Synthesis of some new 2,4,6-trisubstituted phenyl pyrimidines using 4-nitro and 4-fluorophenacyldimethylsulphonium bromides with aromatic aldehydes

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Abstract: 4-Nitrophenacyldimethylsulphonium bromide and 4-fluorophenacyldimethylsulphonium bromide have been prepared by the reaction of dimethyl sulfoxide with 4-substitutedphenacyl bromide in benzene at reflux temperature under nitrogen atmosphere. These sulphonium salts on treatment with NaOH gave 4-nitrophenacylidenedimethylsulphurane and 4-fluorophenacylidenedimethylsulphurane. The reaction of these sulphonium salts and sulphuranes with various aromatic aldehydes is carried out in presence of ammonium acetate and acetic acid at reflux in an atmosphere of nitrogen to give 2,4,6-triarylpyrimidines in 35-80% yields. Ammonium acetate in acetic acid was used as aza cyclisation agent. The structures of new pyrimidines were confirmed on the basis of IR and NMR spectral data.

Keywords: Aldehyde, pyrimidine, yields, sulphonium salts.

Pyridinium, phosphonium, arsonium and isoquinolinium ylides have gained considerable importance in the synthesis of acyclic, cyclic and heterocyclic compounds. As reported earlier sulphonium salts and sulphuranes are also better potential reagents than corresponding salts and ylides of V-th group elements for the synthesis of cyclic and heterocyclic systems. Further extensions of reaction of sulphonium ylides leading to the pyrimidine nucleus seems to be pertinent with a view to test the domain of applicability of sulphonium ylides. In the present investigation 4-nitrophenacyldimethylsulphonium bromide and 4-fluorophenacyldimethylsulphonium bromide as well as their corresponding sulphuranes have been coupled with a wide range of aromatic aldehydes in the presence of ammonium acetate and acetic acid at reflux temperature leading to ring closure to form pyrimidine nucleus.

Results and discussion

Reaction of dimethylsulfoxide with 4-nitrophenacyl bromide and 4-fluorophenacyl bromide in benzene at reflux temperature gave 4-nitrophenacyl bromide (1a) 4-fluorophenacyldimethylsulphonium bromide (1b) in fair to good yields. The structure of sulphonium salts (1a-b) were confirmed by comparision of melting points of salts with those reported in the literature and by spectral data. The IR spectra of salts (1a-b) showed a characteristic absorption band due to C-O stretching vibrations in the region 1670-1690 cm⁻¹ for carbonyl group. The diagnostic absorption bands in the region 3300-3000 cm⁻¹ were observed due to C-H stretching vibrations of methylene group attached to sulfur atom.

The treatment of these salts (1a-b) with aqueous sodium hydroxide/potassium carbonate gave 4-nitrophenacylidimethylsulphurane (2a) and 4-fluorophenacyldimethylsulphurane (2b) which are highly unstable. The reaction was, therefore, carried out by generating the ylide...
intermediates (2a-b) in situ from the corresponding salts (1a-b). Heating the mixture of sulfonium salts (1a-b) with substituted benzaldehyde (3a-l) in presence of ammonium acetate and glacial acetic acid at reflux temperature gave 2,4,6-triarylpyrimidines (5a-l, 6a-l) in 35–80% yields (Scheme 1).

Further attempts were made to synthesize symmetrical pyrimidines having identical substituents at 2,4,6-positions. For this purpose 4-nitrophenoacyldimethylsulfonyl bromide (1a) with 4-nitrobenzaldehyde and 4-fluorophenoacyldimethylsulfonyl bromide (1b) with 4-fluorobenzaldehyde were heated in a mixture of ammonium

Table 1. Physical properties of 2,4,6-triarylpyrimidines (5a-l, 6a-l)

| Compd. | X     | Y     | Yield (%) | M.p. (°C) | Recrystn. | Analysis (%): Found (Calcd.) | C   | H   | N   |
|--------|-------|-------|-----------|-----------|-----------|----------------------------|------|------|------|
| 5a     | 4-NO₂ | H     | 45        | 110-112   | A         | 74.02 (74.05) 4.35 (4.37) 12.20 (12.24) |
| b      | 4-NO₂ | 4-CH₃ | 40        | 96-98     | B         | 75.61 (75.59) 4.93 (4.98) 11.04 (11.02) |
| c      | 4-NO₂ | 4-N(CH₃)₂ | 45   | 120-122   | A         | 71.03 (71.07) 5.67 (4.98) 15.99 (15.95) |
| d      | 4-NO₂ | 4-OCH₃ | 60        | 128-130   | C         | 69.70 (69.73) 4.62 (4.60) 10.14 (10.07) |
| e      | 4-NO₂ | 4-Cl   | 65        | 78-80     | A         | 62.54 (62.56) 3.04 (3.08) 10.07 (10.05) |
| f      | 4-NO₂ | 4-Br   | 55        | 86-98     | B         | 55.76 (55.81) 2.71 (2.75) 8.82 (8.88) |
| g      | 4-NO₂ | 4-F    | 65        | 110-112   | C         | 67.80 (67.87) 3.36 (3.34) 9.27 (9.26) |
| h      | 4-NO₂ | 3,4-di(OCH₃) | 48   | 122-124   | A         | 70.40 (70.59) 5.68 (5.64) 9.42 (9.48) |
| i      | 4-NO₂ | 4-NO₂  | 80        | 132-134   | C         | 59.55 (59.59) 2.90 (2.93) 15.82 (15.80) |
| 6a     | 4-F   | H     | 48        | 98-100    | D         | 80.92 (80.98) 4.62 (4.60) 11.62 (11.64) |
| b      | 4-F   | 4-CH₃ | 45        | 112-114   | B         | 81.34 (75.59) 5.37 (4.98) 7.92 (11.02) |
| c      | 4-F   | 4-N(CH₃)₂ | 41   | 124-126   | C         | 75.70 (75.59) 6.06 (6.07) 13.52 (13.59) |
| d      | 4-F   | 4-OCH₃ | 42        | 130-320   | A         | 78.42 (78.47) 5.15 (5.17) 7.64 (7.62) |
| e      | 4-F   | 4-Cl   | 50        | 76-78     | C         | 66.80 (66.84) 3.26 (3.29) 7.05 (5.79) |
| f      | 4-F   | 4-Br   | 55        | 88-90     | A         | 57.80 (57.85) 2.67 (2.69) 5.75 (5.79) |
| g      | 4-F   | 4-F    | 60        | 108-110   | B         | 72.90 (72.93) 3.52 (3.59) 7.70 (7.73) |
| h      | 4-F   | 3,4-di(OCH₃) | 50   | 124-126   | A         | 69.94 (69.99) 5.13 (5.15) 6.24 (6.28) |
| i      | 4-F   | 4-NO₂  | 45        | 128-130   | C         | 63.42 (63.46) 3.10 (3.12) 13.42 (13.46) |

A=CH₃OH : CHCl₃, B=C₆H₅ : CHCl₃, C=C₅H₅N : CH₃OH
acetate and glacial acetic acid to give corresponding symmetrical pyrimidines viz. 2,4,6-tri-(4-nitrophenyl) pyrimidine (5i) and 2,4,6-tri-(4-fluorophenyl) pyrimidine (6g) respectively in 60% and 65% yields (Scheme 2).

The reaction takes place through Mannich type reaction. The methylene group of salt (1a-b) with aromatic aldehydes (3a-l) in presence of ammonium acetate forms Mannich base sulfonium to form sulfonium salt (4a) which, in turn, undergoes condensation with another molecule of benzaldehyde in presence of ammonia to form sulfonium salt intermediate (4b). The later, undergoes elimination of dimethylsulfonium hydrobromide to form 2,4,6-triarylpyrimidines (5a-l, 6a-l).

A number of 2,4,6-triarylpyrimidine (5a-l) and (6a-l) synthesized by the above route are listed in Table 1. All the pyrimidines gave satisfactory elemental and spectral analysis. The IR spectral data showed (Table 2) characteristic absorption bands in the region 3100-3000 cm⁻¹ which were assigned due to C-H stretching mode of pyrimidine ring. The bands in the region 1600-1500 cm⁻¹ were due to interaction between C=C and C=N vibrations of the ring. The NMR spectra (Table 3) of pyrimidines showed pyrimidyl protons at δ 6.60-6.80 and aromatic protons at δ 6.60-8.40.

Experimental

All the reagents were obtained from commercial source (E. Merck, B.D.H., Sisco etc.). Starting materials 4-nitrophenacyl bromide and 4-fluorophenacyl bromide were prepared according to the procedure reported in literature.

Note

| Compd. | IR data (KBr) (cm⁻¹) 2,4,6-triarylpurimidines (5a-l, 6a-l) |
|--------|----------------------------------------------------------|
|        | v C-H v C=C v C-N v C-H v C-nNO₂                        |
| 5a     | 3110 1605 1510 995 1555, 1325                            |
| b      | 3085 1615 1525 990 1575, 1330                            |
| c      | 3105 1605 1510 995 1580, 1335                            |
| d      | 3115 1610 1520 992 1585, 1335                            |
| e      | 3060 1608 1505 990 1580, 1340                            |
| f      | 3110 1595 1500 1000 1575, 1320                            |
| g      | 3080 1598 1505 1005 1570, 1325                            |
| h      | 3108 1605 1510 1000 1580, 1330                            |
| i      | 3070 1610 1510 1005 1575, 1320                            |
| 6a     | 3090 1600 1505 998                                      |
| b      | 3105 1605 1510 1005                                      |
| c      | 3100 1615 1500 992                                      |
| d      | 3065 1598 1500 1000                                      |
| e      | 3080 1605 1510 1010                                      |
| f      | 3100 1615 1505 992                                      |
| g      | 3105 1614 1505 995                                      |
| h      | 3080 1600 1500 998                                      |
| i      | 3095 1608 1505 990                                      |

υ = Stretching vibrations; ϕ = out-of-plane deformation of hydrogen attached to aromatic nucleus (5a-l, 6a-l).

Preparation of 4-substituted phenacyldimethyl sulfonium bromide (1a-b):

A solution of 100 mmol of 4-nitrophenacyl bromide and 100 mmol of dimethyl sulfide in 100 ml of anhydrous acetone was stirred for 6-8 h at room temperature in an atmosphere of nitrogen gave solid mass which was filtered, washed twice with acetone and crystallized from benzene pet. as detailed below.

| 4-Nitrophenacyldimethyl sulfonium bromide (1a), yellow coloured microcrystals m.p. 150–152 °C (lit.² m.p. 152–154 °C); IR data (KBr) 1680 (C=O), 1570, 1330 cm⁻¹ (C-NO₂); NMR (CDCl₃) δ 3.30 (6H, s, di-CH₃), 5.50 (2H, s, CH₂), 7.30–7.90 (4H, m, ArH). |
| 4-Fluorophenacyldimethyl sulfonium bromide (1b), white colourless microcrystals m.p. 140–142 °C (lit.³ m.p. 142–144 °C); IR data (KBr) 3100 (ArH), 1675 cm⁻¹ (C=O); NMR (CDCl₃) δ 3.26 (6H, s, di-CH₃), 8.45 (2H, s, CH₂), 7.25–7.85 (4H, m, ArH). |
Table 3. NMR (CDCl₃) data of 2,4,6-triarylpyrimidines (5a-l, 6a-l)

| Compd. | δ (ppm) | No. of protons | Assignment of protons |
|--------|---------|----------------|-----------------------|
|        |         |                |                       |
| 5a     | 6.65s   | 1H             | PyH (C₅-H)            |
|        | 6.85-6.88m | 14H            | Ar-H                  |
| b      | 6.25s   | 1H             | PyH (C₅-H)            |
|        | 2.35s   | 6H             | di-CH₃                |
|        | 6.95-8.20m | 12H            | Ar-H                  |
| c      | 6.65s   | 1H             | PyH (C₅-H)            |
|        | 3.95s   | 12H            | di-(OCH₃)             |
|        | 6.75-7.85m | 12H            | Ar-H                  |
| d      | 6.66s   | 1H             | PyH (C₅-H)            |
|        | 3.85s   | 6H             | di-(OCH₃)             |
|        | 6.95-8.35m | 12H            | Ar-H                  |
| e      | 6.78s   | 1H             | PyH (C₅-H)            |
|        | 7.0-8.25m | 12H            | Ar-H                  |
| f      | 5.80s   | 1H             | PyH (C₅-H)            |
|        | 6.95-8.20m | 12H            | Ar-H                  |
| g      | 6.75s   | 1H             | PyH (C₅-H)            |
|        | 7.10-8.35m | 12H            | Ar-H                  |
| h      | 6.65s   | 1H             | PyH (C₅-H)            |
|        | 3.95d   | 12H            | di-(3,4-di-OCH₃)       |
|        | 6.85-7.85m | 10H            | Ar-H                  |
| i      | 6.75s   | 1H             | PyH (C₅-H)            |
|        | 7.05-8.35m | 12H            | Ar-H                  |
| 6a     | 6.60s   | 1H             | PyH (C₅-H)            |
|        | 6.75-7.95m | 14H            | Ar-H                  |
| b      | 6.65s   | 1H             | PyH (C₅-H)            |
|        | 2.50s   | 6H             | di-CH₃                |
|        | 6.85-8.15m | 12H            | Ar-H                  |
| c      | 6.70s   | 1H             | PyH (C₅-H)            |
|        | 2.95s   | 12H            | di-(OCH₃)             |
|        | 6.85-7.15m | 12H            | Ar-H                  |
| d      | 6.60s   | 1H             | PyH (C₅-H)            |
|        | 3.95s   | 6H             | di-(OCH₃)             |
|        | 6.95-8.35m | 12H            | Ar-H                  |
| e      | 6.75s   | 1H             | PyH (C₅-H)            |
|        | 7.05-8.35m | 12H            | Ar-H                  |
| f      | 6.70s   | 1H             | PyH (C₅-H)            |
|        | 7.15-8.45m | 12H            | Ar-H                  |
| g      | 6.85s   | 1H             | PyH (C₅-H)            |
|        | 7.10-8.35m | 12H            | Ar-H                  |
| h      | 6.65s   | 1H             | PyH (C₅-H)            |
|        | 3.85d   | 12H            | di-(3,4-di-OCH₃)       |
|        | 6.95-8.28m | 10H            | Ar-H                  |
| i      | 6.70s   | 1H             | PyH (C₅-H)            |
|        | 7.10-8.35m | 12H            | Ar-H                  |

s = singlet; m = multiplet; d = doublet

**Preparation of 2,4,6-triarylpyrimidines (5a-l, 6a-l):**

**General procedure:**

A mixture of 3 mmol 4-substituted phenacyldimethylsulphonium bromide (1a-b) and 6 mmol of aromatic aldehyde (3) and 3 g of ammonium acetate in 50 ml of glacial acetic acid was stirred at room temperature. The mixture was then poured into ice cold water (50 ml) which was continually stirred. The solid mass was precipitated, filtered and washed twice with water and then with methanol and dried. The product, was chromatographed over neutral alumina and chlorform: pet. ether as mobile solvent gave crystalline products which were recrystallised from suitable solvent to give 2,4,6-triarylpyrimidine (5a-l) and (6a-l) in good yields as computed in Table 1.

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