Studies on Chromone Derivatives. A Direct and Efficient One-pot Synthesis of 4-Chromone-linked 3-(*N*-Acylamino)azetidin-2-ones from Imines and *N*-Acylalanine

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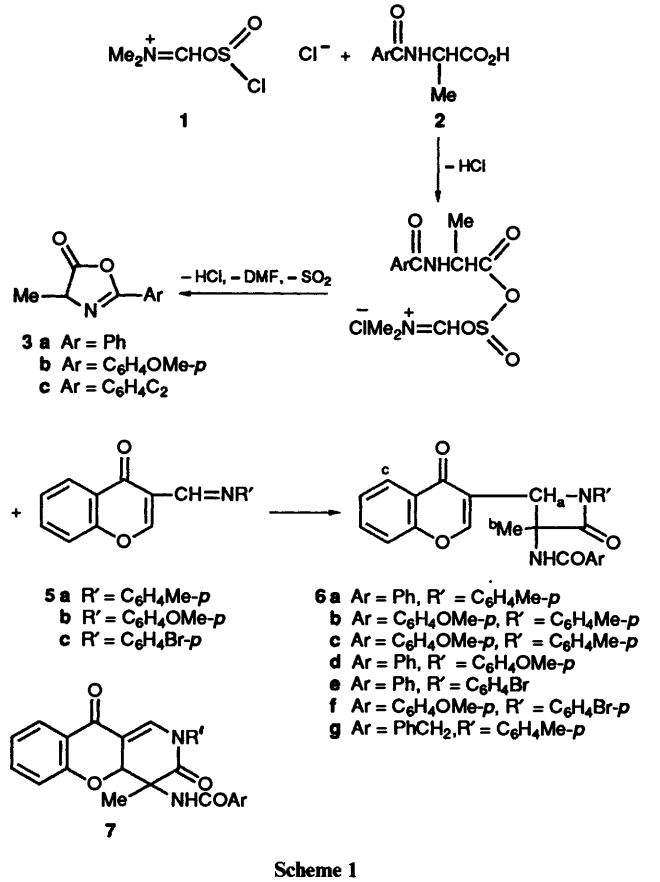
Chlorosulfonylmethylene(dimethyl)ammonium chloride **1** is found to be an efficient cyclodehydrating agent for the one-pot synthesis of various novel chromone-linked azetidin-2-ones **6** *via* cycloaddition reactions of 3-(aryliminomethyl)chromones **5** with *in situ* generated oxazolones **3**, directly from the corresponding *N*-benzoylamino acids and there is no evidence for the formation of pyridones **7**. The azetidinones **6a–g** were obtained in 85–90% yields and their structures are fully corroborated by spectral and elemental analyses.

The biological activity of many of the naturally occurring compounds which incorporate a 1-benzopyran-4(4*H*)-one (chromone) ring system[1] has resulted in several applications of which khellin and disodium cromoglycate are well known anti-asthmatic agents.[2] Chromones bearing electron-withdrawing substituents at C-3 are capable of acting as Michael acceptors[3] or heterodienes[4] and undergoing various rearrangements on treatment with nucleophiles.[5] However their use as 2π components in [4 + 2] cycloadditions has received surprisingly little attention† despite their obvious potential for such a role. The imines **5** are very attractive synthons for the preparation of chromone-bearing heterocyclic systems which in turn can be readily obtained from 3-formyl-1-benzopyran-4(4*H*)-one (3-formylchromone) by reaction with primary amines. However controversial claims are reported for the synthesis of 3-formylchromone imine.[7] As part of our continued interest in the site selectivity of cycloaddition reactions,[8] we report herein a direct and efficient one-pot procedure for the preparation of various novel chromone-linked β-lactams using 2-oxazolin-5-ones and the relatively less explored chlorosulfonylmethylene(dimethyl)ammonium chloride **1**.‡ We selected 3-(aryliminomethyl)chromones, a bifunctional substrate, where 2-oxazolin-5-ones could react either at the chromone double bond or at the azomethine function. These 2-oxazolin-5-ones are typical mesoionic compounds and undergo cycloaddition reactions with a variety of multiple bonds to provide novel heterocycles.[10] Several other methods such as, dehydrohalogenation of an appropriately substituted acid halides and zinc dehalogenation of an α-halogenoacid halides[11] have also been used for the synthesis of various azetidinones. Our method appears to be convenient and facile as it does not require a large excess of cyclodehydrating agent, it involves a simple work-up procedure, the products yields are excellent and the reaction conditions are mild. This reagent **1** has earlier been used for the activation of carboxylic acid groups[12] in the facile preparation of acid chlorides,[13] alkyl chlorides[14] and gem-dichlorides.[15]

The imines **5** were readily obtained by allowing 3-formylchromone to react with aromatic amines in refluxing benzene with azeotropic removal of water (Dean–Stark apparatus) and using a catalytic amount of toluene-*p*-sulfonic acid.[8a] These imines **5** were prepared in good yields without the formation of any side products arising from Michael type additions onto the carbon–carbon double bond of the chromone moiety[16] or rupture of the chromone moiety itself. Generation of oxazolone§ **3** and its cycloaddition reactions were carried out by the addition of a dichloromethane solution of cyclodehydrating agent **1** to a dichloromethane solution of *N*-benzoylalanine followed by 3-(tolyliminomethyl)chromone **5a** and dry triethylamine (see Experimental section) (Scheme 1). The structural



Scheme 1

† 3-Substituted chromones appear to function as dienophiles in some dimerisation reactions.[6]

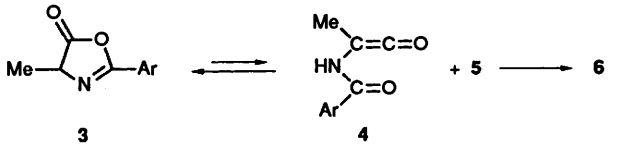
‡ For the preparation and application of reagent **1** see ref. 9.

§ For the physical and spectroscopic data for compound **3** see ref. 17.

assignment for azetidin-2-one **6a** thus obtained is fully established on the basis of elemental analysis and spectral results. The diagnostic signal for the azomethine proton which showed at δ 8.30 was absent in the cycloadduct, whilst the upfield shift of this proton from δ 8.30 to 5.39 showed that cycloaddition had occurred at the azomethine function which clearly ruled out the possibility of any formation of the pyridone **7**. The IR spectrum (KBr) showed a strong band at ν/cm^{-1} 1745 indicating the presence of a β-lactam ring, other bands at ν/cm^{-1} 1650 and 3250 correspond to a chromone carbonyl and NH groups respectively.[18] It is quite interesting to observe the site selectivity followed by the dipole,[19] cycloaddition occurring only across the azomethine function leaving the chromone double bond intact. This site selectivity seems to be a remarkable contrast in view of the reactivity of chromone double bond towards a variety of nucleophiles and the typical 1,3-dipole diazomethane reaction at this site which is well documented.[20] In our opinion this site selectivity is the result of non-involvement of the ketene tautomer of oxazolone **3**. It is well precedented in literature that tautomeric ketenes can exist in equilibrium with oxazolones at high temperature and in the present case the reactions are carried out only at ambient temperatures. The reaction was generalised by varying the substituents on the imine and oxazolone partners and the characteristics of cycloadducts thus obtained are recorded in the Experimental section.

When the same reaction was performed using acetic anhydride as the cyclodehydrating agent for the generation of mesoionic oxazolones **3** and its subsequent cycloaddition reaction with chromone imines **5** the corresponding β-lactams **6** were obtained in poor yields. The reaction between the imine **5a** and 4-methyl-2-phenyl-2-oxazolin-5-one **3a** was carried out by dissolving equimolar amounts in dry benzene and stirring the reaction mixture under nitrogen for 24 h, removal of solvent gave **6a** in 25% yield. The structural assignment of this product was confirmed by comparing it with synthetic azetidin-2-one **6a**. Similarly β-lactams **6b–g** were obtained in only 15–25% yields.

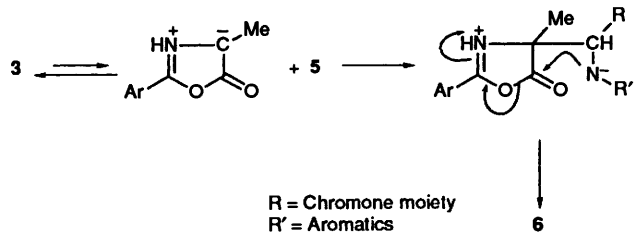
The mechanistic pathway for the formation of β-lactams **6** from 2-oxazolin-5-ones **3** can be explained in three ways. Firstly, the 2-oxazolin-5-ones are known to undergo[21] [4 + 2] cycloadditions involving the valence tautomeric ketene intermediate and azetidinones may be formed analogously by a ketene imine reaction (Scheme 2). Secondly, the reaction may be initiated by



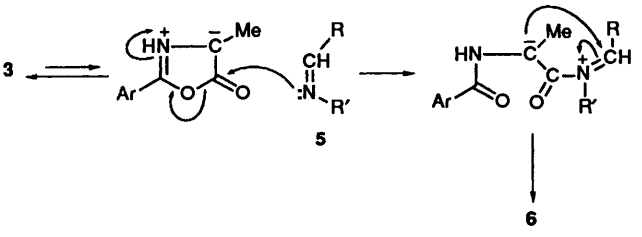
Scheme 2

the attack of the N atom of the imine at the carbonyl group of 2-oxazolin-5-one and subsequent cyclisation may yield the corresponding β-lactam. This is analogous to the mechanism proposed by Knowles *et al.*[22] for the reaction between oxazolium perchlorate and Schiffs bases. Thirdly the reaction may be initiated by the attack of the oxazolone in its carbanion form at the azomethine double bond of the imine and subsequent cyclisation may yield β-lactam **6**. As these reactions proceed at room temperature where there is no probability of the formation of the corresponding thermal equilibrating ketene tautomer **4** from the 2-oxazoline-5-one, either of the mechanisms shown in Schemes 3 and 4 is plausible.

In conclusion, the present report outlines an efficient method for the preparation of various chromone-linked β-lactams, with simple work-up, mild reaction conditions and the production of virtually pure products in excellent yield.



Scheme 3



Scheme 4

Experimental

M.p.s were determined using a Büchi melting point apparatus and are uncorrected. The IR spectra were recorded in KBr discs on a Perkin-Elmer 237B IR spectrophotometer. Microanalyses were performed on a Perkin-Elmer 240C analyser. The 90 MHz ^{1}H NMR spectra were recorded at IISC Bangalore. The 60 MHz ^{1}H NMR spectra were recorded on a Varian T-60 machine using tetramethyl silane (TMS) as the internal standard. The chemical shifts are recorded as δ values, J values are given in Hz. Mass spectra were recorded on AEIMS 30 instrument by the electron impact method. Solvents were dried according to standard procedures. Light petroleum is the fraction with b.p. 60–80 °C.

Preparation of Chlorosulfonylmethylene(dimethyl)ammonium Chloride **1**.—In a 25 cm^3 pressure equalising funnel, dry benzene (10 cm^3) dimethylformamide (DMF) (2 cm^3, 20.4 mmol) and thionyl chloride (1.6 cm^3, 22 mmol) were added consecutively. After 5 min the two phases were separated and the reagent (lower layer) was used directly for the cyclodehydration reactions.

3-(*Aryliminomethyl*)*chromones* **5**.—Toluene-*p*-sulfonic acid (10 mg) was added to a solution of 3-formyl-1-benzopyran-4(4*H*)-one (1.74 g, 10 mmol) and *p*-toluidine (1.08 g, 10 mmol) in dry benzene (80 cm^3) and the resulting mixture was heated under reflux using a Dean–Stark water trap for 30 min. The mixture was then evaporated under reduced pressure and the product **5a** m.p. 128–129 °C thus obtained was recrystallised from benzene–light petroleum (1 : 1) (72%); δ_H(60 MHz; $CDCl_3$) 8.70 (1 H, s), 8.33 (1 H, s), 6.79–7.81 (8 H, m, ArH) and 2.02 (3 H, s, CH_3); *m/z* 263 (M^+) (Found: C, 77.65; H, 5.1; N, 5.2. $C_{17}H_{13}NO_2$ requires C, 77.52; H, 4.94; N, 5.32%).

3-(p-*Methoxyphenyliminomethyl*)-1-*benzopyran*-4(4H)-*one* **5b**.—M.p. 153–155 °C (70%); δ_H(60 MHz; $CDCl_3$) 8.68 (1 H, s), 8.30 (1 H, s), 6.78–7.80 (8 H, m, ArH) and 3.82 (3 H, s, OCH_3); *m/z* 279 (M^+) (Found: C, 72.85; H, 4.85; N, 6.9. $C_{17}H_{13}NO_3$ requires C, 73.14; H, 4.65; N, 5.01%).

3-(p-*Bromophenyliminomethyl*)*chromone* **5c**. M.p. 134–135 °C (65%); δ_H(60 MHz; $CDCl_3$) 8.72 (1 H, s), 8.35 (1 H, s) and 6.77–7.80 (8 H, m, ArH); *m/z* 328 (M^+) (Found: C, 58.7; H, 3.2; N, 4.15. $C_{16}H_{10}BrNO_2$ requires C, 58.57; H, 3.04; N, 4.27%).

Preparation of 3-(N-*Acylamino*)*azetidin*-2-*ones* **6a–g**.—*Method A*. To a solution of DL-benzoylalanine (0.97 g, 5 mmol) in absolute dichloromethane (20 cm^3) was added, at 0–5 °C,

freshly prepared reagent **1** (1.44 g, 7.5 mmol) dropwise. After stirring at this temperature for 10 min, freshly prepared 3-(*p*-tolyliminomethyl)chromone **5a** (1.31 g, 5 mmol) was added followed by dry triethylamine (1.01 g, 10 mmol) in dichloromethane (10 cm^3), dropwise. The resulting mixture was then stirred at room temp. for 4 h (monitored by TLC). On completion of the reaction the mixture was quenched with cold water and extracted with dichloromethane (2 × 40 cm^3). The dichloromethane extract was washed with cold water (50 cm^3), dried (Na_2SO_4) and evaporated under reduced pressure to furnish a residue which was purified by TLC using silica gel as adsorbent and chloroform–methanol (9:1) as eluent. The product azetidin-2-one **6a** thus obtained as a white crystalline solid m.p. 191–192 °C in 90% yield. Similarly compounds **6b–g** were prepared in 85–90% yields by purifying the residue after removal of the solvent. The characteristics are shown below under Method B.

Preparation of 2-*Aryl*-4-*methyl*-2-*oxazolin*-5-*ones* **3**.—A suspension of DL-benzoyl alanine (1.93 g, 10 mmol) in acetic anhydride (10 cm^3) was warmed to 50 °C. A clear solution was obtained after about 15 min. Acetic acid and excess of acetic anhydride were rapidly removed under reduced pressure at 50 °C and the residue thus obtained was dissolved in dry benzene (5 cm^3) and used directly in the cycloaddition reactions.

Azetidin-2-*ones* **6a–g**.—*Method B.* To a stirred solution of 3-(*p*-tolyliminomethyl)-1-benzopyran-4(4*H*)-one **5a** (2.63 g, 10 mmol) in dry benzene (10 cm^3) at room temp. was added dropwise a solution of 4-methyl-2-phenyl-2-oxazolin-5-one **3a** (10 mmol) in dry benzene (5 cm^3). The mixture was stirred at room temp. for 2 h and then allowed to stand overnight. Removal of benzene under reduced pressure afforded a residue which on repeated crystallisation from benzene–light petroleum yielded a white crystalline solid m.p. 191–192 °C, (25%). This product was then further purified by column chromatography using benzene–chloroform (10:1) as eluent. Similarly azetidinones **6b–g** were prepared and their characteristics are recorded below.

3-(N-*Benzoylamino*)-3-*methyl*-4-(4-*oxobenzopyran*-3-*yl*)-N-p-*tolylazetidin*-2-*one* **6a**. δ_H(90 MHz; $CDCl_3$) 1.94 (3 H, s, CH_3), 2.38 (3 H, s, CH_3), 5.39 (1 Ha, s), 6.93 (1 H, s, NH), 7.09–7.75 (12 H, m, ArH, 1 Hb) and 8.02 (1 Hc, dd); ν_{max}(KBr)/cm^{-1} 1650, 1745 and 3300; *m*/*z* 438 (M^+) (Found: C, 74.0; H, 5.15. $C_{27}H_{22}N_2O_4$ requires C, 73.96; H, 5.05%).

3-(N-p-*Anisoylamino*)-3-*methyl*-4-(4-*oxobenzopyran*-3-*yl*)-N-p-*tolylazetidin*-2-*one* **6b**. M.p. 197–199 °C (85%); δ_H(90 MHz; $CDCl_3$) 1.92 (3 H, s, CH_3), 2.37 (3 H, s, CH_3), 3.82 (3 H, s, OCH_3), 5.37 (1 Ha, s), 6.83–7.75 (11 H, m, ArH, 1 Hb, 1 H, NH) and 8.02 (1 Hc, dd); ν_{max}(KBr)/cm^{-1} 1655, 1750 and 3250; *m*/*z* 468 (M^+) (Found: C, 71.65; H, 5.05. $C_{28}H_{24}N_2O_5$ required C, 71.79; H, 5.16%).

3-(N-p-*Anisoylamino*)-N-p-*methoxyphenyl*-3-*methyl*-4-(4-*oxobenzopyran*-3-*yl*)*azetidin*-2-*one* **6c**. M.p. 203–205 °C (90%); δ_H(90 MHz; $CDCl_3$) 1.94 (3 H, s, CH_3), 3.80 (6 H, s, OCH_3), 5.41 (1 Ha, s), 6.80–7.82 (11 H, m, ArH, 1 Hb, 1 H, NH) and 8.04 (1 Hc, dd); ν_{max}(KBr)/cm^{-1} 1650, 1745 and 3350; *m*/*z* 484 (M^+) (Found: C, 69.35; H, 4.8. $C_{28}H_{24}N_2O_6$ requires C, 69.42; H, 4.99%).

3-(N-*Benzoylamino*)-N-p-*methoxyphenyl*-3-*methyl*-4-(4-*oxobenzopyrano*-3-*yl*)*azetidin*-2-*one* **6d**. M.p. 194–195 °C (87%); δ_H(90 MHz; $CDCl_3$) 1.96 (3 H, s, CH_3), 3.81 (3 H, s, OCH_3), 5.38 (1 Ha, s), 6.85–7.76 (12 H, m, ArH, 1 Hb, 1 H, NH) and 8.02 (1 Hc, dd); ν_{max}(KBr)/cm^{-1} 1660, 1735 and 3300; *m*/*z* 454 (M^+) (Found: C, 71.25; H, 4.95. $C_{27}H_{22}N_2O_5$ requires C, 71.36; H, 4.87%).

3-(N-Benzoylamino)-N-p-*bromophenyl*-3-*methyl*-4-(4-*oxobenzopyrano*-3-*yl*)*azetidin*-2-*one* **6e**. M.p. 214–216 °C (85%). δ_H(90 MHz; $CDCl_3$) 1.98 (3 H, s, CH_3), 5.40 (1 Ha, s), 6.83–7.80 (12 H, m, ArH, 1 Hb, 1 H, NH) and 8.03 (1 Hc, dd); ν_{max}(KBr)/cm^{-1} 1650, 1745 and 3350; *m*/*z* 503 (M^+) (Found: C, 62.15; H, 3.9. $C_{26}H_{19}BrN_2O_4$ requires C, 62.04; H, 3.8%).

3-(N-p-*Anisoylamino*)-N-p-*bromophenyl*-3-*methyl*-4-(4-*oxobenzopyran*-3-*yl*)*azetidin*-2-*one* **6f**. M.p. 201–202 °C (86%); δ_H(90 MHz; $CDCl_3$) 1.92 (3 H, s, CH_3), 5.38 (1 Ha, s), 6.82–7.84 (11 H, m, ArH, 1 Hb, 1 H, NH) and 8.04 (1 Hc, dd); ν_{max}(KBr)/cm^{-1} 1650, 1750 and 3250; *m*/*z* 533 (M^+) (Found: C, 60.85; H, 3.9. $C_{22}H_{21}BrN_2O_5$ requires C, 60.80; H, 3.96%).

3-(N-*Phenylacetylamino*)-4-(4-*oxobenzopyran*-3-*yl*)-3-*methyl*-N-p-*tolylazetidin*-2-*one* **6g**. M.p. 183–184 °C (85%) δ_H(90 MHz; $CDCl_3$) 1.92 (3 H, s, CH_3), 2.36 (3 H, s, CH_3), 5.36 (1 Ha, s), 4.02 (2 H, s, CH_2), 6.82–7.76 (12 H, m, ArH, 1 Hb, 1 H, NH) and 8.06 (1 Hc, dd); ν_{max}(KBr)/cm^{-1} 1650, 1745 and 3300; *m*/*z* 452 (M^+) (Found: C, 74.4; H, 5.35. $C_{28}H_{24}N_2O_4$ requires C, 74.32; H, 5.34%).

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References

1 F. M. Dean, *Naturally Occurring Oxygen Ring Compounds*, Butterworths, London, 1963; G. P. Ellis and I. M. Lockhart, *Chromans and Tocopherols*, Wiley, New York, 1981.
2 S. G. Cox, *Nature* (*London*), 1967, **216**, 1328; A. K. Baruah, D. Prajapati and J. S. Sandhu, *J. Chem. Soc., Perkin Trans. 1*, 1987, 1995.
3 T. W. Wallace, *Tetrahedron Lett.*, 1984, **25**, 4299; P. D. Clarke, A. O. Fitton, H. Suschitzky, T. W. Wallace, H. A. Dowlatshahi and J. L. Suschitzky, *Tetrahedron Lett.*, 1986, **27**, 91; S. T. Saengechanthra and T. W. Wallace, *J. Chem. Soc., Chem. Commun.*, 1986, 1592.
4 S. T. Saengechanthra and T. W. Wallace, *J. Chem. Soc., Perkin Trans. 1*, 1986, 789 and refs. cited therein.
5 G. P. Ellis, *Chromones, Chromanones and Chromenes*, Wiley, New York, 1977, ch. 7; C. K. Ghosh, *J. Heterocycl. Chem.*, 1983, **20**, 1437; B. Chantegrel, A. I. Nadi and S. Gelin, *J. Org. Chem.*, 1984, **49**, 4419.
6 C. K. Ghosh, A. Bhattacharyya and C. Bandyopadhyay, *J. Chem. Soc., Chem. Commun.*, 1984, 1319.
7 A. Nohara, T. Umetani and Y. Sanno, *Tetrahedron*, 1975, **30**, 3553; Z. Jarzmanowska, W. Basinski and L. Zielinkska, *Pol. J. Chem.*, 1980, 383.
8 (*a*) A. K. Baruah, D. Prajapati and J. S. Sandhu, *Tetrahedron*, 1988, **44**, 1241, 6187; (*b*) B. Sain, S. P. Singh and J. S. Sandhu, *Tetrahedron Lett.*, 1991, **32**, 5151.
9 S. P. Singh, A. R. Mahajan, D. Prajapati and J. S. Sandhu, *Synthesis*, 1991, 1026.
10 E. Funke and R. Huisgen, *Chem. Ber.*, 1971, **104**, 3222; H. Gotthardt, R. Huisgen and H. O. Bayer, *J. Am. Chem. Soc.*, 1970, **92**, 4340; H. O. Bayer, H. Gotthardt and R. Huisgen, *Chem. Ber.*, 1970, **103**, 2356, 2368.
11 R. D. Ward in *The Chemistry of Ketenes, Allenes and Related Compounds*, ed., S. Patai, Interscience Publications, New York, 1980, pp. 223–277; Y. Ohshiro, M. Komatsu, M. Uesaka and T. Agawa, *Heterocycles*, 1984, **22**, 549 and refs. cited therein.
12 M. Ballester, J. Riers, J. Castaner, C. Rovira, J. Veciana and C. Onrubia, *J. Org. Chem.*, 1983, **48**, 3716; A. L. Palomo and E. Torrens, *Afinidad*, 1971, **28**, 975; *Chem. Abstr.*, 1972, **76**, 99538; A. L. Palomo, *An. Real Soc. Esp. Fis. Quim.*, 1969, **65**, 1167; *Chem. Abstr.*, 1970, **72**, 110736.
13 H. H. Bosshard, R. Mory, M. Schmid and Hch. Zollinger, *Helv. Chim. Acta*, 1959, **42**, 1653; *Chem. Abstr.*, 1960, **54**, 3296c.
14 A. L. Palomo and G. Ferrar, *An. Real Soc. Esp. Fis. Quim.*, 1969, **65**, 163; *Chem. Abstr.*, 1969, **71**, 2894.
15 M. S. Newman and P. K. Sujeeyth, *J. Org. Chem.*, 1978, **43**, 4367.
16 A. O. Fitton, J. R. Frost and H. Suschitzky, *Tetrahedron Lett.*, 1975, 2099.

17 B. Sain, J. N. Baruah and J. S. Sandhu, *J. Heterocycl. Chem.*, 1982, **19**, 1511.
18 B. Sain and J. S. Sandhu, *Heterocycles*, 1985, **23**, 1611.
19 Y. Ohshiro, M. Komatsu, M. Uesaka and T. Agawa, *Heterocycles*, 1984, **22**, 549.
20 C. K. Ghosh, C. Bandopadhyay and J. Maiti, *Heterocycles*, 1987, **26**, 1632.
21 J. M. Riordan and C. H. Stammer, *Tetrahedron Lett.*, 1976, 1247; B. Sain, J. N. Baruah and J. S. Sandhu, *J. Chem. Soc., Perkin Trans. 1*, 1985, 773; R. Huisgen, *Aromaticity*, Chem. Soc., Special publication No. 21, 1967, p. 51.
22 A. N. Knowles, A. Lawson, G. V. Boyd and R. A. Newberry, *Tetrahedron Lett.*, 1971, 485.

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