# Conjugated Azoalkenes. Part V. Facile Synthesis of New 1-Aroylamino-3-sulfonylpyrroles by Reaction of Aroylazoalkenes with 1,3-Ketosulfones



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The easy one-pot synthesis of the interesting 1-aroylamino-3-sulfonylpyrroles by reaction of some aroylazoalkenes with 1,3-ketosulfones is reported.

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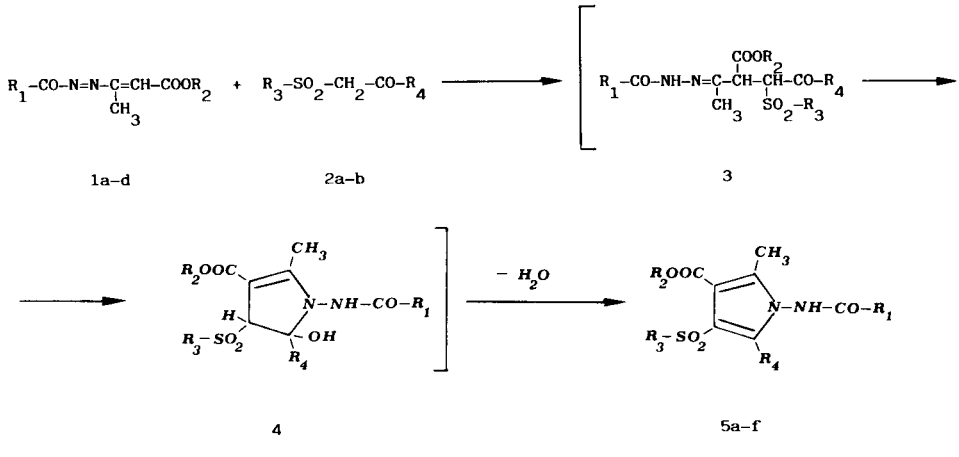
In previous investigations, some of us emphasized the versatility of the reaction between conjugated azoalkenes and compounds containing activated methylene groups as a useful entry to direct synthesis of interesting five-membered heterocycles, such as the widely substituted 1-aminopyrrole rings [1]. This important synthetic objective appears not to be readily achieved by other methods due to the specific problems posed by the preparation of these substances [2]. In addition, many of the molecules obtained by this method can profitably be utilized in the synthesis of organic, natural, pharmaceutical, and phytopharmaceutical products [3,4]. However, unlike the other activated methylene compounds, 1,3-ketosulfones have been rarely involved in these and related reactions, in spite of the potential interest of sulfonylated derivatives as products and intermediates in organic and pharmaceutical chemistry.

By considering the aforementioned reasons we decided to investigate the reaction of some aroylazoalkenes **1a-d** with 1,3-ketosulfones **2a-b** that readily afforded interesting 1-aroylamino-3-sulfonylpyrroles **5a-f**, *via* 1,4-conjugate addition of activated methylene compounds to the azo-ene system **3** according to previous findings on this subject [1]. The subsequent intramolecular condensation in the 1,4-adduct between the hydrozone nitrogen atom and the carbonyl group determines the ring closure producing the

Scheme



| 1 | $R_1$ | $R_2$ |
|---|---|---|
| a | $C_6H_5$ | $CH_3$ |
| b | m-$ClC_6H_4$ | $CH_3$ |
| c | m-$ClC_6H_4$ | $C_2H_5$ |
| d | m-$CH_3C_6H_4$ | $C_2H_5$ |

| 2 | $R_3$ | $R_4$ |
|---|---|---|
| a | $C_6H_5$ | $C_6H_5$ |
| b | p-$CH_3C_6H_4$ | $CH_3$ |

| 5 | $R_1$ | $R_2$ | $R_3$ | $R_4$ |
|---|---|---|---|---|
| a | $C_6H_5$ | $CH_3$ | p-$CH_3C_6H_4$ | $CH_3$ |
| b | m-$ClC_6H_4$ | $CH_3$ | $C_6H_5$ | $C_6H_5$ |
| c | m-$ClC_6H_4$ | $CH_3$ | p-$CH_3C_6H_4$ | $CH_3$ |
| d | m-$ClC_6H_4$ | $C_2H_5$ | $C_6H_5$ | $C_6H_5$ |
| e | m-$ClC_6H_4$ | $C_2H_5$ | p-$CH_3C_6H_4$ | $CH_3$ |
| f | m-$CH_3C_6H_4$ | $C_2H_5$ | p-$CH_3C_6H_4$ | $CH_3$ |

2-hydroxy-4-pyrroline intermediate **4**, in accordance with our recent investigations on the mechanistic behaviour of analogous reactions [5]. The loss of a water molecule from the intermediate **4** gives the 1-aminopyrrole derivative **5**.

All these one-flask events completely occur under very mild conditions (magnetic stirring at room temperature), and in the absence of copper(II) ions that frequently have been required to catalyze analogous reactions [1].

## EXPERIMENTAL

The aroylazoalkenes **1a-d** were prepared as previously reported [6]. The 1,3-ketosulfones **2a-b** were commercial materials and were used without further purification. Melting points were determined in capillary tubes with a Buechi apparatus, and are uncorrected. The products often decomposed at the melting point. The ir and $^1$H nmr spectra were recorded on a Perkin-Elmer 298 and a Varian EM-360L spectrometer at 60 MHz. The $\nu$ and $\delta$ values of characteristic peaks are reported below. The abbreviations used are as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. Merck precoated silica gel $60F_{254}$ plates were employed for analytical thin layer chromatography (tlc), Merck silica gel $PF_{254}$ plates for preparative tlc, and silica gel Kieselgel 60 (0.063-0.200 mm) for column chromatography. All the compounds prepared show a satisfactory elemental analysis (C $\pm$0.35, H $\pm$0.30, N $\pm$0.30).

1-Aroylamino-3-sulfonylpyrroles **5a-f**. General Procedure.

To a stirred solution of aroylazoalkenes **1a-d** (nearly 1.0 mmole) dissolved in tetrahydrofuran (1 ml) was added 1,3-ketosulfones **2a-b** (nearly 1.0 mmole), and the mixture was allowed to stand at room temperature under magnetic stirring until the reaction completion (monitored by silica gel tlc). A precipitate was frequently observed, and the product was isolated in satisfactory purity by filtration. Tetrahydrofuran was removed by evaporation of the filtrate under reduced pressure and the residue was crystallized from methanol to provide further product. Otherwise, preliminary purification of the reaction mixture by chromatography on a silica gel column may be necessary (elution with cyclohexane-ethyl acetate mixtures). In any case, further purification of the products **5a-f** may be obtained by recrystallization from methanol.

1-Benzoylamino-2,5-dimethyl-3-methoxycarbonyl-4-(*p*-toluenesulfonylamino)pyrrole (**5a**).

This compound was obtained by allowing **1a** (0.250 g, 1.08 mmoles) to react with **2b** (0.229 g, 1.08 mmoles) for 23 hours in 49% yield, mp 216-218° (uncorrected) after filtration, evaporation, and crystallization from methanol; ir (nujol): 3210 (NH), 1700 and 1685 (CO), 1340 and 1150 ($SO_2$), 1115 cm$^{-1}$ (CS); $^1$H nmr (dimethylsulfoxide-$d_6$, TMS): $\delta$ 2.23 (3H, s, Me), 2.42 (3H, s, Me), 2.52 (3H, s, *p*-*Me*$C_6H_4$), 3.70 (3H, s, COOMe), 7.38-8.17 (9H, m, *p*-Me$C_6H_4SO_2$ and PhCO), 12.38 (1H, broad s, deuterium oxide exchange).

*Anal.* Calcd. for $C_{22}H_{22}N_2O_2S$: C, 61.96; H, 5.16; N, 6.57. Found: C, 61.82; H, 5.09; N, 6.60.

1-(*m*-Chlorobenzoylamino)-2-methyl-3-methoxycarbonyl-4-benzenesulfonyl-5-phenylpyrrole (**5b**).

This compound was obtained by allowing **1b** (0.250 g, 0.94 mmole) to react with **2a** (0.244 g, 0.94 mmole) for 3 hours in 74% yield, mp 199-201° (uncorrected) after purification by column chromatography; ir (nujol): 3200 (NH), 1695 (CO), 1335 and 1135 ($SO_2$), 1090 cm$^{-1}$ (CS); $^1$H nmr (dimethylsulfoxide-$d_6$, TMS): $\delta$ 2.28 (3H, s, Me), 3.73 (3H, s, COOMe), 7.45 (5H, s, Ph), 7.50-7.95 (9H, m, $PhSO_2$ and *m*-$ClC_6H_4CO$), 12.01 (1H, broad s, deuterium oxide exchange).

*Anal.* Calcd. for $C_{26}H_{21}ClN_2O_5S$: C, 61.36; H, 4.16; N, 5.50. Found: C, 61.22; H, 4.25; N, 5.68.

1-(*m*-Chlorobenzoylamino)-2,5-dimethyl-3-methoxycarbonyl-4-(*p*-toluenesulfonyl)pyrrole (**5c**).

This compound was obtained by allowing **1b** (0.250 g, 0.94 mmole) to react with **2b** (0.199 g, 0.94 mmole) for 6.5 hours in 45% yield, mp 245-247° (uncorrected) after filtration, evaporation, and crystallization from methanol; ir (nujol): 3260 (NH), 1720 and 1705 (CO); 1340 and 1150 ($SO_2$), 1110 cm$^{-1}$ (CS); $^1$H nmr (dimethylsulfoxide-$d_6$, TMS): $\delta$ 2.23 (3H, s, Me), 2.42 (3H, s, Me), 2.50 (3H, s, *p*-*Me*$C_6H_4SO_2$), 3.68 (3H, s, COOMe), 7.40-8.10 (8H, m, *p*-Me$C_6H_4SO_2$ and *m*-$ClC_6H_4CO$), 12.10 (1H, broad s, deuterium oxide exchange).

*Anal.* Calcd. for $C_{22}H_{21}ClN_2O_5S$: C, 57.33; H, 4.59; N, 6.08. Found: C, 57.41; H, 4.68; N, 5.95.

1-(*m*-Chlorobenzoylamino)-2-methyl-3-ethoxycarbonyl-4-benzenesulfonyl-5-phenylpyrrole (**5d**).

This compound was obtained by allowing **1c** (0.250 g, 0.89 mmole) to react with **2a** (0.232 g, 0.89 mmole) for 0.1 hours in 60% yield, mp 171-173° (uncorrected) after purification by column chromatography; ir (nujol): 3190 (NH), 1690 (CO), 1325 and 1140 ($SO_2$), 1090 cm$^{-1}$ (CS); $^1$H nmr (dimethylsulfoxide-$d_6$, TMS): $\delta$ 1.23 (3H, t, J = 7.0 Hz, COOEt), 2.37 (3H, s, Me), 4.35 (2H, q, J = 7.0 Hz, COOEt), 7.67 (5H, s, Ph), 7.75-8.20 (9H, m, $PhSO_2$ and *m*-$ClC_6H_4CO$), 12.33 (1H, broad s, deuterium oxide exchange).

*Anal.* Calcd. for $C_{27}H_{23}ClN_2O_5S$: C, 62.01; H, 4.43; N, 5.35. Found: C, 61.88; H, 4.55; N, 5.21.

1-(*m*-Chlorobenzoylamino)-2,5-dimethyl-3-ethoxycarbonyl-4-(*p*-toluenesulfonyl)pyrrole (**5e**).

This compound was obtained by allowing **1c** (0.250 g, 0.89 mmole) to react with **2b** (0.190 g, 0.89 mmole) for 4.5 hours in 66% yield, mp 215-217° (uncorrected) after filtration, evaporation, and crystallization from methanol; ir (nujol): 3260 (NH), 1720 and 1705 (CO), 1340 and 1140 ($SO_2$), 1110 cm$^{-1}$ (CS); $^1$H nmr (dimethylsulfoxide-$d_6$, TMS): $\delta$ 1.18 (3H, t, J = 7.0 Hz, COOEt), 2.25 (3H, s, Me), 2.42 (3H, s, Me), 2.50 (3H, s, *p*-*Me*$C_6H_4SO_2$), 4.20 (2H, q, J = 7.0 Hz, COOEt), 7.38-8.12 (8H, m, *p*-Me$C_6H_4SO_2$ and *m*-$ClC_6H_4CO$), 12.13 (1H, broad s, deuterium oxide exchange).

*Anal.* Calcd. for $C_{23}H_{23}ClN_2O_5S$: C, 58.16; H, 4.88; N, 5.90. Found: C, 58.01; H, 4.99; N, 6.09.

1-(*m*-Toluoylamino)-2,5-dimethyl-3-ethoxycarbonyl-4-(*p*-toluenesulfonyl)-pyrrole (**5f**).

This compound was obtained by allowing **1d** (0.250 g, 0.96 mmole) to react with **2b** (0.204 g, 0.96 mmole) for 36 hours in 43% yield, mp 136-138° (uncorrected) after purification by column chromatography; ir (nujol): 3200 (NH), 1745 (CO), 1320 and 1145 ($SO_2$), 1080 cm$^{-1}$ (CS); $^1$H nmr (dimethylsulfoxide-$d_6$, TMS): $\delta$ 1.13 (3H, t, J = 7.0 Hz, COOEt), 2.32 (3H, s, Me), 2.42 (3H, s, Me), 3.47 (6H, s, *p*-*Me*$C_6H_4SO_2$ and *m*-*Me*$C_6H_4CO$), 3.87-4.61 (2H, m, J = 7.0 Hz, COOEt), 7.42-8.02 (8H, m, *p*-Me$C_6H_4SO_2$ and *m*-Me$C_6H_4CO$), 10.93 (1H, broad s, deuterium oxide exchange).

*Anal.* Calcd. for $C_{24}H_{26}N_2O_5S$: C, 63.42; H, 5.77; N, 6.16. Found: C, 63.29; H, 5.91; N, 6.00.

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## REFERENCES AND NOTES

[1] O. Attanasi and L. Caglioti, *Org. Prep. Proced. Int.*, **18**, 299 (1986); and references cited therein.

[2] H. Suschitzky and O. Meth-Cohn, eds, "Heterocyclic Chemistry", Royal Society of Chemistry, London, 1986, Vols **1-5**; A. R. Katritzky and C. W. Rees eds, "Comprehensive Heterocyclic Chemistry", Pergamon Press, London, 1984, Vols **1-8**, and references cited therein.

[3] The anticancer activity of these compounds is presently tested under the auspices of the Developmental Therapeutics Program, Division of Cancer Treatment, National Cancer Institute, Bethesda, Maryland, USA.

[4] Other pharmaceutical and phytopharmaceutical properties of these substances are currently being screened.

[5] O. Attanasi, M. Grossi, F. Serra-Zanetti and E. Foresti, *Tetrahedron*, **43**, 4249 (1987).

[6] O. Attanasi, M. Grossi and F. Serra-Zanetti, *Org. Prep. Proced. Int.*, **17**, 385 (1985).