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A convenient synthesis of 2(2-benzo[*b*]furo)indoles and benzofuropyrazoles

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A short synthesis of benzo[*b*]furo indolyls **3a-g** from 2-acetylbenzofuran **1** in two steps and corresponding pyrazoles **4a-g** is described. An interesting scale-up procedure for the synthesis of 2-acetylbenzofuran is also been reported. Similarly 2-acetylbenzofurohydrazones **2a-g** is prepared from 2-acetyl benzofuran and with various phenylhydrazine hydrochlorides in presence of CH_3COONa/EtOH at RT in excellent yield (90-95%). These 2-acetyl benzofurohydrazones **2a-g** are subjected to Fischer indole cyclisation in presence of $ZnCl_2$ in acetonitrile as solvent to get 2(2-benzo[*b*]furo)indoles **3a-g** in good yield.

Keywords: 2-Acetylbenzofuran, phenylhydrazine hydrochloride, zinc chloride, Fisher indole synthesis, Vilsmeier-Haack reaction

The benzo[*b*]furan ring system occurs in large number of biologically active synthetic compounds[1]. Synthetic benzofuran derivatives have received considerable attention owing to their antifungal *N*-myristoyl transferase inhibitor activity[2] and their activity as potent nonsteroidal reversible inhibitor of P450 aromatase[3]. The benzofuran ring system itself is a common structural element that appears in a large number of medicinally important compounds[4].

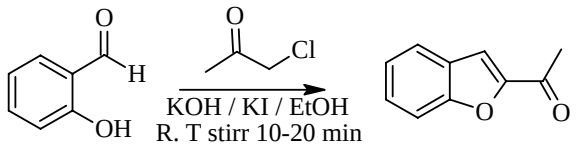
Moreover considerable attention has been directed towards the synthesis of compounds containing the indole nucleus as structural sub unit of a wide variety of biologically active natural products[5-7]. Following all these observation and interest in the synthesis of furan derivatives[8-18] it is envisaged to prepare benzofuroindolyls **3a-g** and benzofuropyrazoles **4a-g** through convenient synthetic approach.

Results and Discussion

For the present study 2-acetylbenzofuran **1** is a useful intermediate for the synthesis of benzofuran coupled with indole derivatives by its reaction with selected phenylhydrazine hydrochlorides. Hence the key precursor 2-acetylbenzofuran is prepared in large scale by adopting the literature method and by suitable modification of earlier reported method[13,19], and the large scale synthesis of 2-acetyl benzofuran in excellent yield (95%) have been successfully achieved (**Scheme I**).

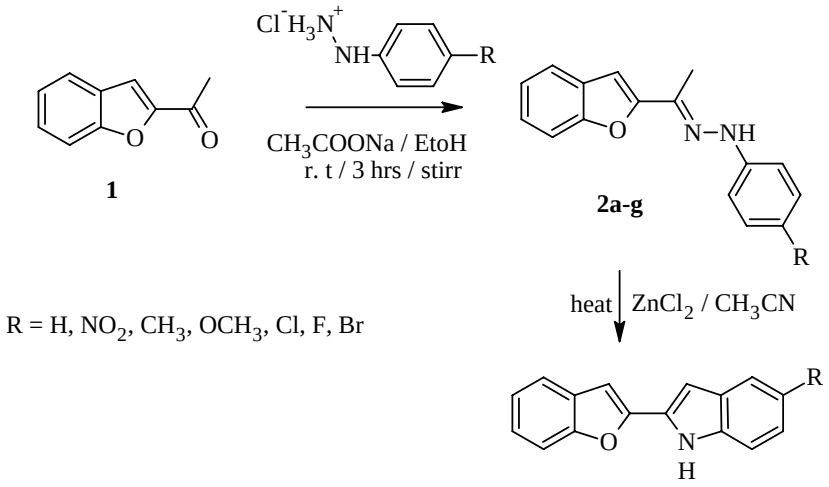
In order to attempt to develop indole coupled at 2-position of benzofuran, the compound **1** was first subjected to react with various phenylhydrazine hydrochlorides in presence of sodium acetate in ethanol to afford corresponding hydrazones **2a-g** in good to excellent yields. These hydrazones are reported to undergo Fischer-indole cyclization reactions. Hence various methods have been employed to accomplish these cyclization reactions. The various methods attempted involve the reaction of hydrazones with polyphosphoric acid, sulphuric acid, phosphorous pentachloride, zinc chloride and acetic acid etc, respectively. All these methods have suffered due to sluggish reactions, tedious work-up and unclean reactions. Hence, to overcome these difficulties, various solvents with fused zinc chloride are used.

Finally zinc chloride-acetonitrile solvent was found to be the best suitable protocol for the conversion of



Scheme I

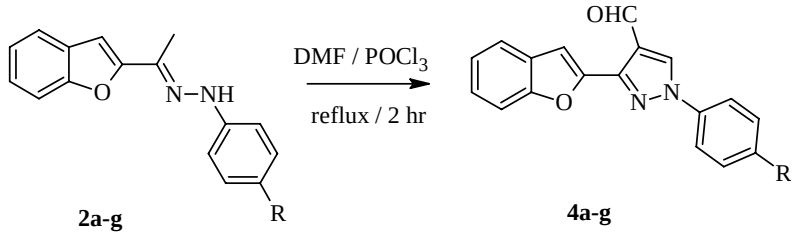
showed absorption band at 1692 cm^{-1} attributed to formyl stretching frequency and the absence of the N-H broad band confirms the cyclization to pyrazole ring. In the ^1H NMR spectrum ($CDCl_3$), a singlet found at δ 10.42 corresponds to formyl proton and the pyrazole ring proton appeared at δ 8.64 as singlet supports the assigned structure. Further, the mass



1 **2a-g** **3a-g**

R = H, NO_2, CH_3, OCH_3, Cl, F, Br

Scheme II



2a-g **4a-g**

R = H, NO_2, CH_3, OCH_3, Cl, F, Br

Scheme III

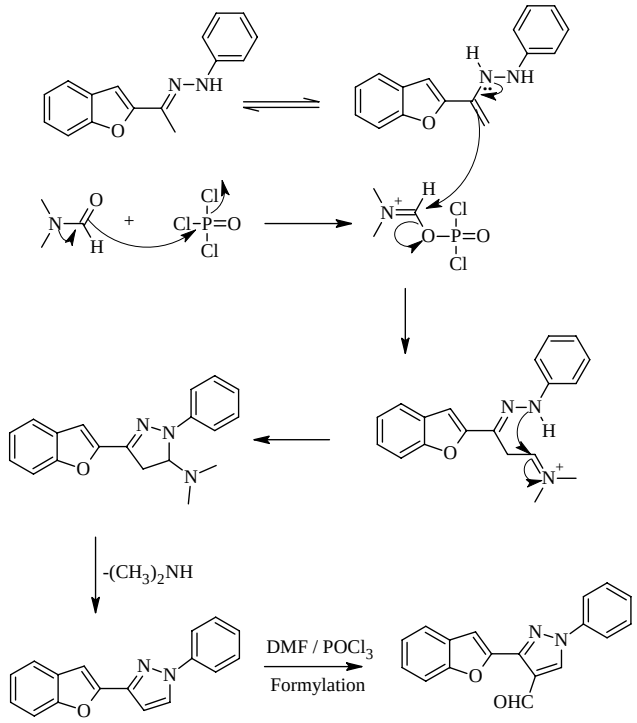
2-acetyl benzofurohydrazones **2a-g** into 2(2-benzofuro) indoles **3a-g** (**Scheme II**). Similarly all other 2-acetylbenzofurohydrazones have been converted into corresponding 2(2-benzofuro)indoles.

Further the 2-acetyl benzofurohydrazones **2a-g** subjected to Vilsmeier-Haack reaction i.e., with $DMF/POCl_3$ at appropriate molar ratio which underwent smooth cyclization followed by formylation afforded 3(1-benzofuran-2-yl)-1-(4-fluoro phenyl)-1*H*-pyrazole-4-carbaldehyde **4a-g** in moderate to good yield (**Scheme III**). The possible mechanism for the synthesis of **4a** is represented in (**Scheme IV**).

Thus, the ring closure was demonstrated by the examination of the structure of **4a** by IR spectrum. It spectrum of **4a** gave a molecular ion peak at *m*/*z* 288**,** and fragmented ion at 186, 118 respectively confirms the structure of the compound.

Experimental Section

All reagents were obtained from Aldrich and used as such. Some of phenylhydrazine hydrochloride have been prepared and are confirmed by comparing with their physical constant with authentic samples. All the melting points were recorded in open capillary the purity of the compounds was checked by TLC on silica gel G plates and were purified by column chromatography on silica gel (60-120 mesh). ^1H NMR spectra were recorded on a Bruker-400 MHz



Scheme IV

spectrometer using TMS as an internal standard. IR spectra were obtained using a FTS-135 spectrometer instrument. Mass spectra were recorded on a JEOL SX 102/DA-6000 (10 kV) FAB mass spectrometer.

General procedure for synthesis of 2-acetylbenzofuran

Salicylaldehyde (12.2 g) was taken in 50 mL of absolute ethanol. To this, KOH (5.6 g) crystals were added and the reaction-mixture was stirred for 5 minutes in ice-bath. To this reaction-mixture chloroacetone (9.2 g) was added drop by drop from dropping funnel about 10 minutes. Further whole reaction-mixture was allowed to stirr for another 20 minutes with catalytic amount of potassium iodide (KI). The resultant solution was poured into crushed ice, the solid obtained was filtered and recrystalized from ethanol to produce 2-acetylbenzofuran in 90-95% yield (9.2 g), melting point was found to be 71-73°C.

Synthesis of 2-acetylbenzofuro phenylhydrazone 2a

A mixture of phenylhydrazine hydrochloride (1.44 g, 0.01mole), sodium acetate (0.82 g, 0.01 mole) in ethanol (10 mL) was stirred at RT for 10 min. To this ethanolic solution, compound **1** (1.60 g, 0.01 mole) was added slowly. The resulting reaction-mixture was allowed to stir for about 2 hr and completion of the reaction was monitored by TLC. The reaction-mixture was then poured into ice water (50 mL) where upon the crude compound was precipitated as yellow solid. The residue obtained after filtration was washed with water and dried. The crude product was purified by recrystallization from absolute alcohol to furnish the pure product **2a** as yellow crystals. Similarly the compounds **2b-g** has been prepared. The yield, melting point and spectral data of compound **2a-g** are as follows.

(1-Benzofuran-2-yl)ethanone phenylhydrazone, 2a. Yellow crystalline solid (2.98 g, 90%); m.p. 155-56°C; IR (KBr, cm^{-1}): 3345-3250 (broad NH), 1618 (C=N); ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.89-7.56 (m, 10H, Ar-H and 1H, -NH), 2.27 (s, 3H, CH_3); MS: *m*/*z* 250 (M^+).

(1-Benzofuran-2-yl)ethanone (4-nitrophenyl) hydrazone, 2b. Yellow crystalline solid (1.38 g, 85%); m.p. 173-75°C; IR (KBr, cm^{-1}): 3340-3245 (broad NH), 1612 (C=N); ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.81-7.51 (m, 9H, Ar-H and 1H, - NH), 2.30 (s, 3H, CH_3); MS: *m*/*z* 295 (M^+).

(1-Benzofuran-2-yl)ethanone (4-methylphenyl)-hydrazone, 2c. Pale yellow: (KBr, cm-1): crystalline solid (1.48 g, 90%); m.p. 142-46°C; crystalline solid (1.48 g, 90%); m.p. 142-46°C; IR: 3352-3257 (broad NH), 1625 (C=N); ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.90-7.62 (m, 9H, Ar-H and 1H, -NH), 2.40 (s, 3H, Ar-CH_3), 2.20 (s, 3H, CH_3); MS: *m*/*z* 264 (M^+).

(1-Benzofuran-2-yl)ethanone (4-methoxyphenyl)-hydrazone, 2d. Pale yellow coloured solid (1.40 g, 80%); m.p. 138-40 °C; IR (KBr, cm^{-1}): 3355-3260 (broad NH), 1622 (C=N); ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.80 (s, 3H, OCH_3), 2.25 (s, 3H, CH_3); MS: *m*/*z* 280 (M^+).

(1-Benzofuran-2-yl)ethanone (4-chlorophenyl) hydrazone, 2e. Yellow crystalline solid (1.23 g, 80%); m.p. 156-58 °C; IR (KBr cm^{-1}) 3350-3255 (broad NH), 1615 (C=N); ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.80-7.51 (m, 9H, Ar-H and ^{1}H, -NH), 2.28 (s, 3H, CH_3); MS: *m*/*z* 284 (M^+).

(1-Benzofuran-2-yl)ethanone (4-fluorophenyl)-hydrazone, 2f. Brown crystalline solid (1.25 g, 85%); m.p. 149-51 °C; IR (KBr, cm^{-1}): 3347-3253 (broad NH), 1620 (C=N); ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.85-7.53 (m, 9Ar-H and ^{1}H, -NH), 2.26 (s, 3H, CH_3); MS: *m*/*z* 268 (M^+).

(1-Benzofuran-2-yl)ethanone (4-bromophenyl)-hydrazone, 2g. Brown coloured solid. (1.43 g, 80%); m.p. 171-72 °C; IR (KBr, cm^{-1}): 3345-3250 (broad

NH), 1618 (C=N); ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.89-7.56 (m, 9H, Ar-H and 1H, -NH), 2.28 (s, 3H, CH_3); MS: *m*/*z* 329 (M^+).

Typical procedure for synthesis of, 2-(1-benzofuran-2-yl)-1*H*-indole, 3a. A mixture of **2a** (2.5g, 0.01 mole), fused $ZnCl_2$ (1.36 g, 0.01 mole) in anhydrous acetonitrile (10 mL) was refluxed for 6 hr. The progress of the reaction was monitored by TLC. After the completion of the reaction, it was filtered and filtrate was poured into ice cooled water. The solid thus obtained was filtered and recrystalized from ethyl acetate to furnish title compound **3a**. Similarly the compounds **3b-g** were synthesized. The yield, melting point and spectral details of compound **3a-g** are as follows.

2-(1-Benzofuran-2-yl)-1*H*-indole, 3a. Brown coloured solid. (1.75 g, 70%); m.p. 195-96^{o}C; IR (KBr, cm-1): 3369-3481 (broad NH); ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.91-7.66 (m, 10Ar-H), 8.7(s, 1H, -NH); MS: *m*/*z* 233 (M^+).

2-(1-Benzofuran-2-yl)-5-nitro-1*H*-indole, 3b. Yellow coloured solid (0.80 g, 70%); m.p. 210-13 ^{o}C; IR (KBr, cm-1): 3350–3481 (broad NH); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.1- 7.5 (m, 9H, Ar-H), 8.6 (s, 1H, NH); MS: *m*/*z* : 278 ($M^{+\cdot}$).

2-(1-Benzofuran-2-yl)-5-methyl-1*H*-indole, 3c. Brown coloured solid (0.79 g, 80%); m.p. 186-88^{o}C; IR (KBr, cm-1): 3337–3482 (broad NH); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.40 (s, 3H, CH_3), 7.0-7.6 (m, 9H, Ar-H), 8.50 (s, ^{1}H, NH); MS: *m*/*z*: 247 ($M^{+\cdot}$).

2-(1-Benzofuran-2-yl)-5-methoxy-1*H*-indole, 3d. Cream coloured solid (0.85 g, 80%); m.p. 178-80 ^{o}C; IR (KBr, cm-1): 3350–3490 (broad NH); ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.9 (s, 3H, OCH_3) 7.1-7.7 (m, 9H, Ar-H), 8.75 (s, ^{1}H, NH); MS: *m*/*z* 263 ($M^{+\cdot}$).

2-(1-Benzofuran-2-yl)-5-chloro-1*H*-indole, 3e. Light yellow coloured solid (0.74 g, 70%); m.p. 185-87^{o}C; IR: (KBr, cm^{-1}): 3347–3490 (broad NH); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.1- 7.6 (m, 9H, Ar-H), 8.65 (s, 1H, NH); MS: *m*/*z* 267 ($M^{+\cdot}$).

2-(1-Benzofuran-2-yl)-5-fluoro-1*H*-indole, 3f. Brown coloured solid. (0.70 g, 70%); m.p. 180-82^{o}C; IR (KBr, cm^{-1}): 3340-3483 (broad, NH); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.0-7.5 (m, 9H, Ar-H), 8.5 (s, 1H, NH); MS: *m*/*z* 251 ($M^{+\cdot}$).

2-(1-Benzofuran-2-yl)-5-bromo-1*H*-indole, 3g. Cream coloured solid. (0.87g, 70%); m.p. 205-08^{o}C; IR (KBr, cm^{-1}): 3348-3482 (broad, NH); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.1-7.6 (m, 9H, Ar-H), 8.65 (s, 1H, NH); MS: *m*/*z* 312 ($M^{+\cdot}$).

Typical procedure for synthesis of 3-(1-benzofuran-2-yl)-1-(phenyl)-1*H*-pyrazole-4-carbaldehyde, 4a

Dimethylformamide (2.19 g, 0.03 mole) was cooled to below 5°C and $POCl_3$ (4.59 g, 0.03 mole) was added drop-wise under stirring for 30 min. To this mixture (2.68 g, 0.01 mole) of compound **2** was added. The resulting mixture was refluxed for 2 hr on water-bath. The precipitate obtained by pouring into ice-cold water was collected by filtration and recrystallized from absolute ethanol. The yield, melting point and spectral data of compound **4a-g** are as follows.

3-(1-Benzofuran-2-yl)-1-phenyl-1*H*-pyrazole-4-carbaldehyde, 4a. Pale yellow solid (1 g, 85%); m.p. 165-68^{o}C; IR (KBr, cm^{-1}): 1680 (CHO), 1620 (C=N), 1595 (C=C); ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.42 (s, 1H, CHO), 8.64 (s, 1H, pyrazole-H), 7.24-7.80 (m, 10H, Ar-H); MS: *m*/*z* 288 (M^+), 186, 118.

3-(1-Benzofuran-2-yl)-1-(4-nitrophenyl)-1*H*-pyrazole-4-carbaldehyde, 4b. Yellow coloured solid. (0.93 g, 70%); m.p. 190-93^{o}C; IR (KBr, cm^{-1}): 1675 (CHO), 1615(C=N), 1590 (C=C); ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.45 (s, 1H, CHO), 8.50 (s, ^{1}H, pyrazole-H), 7.28-7.85 (m, 9H, Ar-H); MS: *m*/*z* 333(M^+).

3-(1-Benzofuran-2-yl)-1-(4-methylphenyl)-1*H*-pyrazole-4-carbaldehyde, 4c. Brown coloured solid. (0.96 g, 80%); m.p. 195-96^{o}C; IR (KBr, cm^{-1}): 1682(CHO), 1622 (C=N), 598 (C=C); ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.48 (s, 1H, CHO), 8.55 (s, ^{1}H, pyrazole-H), 7.34-7.98 (m, 9H, Ar-H), 2.45 (s, 3H, CH_3); MS: *m*/*z* 302 (M^+).

3-(1-Benzofuran-2-yl)-1-(4-methoxyphenyl)-1*H*-pyrazole-4-carbaldehyde, 4d. Cream coloured solid. (1.01 g, 80%); m.p. 175-78^{o}C; IR (KBr, cm^{-1}): 1685 (CHO), 1624 (C=N), 1602 (C=C); ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.52 (s, 1H, CHO), 8.50 (s, 1H, pyrazole-H), 7.32-7.96 (m, 9H, Ar- H),3.75 (s, 3H, OCH_3); MS: *m*/*z* 318 (M^+).

3-(1-Benzofuran-2-yl)-1-(4-chlorophenyl)-1*H*-pyrazole-4-carbaldehyde, 4e. Yellow coloured solid. (0.90 g, 70%); m.p. 170-72^{o}C; IR (KBr, cm^{-1}): 1672 (CHO), 1614 (C=N), 1592 (C=C); ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.40 (s, 1H, CHO), 8.38 (s, 1H, pyrazole-H), 7.30-7.86 (m, 9H, Ar-H); MS: *m*/*z* 322 (M^+).

3-(1-Bezofuran-2-yl)-1-(4-fluorophenyl)-1*H*-pyrazole-4-carbaldehyde, 4f. Yellow coloured solid. (0.85 g, 70%); m.p. 155-58^{o}C; IR (KBr, cm^{-1}): 1670 (CHO), 1612(C=N), 1590 (C=C); ^{1}H NMR

(400 MHz, $CDCl_3$): δ 10.30 (s, 1H, CHO), 8.35 (s, ^{1}H, pyrazole-H), 7.28-7.85 (m, 9H, Ar-H and 1H, -NH); MS: *m*/*z* 306 (M^+).

3-(1-Benzofuran-2-yl)-1-(4-bromophenyl)-1*H*-pyrazole-4-carbaldehyde, 4g. Yellow coloured solid. (1.10 g, 75%); m.p. 201-03°C; IR (KBr, cm^{-1}): 1668 (CHO), 1615 (C=N), 1593 (C=C); ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.45 (s, 1H, CHO), 8.30 (s, 1H, pyrazole-H), 7.25-7.80 (m, 9H, Ar-H); MS: *m*/*z* 367 (M^+).

References

1 Katritzky A R, Fali C N & Li J, *J Org Chem*, 62, **1997**, 8205.
2 Masubuchi M, Kawasaki K, Ebiike H I, Keda Y, Tsujii S, Fujii T, Sakata K, Shiratori Y, Aoki Y, Ohtsuka T & Shimma N, *Bioorg Med Chem Lett*, 11, **2001**, 1833.
3 Whomsley R, Fernandez E, Nicholk P J, Smith H J, Lombardi P & Pestellini V J, *Steroid Biochem*, 44, **1993**, 675.
4 Yoo S E, Lee S H & Kim S K, *Bioorg Med Chem*, 5, **1997**, 445.
5 Hegedur L S & Angew *Chem, Int Ed Engl*, 27, **1989**, 1113.
6 Sexton J E, *Nat Prod Rep*, 13, **1996**, 327.
7 Thara M & Fukumoto K, *Nat Prod Rep*, 14, **1997**, 413.
8 Aruna Kumar D B, Prakash G K, Nandeshwarappa B P, Kiran B M, Sherigara B S & Mahadevan K M, *Indian J Pharm Sci*, 68, **2006**, 809.
9 Nagaraja G K, Prakash G K, Kumaraswamy M N, Vaidya V P & Mahadevan K M, *Arkivoc*, XV, **2006**, 160.
10 Nagaraja G K, Prakash G K, Satyanarayana N D, Vaidya V P,& Mahadevan K M, *Arkivoc***,** XV, **2006**, 142.
11 Nagaraja G K, Kumaraswamy M N & Mahadevan K M, *Indian J Heterocyclic Chem*, 16, **2006**, 89.
12 Nagaraja G K, Kumaraswamy M N, Vaidya V P & Mahadevan K M, *Arkivoc*, X, **2006**, 211.
13 Aruna Kumar D B, Prakash G K, Kumaraswamy M N, Nandeshwarappa B P, Sherigara B S, & Mahadevan K M, *Indian J Chem*, 45B, **2006**, 1699.
14 Vaidya V P, Vagdevi H M, Mahadevan K M & Shreedhara C S, *Indian J Chem*, 43B, **2004**, 1537.
15 Mahadevan K M & Vaidya V P, *Indian J Pharm Sci*, 65, **2003**, 128.
16 Basavaraj K M, Agasimundin Y S, Mahadevan K M & Vaidya V P, *Indian J Heterocycl Chem*, 13, **2003**, 155.
17 Mahadevan K M, Vagdevi H M & Vaidya V P, *Indian J Chem*, 42B, **2003**, 1931.
18 Mahadevan K M, Basavaraj Padmashali & Vaidya V P, *Indian J Heterocycl Chem*, 11, **2001**, 15.
19 Elliot E D, *J Am Chem Soc*, 73, **1951**, 754.