conditions (4.0 h) and the required compounds are obtained in better yields. Comparison of time and yield in the thermal and microwave method is given in Table 1.

In conclusion, it can be stated that the present protocol is highly efficient one and avoids the prior conversion of 3-acetylcoumarins into 3-(2-bromoacetyl)coumarins which are quite lachrymatory and difficult to handle.



Scheme 1

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Table 1 Comparison of time and yield under thermal and microwave methods

Comp.	R^1	R^2	Thermal method %Yield/Time (h)	MW irradiation %Yield/Time (s)
3a	H	H	65/4.0	82/100
3b	CH_3	H	59/4.5	83/90
3c	C_2H_5	H	60/5.0	81/90
3d	C_3H_7	H	63/4.0	82/80
3e	H	CH_3	65/3.5	80/70
3f	CH_3	CH_3	64/3.0	78/75
3g	C_2H_5	CH_3	67/3.0	81/60
3h	C_3H_7	CH_3	66/3.5	83/65
3i	2-OHC_6H_4	H	75/5.0	88/20
3j	3-$CH_3C_6H_4$	H	70/7.5	82/30
3k	4-ClC_6H_4	H	80/6.0	88/35
3l	2-OHC_6H_4	CH_3	87/1.5	92/20
3m	3-$CH_3C_6H_4$	CH_3	75/4.0	83/25
3n	4-ClC_6H_4	CH_3	85/3.0	90/30

Experimental

General procedure

All the melting points were determined in open capillary tubes using liquid paraffin bath and are uncorrected. IR spectra (KBr) were recorded in Perkin-Elmer spectrophotometer, ^{1}H NMR on Bruker Avance II 400 MHz spectrometer and elemental analysis on Perkin-Elmer 2400 CHN elemental analyser. All the solvents were distilled and dried according to the literature procedures.

The 4-amino-3-alkyl/aryl-5-mercapto[1,2,4]triazoles[27,28] and 3-acetylcoumarin[29] were prepared according to literature procedures.

Synthesis of 3-alkyl/aryl-6-(6-substituted-2-oxochromen-3-yl)-7H [1,2,4]triazolo[3,4-b][1,3,4]thiadiazines **(3a–n);** *general procedure*

1. Under thermal conditions

A mixture of 4-amino-5-mercapto[1,2,4]triazole (5 mmol), 3-acetylcoumarin (5 mmol) and I_2 (0.42 mmol) in absolute ethanol (25 mL) was refluxed on the water bath in a 100 mL round bottom flask. The progress of the reaction was checked on TLC. The reaction mixture was cooled and poured on crushed ice when solid separates out. The solid was filtered under suction, washed with water and recrystallised from DMF–ethanol (2:3).

2. Under microwave irradiations

A mixture of 4-amino-5-mercapto[1,2,4]triazole (1 mmol), 3-acetylcoumarin (1 mmol) and I_2 (0.042 mmol) in DMF (5 mL) was taken in a loosely stoppered 20 mL round bottom flask and was irradiated in a Samsung Trio CE1031LFB microwave oven at 160 °C and 400 W for 100 s. The completion of reaction was checked on TLC. The reaction mixture was diluted with ice cold water (20 mL), when a solid separated out which was filtered, washed with water and recrystallized from DMF–ethanol (2:3).

The physical and spectral data of the compounds **3a–n** are as follows:

6-(2-Oxochromen-3-yl)-7H[1,2,4]*triazolo[3,4-b][1,3,4]thiadiazine* **(3a)**: M.p. 218–220 °C (lit.[24] 216–218 °C). IR (KBr) (cm^{-1}): 1717 (C=O), 1604 (C=N), 1549 (C=C), 1494 (C–N). ^{1}H NMR (DMSO-d_6): δ 4.20 (s, 2H, SCH_2), 7.40–7.44 (m, 2H, $H_{5',6'}$), 7.69–7.75 (m, 2H, $H_{7',8'}$), 8.47 (s, 1H, $H_{4'}$), 8.71 (s, 1H, H_3).

6-(2-Oxochromen-3-yl)-3-methyl-7H[1,2,4]*triazolo[3,4-b][1,3,4] thiadiazine* **(3b)**: M.p. 244–246 °C (lit.[24] 250–252 °C). IR (KBr) (cm^{-1}): 1715 (C=O), 1620 (C=N), 1578 (C=C), 1506 (C–N). ^{1}H NMR (DMSO-d_6): δ 2.59 (s, 3H, CH_3), 4.11 (s, 2H, SCH_2), 7.40–7.44 (m, 2H, $H_{5',6'}$), 7.69–7.75 (m, 2H, $H_{7',8'}$), 8.43 (s, 1H, $H_{4'}$).

6-(2-Oxochromen-3-yl)-3-ethyl-7H[1,2,4]*triazolo[3,4-b][1,3,4] thiadiazine* **(3c)**: M.p. 208–210 °C (lit.[24] 211–213 °C). IR (KBr) (cm^{-1}): 1725 (C=O), 1606 (C=N), 1563 (C=C), 1510 (C–N). ^{1}H NMR (DMSO-d_6): δ 1.43–1.47 (t, 3H, CH_2CH_3, J = 8.60 Hz), 3.05–3.10 (q, 2H, CH_2CH_3, J = 8.60 Hz), 4.25 (s, 2H, SCH_2), 7.41–7.45 (m, 2H, $H_{5',6'}$), 7.70–7.75 (m, 1H, $H_{7'}$), 7.78–7.80 (m, 1H, $H_{8'}$), 8.51 (s, 1H, $H_{4'}$).

6-(2-Oxochromen-3-yl)-3-n-propyl-7H[1,2,4]*triazolo[3,4-b][1,3,4] thiadiazine* **(3d)**: M.p. 196–199 °C (lit.[24] 198–200 °C). IR (KBr) (cm^{-1}): 1721 (C=O), 1611 (C=N), 1564 (C=C), 1493 (C–N). ^{1}H NMR (DMSO-d_6): δ 0.98–1.00 (t, 3H, $CH_2CH_2CH_3$), 1.66–1.75 (h, 2H, $CH_2CH_2CH_3$), 2.55–2.59 (t, 2H, $CH_2CH_2CH_3$), 4.17 (s, 2H, SCH_2), 7.37–7.41 (m, 2H, $H_{5',6'}$), 7.65–7.73 (m, 2H, $H_{7',8'}$), 8.44 (s, 1H, $H_{4'}$).

6-(6-Methyl-2-oxochromen-3-yl)-7H[1,2,4]*triazolo[3,4-b][1,3,4] thiadiazine* **(3e)**: M.p. 158–161 °C. IR (KBr) (cm^{-1}): 1720 (C=O), 1605 (C=N), 1560 (C=C), 1496 (C–N). ^{1}H NMR (DMSO-d_6): δ 2.44 (s, 3H, CH_3), 4.12 (s, 2H, SCH_2), 7.31–7.49 (m, 3H, $H_{5',7',8'}$), 8.27 (s, 1H, $H_{4'}$), 8.68 (s, 1H, H_3). Anal. Calcd for $C_{14}H_{10}N_4O_2S$: C, 56.36; H, 3.37; N, 18.78. Found: C, 56.24; H, 3.26; N, 18.91%.

3-Methyl-6-(6-methyl-2-oxochromen-3-yl)-7H[1,2,4]*triazolo[3,4-b] [1,3,4]thiadiazine* **(3f)**: M.p. 120–122 °C. IR (KBr) (cm^{-1}): 1728 (C=O), 1617 (C=N), 1565 (C=C), 1502 (C–N). ^{1}H NMR (DMSO-d_6): δ 2.46 (s, 3H, CH_3), 2.58 (s, 3H, CH_3), 4.12 (s, 2H, SCH_2), 7.29–7.42 (m, 3H, $H_{5',7',8'}$), 8.29 (s, 1H, $H_{4'}$). Anal. Calcd for $C_{15}H_{12}N_4O_2S$: C, 57.68; H, 3.87; N, 17.93. Found: C, 57.58; H, 3.76; N, 18.02%.

3-Ethyl-6-(6-methyl-2-oxochromen-3-yl)-7H[1,2,4]*triazolo[3,4-b] [1,3,4]thiadiazine* **(3g)**: M.p. 112–114 °C. IR (KBr) (cm^{-1}): 1722 (C=O), 1610 (C=N), 1570 (C=C), 1495 (C–N). ^{1}H NMR (DMSO-d_6): δ 1.42–1.45 (t, 3H, CH_2CH_3, J = 8.64 Hz), 2.47 (s, 3H, CH_3), 3.07–3.12 (q, 2H, CH_2CH_3, J = 8.64 Hz), 4.20 (s, 2H, SCH_2), 7.27–7.32 (m, 3H, $H_{5',7',8'}$), 8.32 (s, 1H, $H_{4'}$). Anal. Calcd for $C_{16}H_{14}N_4O_2S$: C, 58.88; H, 4.32; N, 17.16. Found: C, 58.84; H, 4.20; N, 17.31%.

6-(6-Methyl-2-oxochromen-3-yl)-3-n-propyl-7H[1,2,4]*triazolo [3,4-b][1,3,4]thiadiazine* **(3h)**: M.p. 150–152 °C. IR (KBr) (cm^{-1}): 1721 (C=O), 1614 (C=N), 1568 (C=C), 1501 (C–N). ^{1}H NMR (DMSO-d_6): δ 1.01–1.05 (t, 3H, $CH_2CH_2CH_3$), 1.80–1.89 (h, 2H, $CH_2CH_2CH_3$), 2.49 (s, 3H, CH_3), 2.88–2.95 (t, 2H, $CH_2CH_2CH_3$), 4.06 (s, 2H, SCH_2), 7.29–7.44 (m, 3H, $H_{5',7',8'}$), 8.29 (s, 1H, $H_{4'}$). Anal. Calcd for $C_{17}H_{16}N_4O_2S$: C, 59.98; H, 4.73; N, 16.45. Found: C, 59.84; H, 4.56; N, 16.63%.

6-(2-Oxochromen-3-yl)-3-(2-hydroxyphenyl)-7H[1,2,4]*triazolo [3,4-b][1,3,4]thiadiazine* **(3i)**: M.p. 275–279 °C (lit.[24] 282–284 °C). IR (KBr) (cm^{-1}): 1720 (C=O), 1606 (C=N), 1552 (C=C), 1505 (C–N). ^{1}H NMR (DMSO-d_6): δ 4.14 (s, 2H, SCH_2), 6.90–7.72 (m, 7H, $H_{5',6',7',8',3'',4'',5''}$), 8.15-8.17 (dd, 1H, $H_{6''}$, J = 1.6 and 8.08 Hz), 8.42 (s, 1H, $H_{4'}$), 11.57 (s, 1H, OH).

6-(2-Oxochromen-3-yl)-3-(3-methylphenyl)-7H[1,2,4]*triazolo[3,4-b] [1,3,4]thiadiazine* **(3j)**: M.p. 245–246 °C. IR (KBr) (cm^{-1}): 1718 (C=O), 1614 (C=N), 1570 (C=C), 1501 (C–N). ^{1}H NMR (DMSO-d_6): δ 2.44 (s, 3H, CH_3) 4.17 (s, 2H, SCH_2), 7.31–7.44 (m, 4H, $H_{5',6',7',8'}$),7.67–7.72 (m, 2H, $H_{4'',5''}$), 7.80–7.81 (dd, 1H, $H_{6''}$, J = 1.64 and 7.68 Hz), 7.88 (s, 1H, $H_{2''}$), 8.39 (s, 1H, $H_{4'}$). Anal.Calcd for $C_{20}H_{14}N_4O_2S$ requires: C, 64.15; H, 3.76; N, 14.96. Found: C, 64.03; H, 3.52; N, 15. 22%.

3-(4-Chlorophenyl)-6-(2-oxochromen-3-yl)-7H[1,2,4]*triazolo[3,4-b] [1,3,4]thiadiazine* **(3k)**: M.p. 224–227 °C (lit.[24] 226–228 °C). IR (KBr) (cm^{-1}): 1722 (C=O), 1608 (C=N), 1565 (C=C), 1495 (C–N). ^{1}H NMR (DMSO-d_6): δ 4.15 (s, 2H, SCH_2), 7.38–7.47 (m, 4H, $H_{5',6',7',8'}$), 7.65–7.72 (m, 2H, $H_{3'',5''}$), 8.02–8.04 (m, 2H, $H_{2'',6''}$) 8.35 (s, 1H, $H_{4'}$).

3-(2-Hydroxyphenyl)-6-(6-methyl-2-oxochromen-3-yl)-7H[1,2,4] *triazolo[3,4-b][1,3,4] thiadiazine* **(3l)**: M.p. >250 °C. IR (KBr) (cm^{-1}): 1721 (C=O), 1607 (C=N), 1562 (C=C), 1503 (C–N). ^{1}H NMR (DMSO-d_6): δ 2.58 (s, 3H, CH_3), 4.24 (s, 2H, SCH_2), 7.22–7.43 (m, 3H, $H_{5',7',8'}$), 7.92–8.28 (m, 3H, $H_{3'',4'',5''}$), 8.24–8.26 (dd, 1H, $H_{6''}$, J = 1.64 and 8.12 Hz), 8.48 (s, 1H, $H_{4'}$), 11.42 (s, 1H, OH). Anal. Calcd for $C_{20}H_{14}N_4O_3S$: C, 61.52; H, 3.61; N, 14.35. Found: C, 61.35; H, 3.32; N, 14.53%.

6-(6-Methyl-2-oxochromen-3-yl)-3-(3-methylphenyl)-7H[1,2,4] *triazolo[3,4-b][1,3,4] thiadiazine* **(3m)**: M.p. 211–213 °C. IR (KBr) (cm^{-1}): 1726 (C=O), 1615 (C=N), 1568 (C=C), 1501 (C–N). ^{1}H NMR (DMSO-d_6): δ 2.44 (s, 6H, 2×CH_3), 4.26 (s, 2H, SCH_2), 7.30–7.42 (m, 3H, $H_{5',7',8'}$), 7.50–7.52 (m, 2H, $H_{4'',5''}$), 7.82–7.84 (dd, 1H, $H_{6''}$, J = 1.60 and 7.64 Hz), 7.87 (s, 1H, $H_{2''}$), 8.40 (s, 1H, $H_{4'}$). Anal. Calcd for $C_{21}H_{16}N_4O_2S$ requires: C, 64.93; H, 4.15; N, 14.42. Found: C, 64.76; H, 3.97; N, 14. 62%.

3-(4-Chlorophenyl)-6-(6-methyl-2-oxochromen-3-yl)-7H[1,2,4] *triazolo[3,4-b][1,3,4] thiadiazine* **(3n)**: M.p. 244–246 °C. IR (KBr) (cm^{-1}): 1720 (C=O), 1609 (C=N), 1560 (C=C), 1502 (C–N). ^{1}H NMR (DMSO-d_6): δ 2.44 (s, 3H, CH_3), 4.14 (s, 2H, SCH_2), 7.32–7.51 (m, 5H, $H_{5',7',8',3''\text{ and }5''}$), 8.01–8.03 (m, 2H, $H_{2''\text{ and }6''}$) 8.29 (s, 1H, $H_{4'}$). Anal. Calcd for $C_{20}H_{13}N_4O_2SCl$: C, 58.75; H, 3.20; N, 13.70. Found: C, 58.53; H, 2.95; N, 13.92%.

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References

1 I. Manolov and N.D. Danchev, *Eur. J. Med. Chem. Chim. Ther.*, 1995, **30**, 531.
2 R.B. Arora and C.N. Mathur, *Brit. J. Pharmacol.*, 1963, **20**, 29.
3 E. Ziegler and U. Rossmann, *Montash Chem.*, 1957, **88**, 25.
4 M.A. Al-Haiza, M.S. Mostafa and M.Y. El-Kady, *Molecules*, 2003, **8**, 275.
5 C.J. Dutton, J. Sutcliffe and B. Yang, *US 1993/006308*, 1994.
6 V.S. Parmar, K.S. Bisht, R. Jain, S. Singh, S.K. Sharma, S. Gupta, S. Malhotra, O.D. Tyagi, A. Vardhan, H.N. Pati,, *Indian J. Chem.*, 1996, **35B**, 220.
7 T. Ishikawa, K.L. Kotake and H. Ishii, *Chem. Pharm. Bull.*, 1995, **43**, 1039.
8 Z.M. Nofal, M.I. El-Zahar and S.S. El-Karim, *Molecules*, 2000, **5**, 99.
9 L. Raev, E. Voinova, I. Ivanov and D. Popov, *Pharmazie*, 1990, **45**, 696.
10 P. Valenti, A. Rampa, M. Recanatini, A. Bisi, F. Belluti, R.P. Da, M. Carrara and L. Cima, *Anticancer Drug Des.*, 1997, **12**, 443.
11 A. Shah, Y. Naliapara, D. Sureja, N. Motohashi, M. Kawase, C. Miskolci, D. Szabo, J. Molnar, *Anticancer Res.*, 1998, **18**, 3001.
12 A.M. El-Sayed and O.A. Abd-Allah, *Phosphorus, Sulfur Silicon*, 2001, **170**, 75.
13 A.M. El-Agrody, M.S. El-Latif, N.A. El-Hady, A.H. Fakery and A.H. Bedair, *Molecules*, 2001, **6**, 519.
14 E.A.A. Giota, K.C. Fylaktakidou, H.D.J. Litina, K.E. Litinas and D.N. Nicolaides, *J. Het. Chem.*, 2001, **38**, 717.
15 C. Spino, M. Dodier and S. Sotheeswaran, *Bioorg. Med. Chem. Lett.*, 1998, **8**, 3475.
16 S. Thaisrivongs, K.D. Watenpaugh, W.J. Howe, P.K. Tomich, L.A. Dolak, K.T. Chong, C.S.C. Tomich, A.G. Tomasselli, S.R. Turner, J.W. Strohbach, A.M. Mulichak, M.N. Janakiraman, J.B. Moon, J.C. Lynn, M.M. Horng, R.R. Hinshaw, K.A. Curry and D.J. Rothrock, *J. Med. Chem.*, 1995, **38**, 3624.
17 S. Gaddam, A. Khilevich, C. Filer, J.D. Rizzo, J. Giltner, M.T. Flavin, Z.Q. Xu, *J. Label. Comp. Radiopharm.*, 1997, **39**, 901.
18 H. Zhao, N. Neamati, H. Hong, A. Mazumder, S. Wang, S. Sunder, G.W.A. Milne, Y. Pommier, and T.R. Burke Jr., *J. Med. Chem.*, 1997, **40**, 242.
19 W. Baker and C.S. Howese, *J. Chem. Soc.*, 1953, 119.
20 K. Srimanth, V.R. Rao and D.R. Krishna, *Arzneim. Forsch.*, 2002, **52**, 388.
21 P.V. Kumar and V.R. Rao, *Indian J. Chem.*, 2008, **47B**, 106.
22 B. Kalluraya and P. Vishavanath, *Boll. Chim. Farm.*, 1998, **137**, 169.
23 V.R. Rao., V.R. Kumar and V.A. Vardhan, *Phosphorus, Sulfur and Silicon*, 1999, **152**, 257.
24 B. Kalluraya, P. Vishwanatha, A.M. Isloor and B.R. Ganesh, *J. Ind. Council Chemists*, 1999, **16(2)**, 26.
25 V.R. Rao and P.V. Kumar, *Indian J. Chem.*, 2008, **47B**, 106.
26 V.R. Kumar and V.R. Rao, *Indian J. Chem.*, 2001, **40B**, 1226.
27 K.S. Dhaka, J. Mohan, V.K. Chadha and H.K. Pujari, *Indian J. Chem.*, 1976, **12**, 485
28 N.F. Eweiss, A.A. Bahajaj and E.A. Elsheribini, *J. Het. Chem.*, 1986, **23**, 1451.
29 E. Knoevenagel, *Ber.*, 1898, **31**, 730.