Synthesis of New 1-Alkoxycarbonylamino-3-sulfonylpyrroles by Reaction of (Alkoxycarbonylazo)alkenes with β-Keto Sulfones

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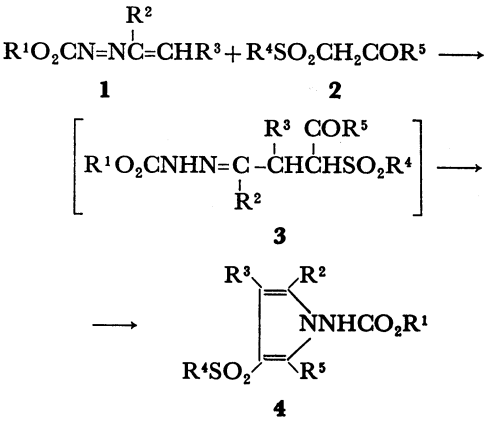
Synopsis. A mild, simple, and direct method for the synthesis of some new 1-alkoxycarbonylamino-3-sulfonylpyrrole derivatives by reaction of (alkoxycarbonylazo)alkenes with β-keto sulfones is reported.

The chemistry of the pyrrole ring received considerable attention by several authors, mainly due to the fact that this heterocycle is present in some natural products. In addition, several pyrrole derivatives manifested to have attractive biological and pharmacological activities.[1]

Considering this wide interest, during the last few years we particularly intended to a detailed and systematic elaboration of a synthetic strategy able to provide a large number of unknown 1-aminopyrrole derivatives containing various functional groups both at the carbon atoms of the pyrrole ring and, especially, on the amino group linked to the nitrogen heteroatom. The direct preparative procedure of 1-aminopyrrole derivatives investigated in our laboratories is in general based on the nucleophilic attack by an activated methylene group on the heterodiene system of a conjugated azoalkene, affording the formation of the 1,4-adduct intermediate. This preliminary 1,4-conjugate addition (Michael-type) may be followed by an intramolecular condensation between the C=N nitrogen atom and a ketonic carbonyl group in δ-position (esteric carbonyl group showing to be inactive), producing the pyrrole ring closure. In rather different way for each case, these reactions were frequently observed to more satisfactorily take place under copper(II) ions catalysis,[2] affording interesting 1-aminopyrrole derivatives that should result to be with difficulty synthesized by other methods.[1,3] NMR spectra,[4] X-ray crystal structures,[5] and biological activities[6] in part have been already examined and in part are presently in progress. Since the synthesis of variously functionalized 1-aminopyrroles appears to be largely dependent on the nature of conjugated azoalkenes, also the preparation of new classes of these latter derivatives have been extensively studied.[7] By these studies, conjugated azoalkenes demonstrated to represent versatile products and useful intermediates in organic chemistry.

Continuing these investigations, in this paper we report the synthesis of new 1-alkoxycarbonylamino-3-sulfonylpyrroles (**4**) by reaction of (alkoxycarbonylazo)alkenes (**1**) with β-keto sulfones (**2**). These reactions easily proceed at room temperature under magnetic stirring, often showing at first the 1,4-adduct intermediate (**3**) formation. This adduct is unambigously revealed by NMR spectra, exhibiting two doublets at δ=4—5 and δ=5.5—6.5 ppm ascribable to the two CH vicinal protons, in accordance with our previous findings on this matter.[2] The subsequent conversion of this 1,4-adduct intermediate (**3**) into related 1-alkoxycarbonylamino-3-sulfonylpyrrole is then observed, and these latter compounds are isolated in good yields without complicated procedures.



R^1	R^2	R^3	R^4	R^5
CH_3	CH_3	CO_2CH_3	CH_3	CH_3
CH_3	CH_3	$CO_2C_2H_5$	p-$CH_3C_6H_4$	CH_3
C_2H_5	CH_3	CO_2CH_3	C_6H_5	C_6H_5
C_2H_5	CH_3	$CO_2C_2H_5$		
$C(CH_3)_3$	CH_3	CO_2CH_3		
$C(CH_3)_3$	CH_3	$CO_2C_2H_5$		

Experimental

Materials and Methods. Yields are of pure isolated products (see Table 1). The reaction times are reported in Table. Melting points were determined in capillary tubes with a Büchi apparatus, and are uncorrected (see Table 1). The products often decompose at melting point. IR spectra were recorded in Nujol mull on a Perkin-Elmer 298 spectrophotometer, and values are expressed in cm^{-1}. ^1H NMR spectra were measured in deuteriochloroform with tetramethylsilane (TMS) as internal standard, using a Varian EM-360L spectrometer at 60 MHz. The chemical shifts are expressed in ppm in respect to TMS, and the coupling constants J in hertz (Hz). The abbreviations used are as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad; D_2O ex, D_2O exchange. Kieselgel 60 was used for chromatography. All the compounds obtained showed a satisfactory elemental analysis. (Alkoxycarbonylazo)alkenes (**1**) were prepared as previously reported.[2] The β-keto sulfones (**2**) were commercial materials, and were used without further purification.

Preparation of 1-Alkoxycarbonylamino-3-sulfonylpyrroles (4a—j). General Procedure. The (alkoxycarbonylazo)alkene (**1**) (2.0 mmol) and β-keto sulfone (**2**) (2.0 mmol) were

Table 1. Preparation of 1-Alkoxycarbonylamino-3-sulfonylpyrroles (**4**)

Pyrrole 4	R^1	R^2	R^3	R^4	R^5	Time h	Yield %	Mp[a] θ_m/°C
4a	CH_3	CH_3	CO_2CH_3	CH_3	CH_3	85	67	197—200
4b	CH_3	CH_3	CO_2CH_3	*p*-$CH_3C_6H_4$	CH_3	75	51	238—240
4c	CH_3	CH_3	CO_2CH_3	C_6H_5	C_6H_5	50	75	67
4d	CH_3	CH_3	$CO_2C_2H_5$	CH_3	CH_3	120	73	157—159
4e	C_2H_5	CH_3	CO_2CH_3	*p*-$CH_3C_6H_4$	CH_3	22	73	168—171
4f	C_2H_5	CH_3	$CO_2C_2H_5$	*p*-$CH_3C_6H_4$	CH_3	24	72	138—141
4g	$C(CH_3)_3$	CH_3	CO_2CH_3	*p*-$CH_3C_6H_4$	CH_3	30	71	108—110
4h	$C(CH_3)_3$	CH_3	CO_2CH_3	C_6H_5	C_6H_5	60	70	80—82
4i	$C(CH_3)_3$	CH_3	CO_2CH_3	*p*-$CH_3C_6H_4$	C_6H_5	48	76	78—82
4j	$C(CH_3)_3$	CH_3	$CO_2C_2H_5$	C_6H_5	C_6H_5	72	63	61—65

a) Melting points are uncorrected and occur with decomposition.

dissolved in tetrahydrofuran (2 ml) and the reaction was allowed to stand at room temperature under magnetic stirring (for reaction time see Table 1) until the reaction is complete (monitored by TLC silica gel). In some cases the formation of the 1,4-adduct intermediate (**3**) was at first observed, and then its conversion into related 1-aminopyrrole (**4**) was revealed. Sometimes the precipitated product (**4**) was isolated in satisfactory purity by filtration, or otherwise tetrahydrofuran was removed under reduced pressure obtaining the crude product (**4**) as residue (for yield see Table 1). The products (**4a—j**) can be further purified by recrystallization from dichloromethane–petroleum ether (40—60 °C) or tetrahydrofuran–pentane (for melting point see Table 1). In some cases, a preliminary purification of the crude product (**4**) by column chromatography on silica gel may be necessary (at first elution with cyclohexane and then with cyclohexane–ethyl acetate mixtures, gradually increasing the amount of ethyl acetate to a 80/20 (v/v) ratio).

Following compounds were prepared by this procedure.

1-Methoxycarbonylamino-2,5-dimethyl-3-methoxycarbonyl-4-(methylsulfonyl)pyrrole (4a). IR: 3275 (NH), 1750, and 1715 (COO), 1290, and 1145 (SO_2). ^{1}H NMR δ=2.27 (6H, s, 2Me), 3.32 (3H, s, SO_2Me), 3.77 (3H, s, COOMe), 3.83 (3H, s, COOMe), 8.91 (1H, s, br, NH, D_2O ex). Found: C, 43.65; H, 5.01; N, 9.02%. Calcd for $C_{11}H_{16}N_2O_6S$: C, 43.42; H, 5.30; N, 9.21%.

1-Methoxycarbonylamino-2,5-dimethyl-3-methoxycarbonyl-4-(*p*-tolylsulfonyl)pyrrole (4b). IR: 3270 (NH), 1765 and 1710 (COO), 1600 (Ar), 1290 and 1150 (SO_2). ^{1}H NMR δ=2.25 (3H, s, Me), 2.4 (3H, s, Me), 2.47 (3H, s, ArMe), 3.66 (3H, s, COOMe), 3.83 (3H, s, COOMe), 7.52 (4H, q, Ar, J=8.7 Hz), 8.73 (1H, s, br, NH, D_2O ex). Found: C, 53.51; H, 5.42; N, 7.43%. Calcd for $C_{17}H_{20}N_2O_6S$: C, 53.68; H, 5.30; N, 7.37%.

1-Methoxycarbonylamino-2-methyl-3-methoxycarbonyl-4-(phenylsulfonyl)-5-phenylpyrrole (4c). IR: 3275 (NH), 1755 and 1720 (COO), 1600 and 1585 (Ar), 1290 and 1140 (SO_2). ^{1}H NMR δ=2.23 (3H, s, Me), 3.52 (3H, s, COOMe), 3.67 (3H, s, COOMe), 7.13—7.92 (10H, m, Ar), 8.28 (1H, s, br, NH, D_2O ex). Found: C, 59.01; H, 4.69; N, 6.38%. Calcd for $C_{21}H_{20}N_2O_6S$: C, 58.88; H, 4.71; N, 6.54%.

1-Methoxycarbonylamino-2,5-dimethyl-3-ethoxycarbonyl-4-(methylsulfonyl)pyrrole (4d). IR: 3260 (NH), 1760 and 1710 (COO), 1290 and 1150 (SO_2). ^{1}H NMR δ=1.37 (3H, t, COOEt), 2.28 (6H, s, 2Me), 3.33 (3H, s, SO_2Me), 3.82 (3H, s, COOMe), 4.32 (2H, q, COOEt), 8.95 (1H, s, br, NH, D_2O ex). Found: C, 45.03; H, 5.69; N, 9.02%. Calcd for $C_{12}H_{18}N_2O_6S$: C, 45.28; H, 5.70; N, 8.80%.

1-Ethoxycarbonylamino-2,5-dimethyl-3-methoxycarbonyl-4-(*p*-tolylsulfonyl)pyrrole (4e). IR: 3280 (NH), 1755 and 1710 (COO), 1600 (Ar), 1295 and 1145 (SO_2). ^{1}H NMR δ=1.3 (3H, t, COOEt), 2.27 (3H, s, Me), 2.37 (3H, s, Me), 2.47 (3H, s, C_6H_4Me), 3.67 (3H, s, COOMe), 4.23 (2H, q, COOEt), 7.5 (4H, q, Ar, J=8.9 Hz), 8.82 (1H, s, br, NH, D_2O ex). Found: C, 54.99; H, 5.47; N, 7.00%. Calcd for $C_{18}H_{22}N_2O_6S$: C, 54.82; H, 5.62; N, 7.10%.

1-Ethoxycarbonylamino-2,5-dimethyl-3-ethoxycarbonyl-4-(*p*-tolylsulfonyl)pyrrole (4f). IR: 3290 (NH), 1755 and 1715 (COO), 1600 (Ar), 1290 and 1150 (SO_2). ^{1}H NMR δ=0.92—1.52 (6H, m, 2COOEt), 2.27 (3H, s, Me), 2.37 (3H, s, Me), 2.47 (3H, s, C_6H_4Me), 3.87—4.5 (4H, m, 2COOEt), 7.5 (4H, q, Ar, J=8.8 Hz), 8.87 (1H, s, br, NH, D_2O ex). Found: C, 55.69; H, 6.06; N, 6.93%. Calcd for $C_{19}H_{24}N_2O_6S$: C, 55.88; H, 5.92; N, 6.86%.

1-(*t*-Butoxycarbonylamino)-2,5-dimethyl-3-methoxycarbonyl-4-(*p*-tolylsulfonyl)pyrrole (4g). IR: 3330 (NH), 1750 and 1730 (COO), 1600 (Ar), 1290 and 1150 (SO_2). ^{1}H NMR δ=1.52 (9H, s, CMe_3), 2.25 (3H, s, Me), 2.37 (3H, s, Me), 2.45 (3H, s, C_6H_4Me), 3.63 (3H, s, COOMe), 7.47 (4H, q, Ar, J=9.0 Hz), 8.46 (1H, s, br, NH, D_2O ex). Found: C, 56.69; H, 6.47; N, 6.69%. Calcd for $C_{20}H_{26}N_2O_6S$: C, 56.87; H, 6.20; N, 6.63%.

1-(*t*-Butoxycarbonylamino)-2-methyl-3-methoxycarbonyl-4-phenylsulfonyl-5-phenylpyrrole (4h). IR: 3295 (NH), 1755 and 1725 (COO), 1600 and 1585 (Ar), 1275 and 1150 (SO_2). ^{1}H NMR δ=1.3 (9H, s, CMe_3), 2.23 (3H, s, Me), 3.65 (3H, s, COOMe), 7.17—8.0 (10H, m, Ar and NH; 1H, D_2O ex). Found: C, 61.45; H, 5.63; N, 5.69%. Calcd for $C_{24}H_{26}N_2O_6S$: C, 61.27; H, 5.57; N, 5.95%.

1-(*t*-Butoxycarbonylamino)-2-methyl-3-methoxycarbonyl-4-(*p*-tolylsulfonyl)-5-phenylpyrrole (4i). IR: 3290 (NH), 1745 and 1725 (COO), 1600 (Ar), 1300 and 1150 (SO_2). ^{1}H NMR δ=1.3 (9H, s, CMe_3), 2.27 (3H, s, Me), 2.37 (3H, s, C_6H_4Me), 3.68 (3H, s, COOMe), 6.93—7.9 (10H, m, Ar and NH; 1H, D_2O ex). Found: C, 62.15; H, 5.86; N, 5.98%. Calcd for $C_{25}H_{28}N_2O_6S$: C, 61.98; H, 5.83; N, 5.78%.

1-(*t*-Butoxycarbonylamino)-2-methyl-3-ethoxycarbonyl-4-phenylsulfonyl-5-phenylpyrrole (4j). IR: 3280 (NH), 1740 and 1715 (COO), 1600 and 1585 (Ar), 1300 and 1150 (SO_2). ^{1}H NMR δ=1.13—1.5 (12H, s, CMe_3 and COOEt), 2.28 (3H, s, Me), 4.22 (2H, q, COOEt), 7.17—7.97 (11H, m, Ar and NH; 1H, D_2O ex). Found: C, 61.87; H, 5.69; N, 5.61%. Calcd for $C_{25}H_{28}N_2O_6S$: C, 61.98; H, 5.83; N, 5.78%.

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