EFFECT OF METAL IONS IN ORGANIC SYNTHESIS. XXIX. SYNTHESIS OF NEW 1-ARYLSULFONYLAMINO-3-CARBOXYPYRROLES BY COPPER(II) ACETATE-CATALYZED REACTION OF ARYLSULFONYLAZOALKENES WITH ß-KETOESTERS

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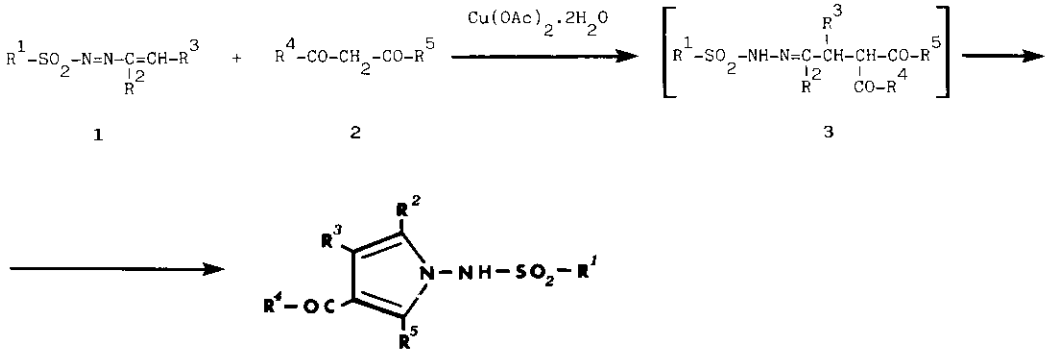
Abstract - The synthesis of a number of new 1-arylsulfonylamino-3-carboxypyrroles by reaction of some arylsulfonylazoalkenes with certain ß-ketoesters under copper(II) acetate monohydrate catalysis is reported.

During the last few years we have investigated the one-flask synthesis of new 1-aminopyrrole derivatives. These products have been in general prepared by copper(II) chloride-catalyzed reaction of azoalkenes with compounds containing activated methylene groups.[1-8] In particular, we previously described the synthesis of some 1-arylamino-3-carbonylpyrroles,[1,2] 1-arylamino-3-carboxypyrroles,[1,2] 1-arylamino-3-aminocarbonylpyrroles,[1,3] 1-ureido-3-carbonylpyrroles,[4] 1-ureido-3-carboxypyrroles,[4] 1-ureido-3-aminocarbonylpyrroles,[5] 1-alkoxycarbonylamino-3-aminocarbonylpyrroles,[6] 1-arylsulfonylamino-3-aminocarbonylpyrroles,[7] and 1-aroylamino-3-aminocarbonylpyrroles[8] by reaction of the appropriate azoalkene derivatives with ß-diketones, ß-ketoesters or ß-ketoamides. Such 1-aminopyrrole derivatives are not easily prepared by other methods.[9] The ^{1}H- and ^{13}C-nmr spectra,[10] the X-ray crystal structures,[2,11] and the biological activities of some of these compounds were studied or are currently under investigation.

In order to tentatively make the present method a more general procedure for the direct synthesis of widely substituted 1-aminopyrrole derivatives, we now present the one-flask synthesis of some new 1-arylsulfonylamino-3-carboxypyrroles (**4**) by reaction of arylsulfonylazoalkenes (**1**) with ß-ketoesters (**2**) under copper(II) acetate monohydrate catalysis. Under analogous experimental conditions, the above-mentioned reagents show no appreciable reaction in the absence of the copper(II) salt. The reaction occurs under mild conditions, frequently provide the products (**4**) in good yields without complicated performance and work-up procedures and does not require strongly acidic or basic agents, or even expensive and less easily available reagents. In fact, arylsulfonylazoalkenes (**1**) are easily accessible compounds,[8] confirming once again azoalkene derivatives to be useful intermediates in organic chemistry,[1-8] while copper(II) acetate monohydrate and ß-ketoesters (**2**) are commercial and relatively cheap materials. The reactions work well with various arylsulfonylazoalkenes and are successfully applicable both to aliphatic



1	R^1	R^2	R^3	2	R^4	R^5
a	4-ClC_6H_4	CH_3	$COOCH_3$	**a**	OCH_3	CH_3
b	4-ClC_6H_4	CH_3	$COOC_2H_5$	**b**	OC_2H_5	CH_3
c	4-$CH_3OC_6H_4$	CH_3	$COOCH_3$	**c**	$OC(CH_3)_3$	CH_3
d	4-$CH_3OC_6H_4$	CH_3	$COOC_2H_5$	**d**	$OCH_2C_6H_5$	CH_3
e	4-$CH_3C_6H_4$	CH_3	$COOCH_3$	**e**	OC_2H_5	C_6H_5
f	4-$CH_3C_6H_4$	CH_3	$COOC_2H_5$			

and aromatic ß-ketoesters. Using a molar ratio between arylsulfonylazoalkenes and copper(II) acetate monohydrate of 10:1, arylsulfonylazoalkenes disappear within 0.5-6 h at room temperature (monitored by tlc on silica gel). The reaction mixtures are then allowed to stand at room temperature until the precipitate formation (generally for additional 12 h), except for the synthesis of product **4ce** for which the reaction mixture is heated under reflux. This particular procedure is due to initial formation of the 1,4-adduct intermediate (**3**) and its gradual conversion into the related 1-aminopyrrole derivative (**4**). This behaviour may be monitored by tlc on silica gel and detected by nmr spectroscopy, in accordance with our previous findings on this matter.[4,5,7,8] The other mechanistic considerations on these reactions seem in principle to remain the same as discussed in detail in previous papers.[1-8]

Thus this method represents an advantageous procedure for the synthesis of 1-arylsulfonyl-3-carboxypyrroles (**4**) which appear to be not readily prepared by other methods.[9,12]

EXPERIMENTAL

The ß-ketoesters **2** and copper(II) acetate monohydrate are commercial materials and are used without further purification. Mps are determined in capillary tubes, and are uncorrected. The

Table - Time, yield, physical properties, and spectral data of compounds **4**

Reagents		Product[a]	Reaction	Yield[b]	Mp (°C)	^{1}H-nmr (DMSO-d_6/TSPSA$_{int}$)[c]
1	2	4	time (h)	(%)		δ ppm
1a	2a	4aa	1	70	205-209	h,l,r,s
	2b	4ab	0.5	69	189-191	d,h,k,r,s
	2c	4ac	1.5	66	170-175	g,h,k,r,s
	2d	4ad	1.5	67	168-169	h,k,n,o,r,s
	2e	4ae	1	56	168-170	7.17 (s, 5H, Ph)[d],i,k,r,s
1b	2b	4bb	0.5	50	222-226	f,h,r,s
	2d	4bd	0.5	57	152-154	e,h,n,o,r,s
1c	2a	4ca	0.5	78	158-159	h,l,m,p,s
	2e	4ce	3.5	42	151-153	6.6-7.5 (m, 9H, Ar)[d],i,k,m,s
1d	2c	4dc	4	51	222-225	e,g,h,m,p,s
	2d	4dd	1	64	140-141	e,h,m,n,o,p,s
1e	2a	4ea	2.5	70	172-174	h,j,l,q,s
	2d	4ed	0.5	58	153-154	7.23-7.9 (m, 9H, Ar)[h],j,k,n,s
1f	2b	4fb	3	66	191-193	f,h,j,q,s
	2c	4fc	6	60	134-138	e,g,h,j,q,s,

[a] Ir (nujol): ν=3110, 1720, 1690, 1355, 1165 cm^{-1}. [b] Yield of pure isolated product. [c] TSPSA=3-(trimethylsilyl)propanesulfonic acid Na salt. [d] Signals at δ=1.12 (t, 3H, COOEt) and δ=4.09 (q, 2H, COOEt) ppm. [e] Signals at δ=1.18 (t, 3H, COOEt) and δ=4.1 (q, 2H, COOEt) ppm. [f] Signals at δ=1.23 (t, 6H, 2COOEt) and δ=4.16 (q, 4H, 2COOEt) ppm. [g] Signal at δ=1.47 (s, 9H, $COOCMe_3$) ppm. [h] Signal at δ=1.95 (s, 6H, 2Me) ppm. [i] Signal at δ=2.42 (s, 3H, Me) ppm. [j] Signal at δ=2.45 (s, 3H, ArMe) ppm. [k] Signal at δ=3.68 (s, 3H, COOMe) ppm. [l] Signal at δ=3.72 (s, 6H, 2COOMe) ppm. [m] Signal at δ=3.89 (s, 3H, OMe) ppm. [n] Signal at δ=5.2 (s, 2H, CH_2) ppm. [o] Signal at δ=7.42 (s, 5H, Ph) ppm. [p] Signal at δ=7.48 (q, 4H, J=9.6 Hz, C_6H_4) ppm. [q] Signal at δ=7.61 (q, 4H, J=8 Hz, C_6H_4) ppm. [r] Signal at δ=7.77 (s, 4H, C_6H_4) ppm; in methanol-d_4 this singulet becomes a quartet. [s] Signal at δ=11.74 (s broad, 1H, NH, D_2O exchange); this signal may be very broad and is more clearly evidenced by addition of trifluoroacetic acid in very small amount.

products often decompose at melting point. Ir and ^{1}H-nmr spectra are recorded on a Perkin-Elmer 298 and a Varian EM-360L spectrometer at 60 MHz, respectively. The indicative ν and δ values of characteristic peacks are below summarized. Kieselgel 60 is used for chromatography. All the compounds obtained showed a satisfactory elemental analysis.

Arylsulfonylazoalkenes 1. These products are prepared as previously reported.[7] The

physico-chemical data for **1e** and **1f** are reported in previous paper.[7] The physico-chemical data for the new derivatives **1a-d** are as follows. **1a**: yield 60%, mp 68-70 °C; **1b**: yield 45%, mp 50-53 °C; **1c**: yield 68%, mp 84-85 °C; **1d**: yield 60%; mp 66-68 °C. Ir (nujol): ν=1720, 1350, 1160 cm^{-1}; ^{1}H-nmr ($CDCl_3$/TMS): δ=1.33 (t, 3H, COOEt), 2.3 (s, 3H, Me), 3.85 (s, 3H, OMe), 3.92 (s, 3H, COOMe); 4.3 (q, 2H, COOEt), 6.77 (s, 1H, CH), 7.5 (q, 4H, J=9.6 Hz, 4-MeOPh), 7.77 (q, 4H, J=9 Hz, 4-ClPh) ppm.

1-Arylsulfonylamino-3-carboxypyrroles 4 - general procedure: the arylsulfonylazoalkene (**1a-f**: 1 mmol), the ß-ketoester (**2a-e**: 1 mmol) and copper(II) acetate monohydrate (0.1 mmol) are dissolved in tetrahydrofuran (2 ml). The mixture is stirred at room temperature until the reaction is complete (whitin 0.5-6 h, monitored by tlc on silica gel). In general, a precipitate forms in additional 12 h, and the product **4** is obtained in satisfactory purity by filtration. In some cases, tetrahydrofuran is removed under reduced pressure and the residue is crystallized from methanol, affording the product **4** in satisfactory purity. In the case of reaction between **1c** and **2e**, the mixture is stirred at room temperature for 3.5 h, and then heated under reflux for an additional 5 h. Products **4** can be further purified by recrystallization from methanol.

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