Effect of Metal Ions in Organic Synthesis: XXXII. Copper(II) Chloride-Catalyzed Synthesis of New 1-Ureido-3-sulfonylpyrroles

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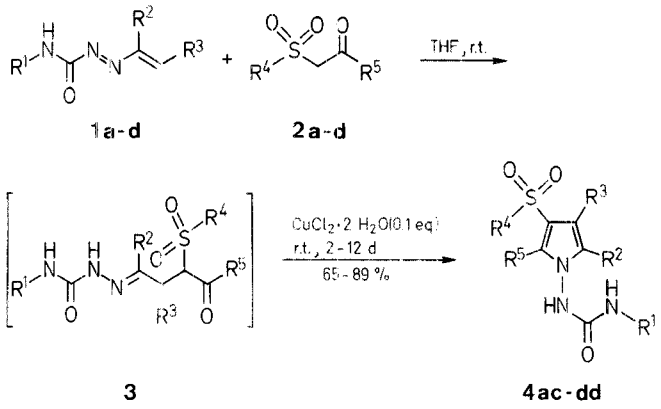
1-Ureido-3-sulfonylpyrroles **4** were prepared by the reaction of aminocarbonylazoalkanes **1** with α-sulfonylketones **2** in the presence of Cu(II) chloride as catalyst.

In contrast with most of other widely investigated pyrrole derivatives,[1] substituted 1-aminopyrroles bearing various functional groups represent a class of compounds about which relatively little is known,[1] in spite of their potential usefulness as intermediates and products in organic and pharmaceutical chemistry.[1-4] In fact, with respect to other pyrrole rings, the synthesis of 1-aminopyrroles poses specific problems that may be satisfactorily resolved mainly by direct reaction of molecules containing an activated methylene group with conjugated azoalkenes.[2] These latter compounds have been extensively studied only within the last twenty years;[2] therefore the chemistry of 1-aminopyrroles is less known as compared to other pyrroles derivatives.[1] Moreover, 1,3-dicarbonyl compounds

have been frequently used as nucleophilic agents, also in the 1,4-addition to the azo-ene system of conjugated azoalkenes, while α-sulfonylketones are much less utilized in these and related reactions, even though the final sulfonylated derivatives often represent interesting products.[2] Indeed, the utilization of α-sulfoxylated, α-sulfenylated, α-sulfinylated, and α-sulfonylated carbonyl carbanions as nucleophiles in organic synthesis are in general relatively less well documented.[5]

In connection with our previous investigations on analogous reactions, we now describe the preparation of new 1-ureido-3-sulfonylpyrroles **4** by reaction of aminocarbonylazoalkenes **1** with α-sulfonylketones **2** in the presence of copper(II) chloride as catalyst.



1	R^1	R^2	R^3
a	H	CH_3	CO_2CH_3
b	H	CH_3	CO_2CH_3
c	C_6H_5	CH_3	$CO_2C_2H_5$
d	C_6H_5	CH_3	$CO_2C_2H_5$

2	R^4	R^5
a	CH_3	CH_3
b	4-$CH_3C_6H_4$	CH_3
c	C_6H_5	C_6H_5
d	4-$CH_3C_6H_4$	C_6H_5

Table 1. Preparation of 1-Ureido-3-sulfonylpyrroles **4**

Educts		Product	React. Time (days)	Yield[a] (%)	m.p.[b] (°C)	Molecular Formula[c]
1a	**2c**	**4ac**	12	74	231–233	$C_{20}H_{19}N_3O_5S$ (413.4)
	2d	**4ad**	9	75	123–126	$C_{21}H_{21}N_3O_5S$ (427.4)
1b	**2c**	**4bc**	8	78	136–139	$C_{21}H_{21}N_3O_5S$ (427.4)
	2d	**4bd**	9	74	118–119	$C_{22}H_{23}N_3O_5S$ (441.5)
1c	**2b**	**4cb**	4	82	222–225	$C_{22}H_{23}N_3O_5S$ (441.5)
	2d	**4cd**	4	65	217–219	$C_{27}H_{25}N_3O_5S$ (503.5)
1d	**2a**	**4da**	2	75	133–137	$C_{17}H_{21}N_3O_5S$ (379.4)
	2b	**4db**	7	73	196–198	$C_{23}H_{25}N_3O_5S$ (455.3)
	2c	**4dc**	3	65	220–224	$C_{27}H_{25}N_3O_5S$ (503.5)
	2d	**4dd**	2	89	164–167	$C_{28}H_{27}N_3O_5S$ (517.6)

[a] Yield of pure isolated product **4** based on **1**.
[b] With decomposition. Uncorrected, measured with a Büchi (Dr. Tottoli) apparatus.
[c] Satisfactory microanalyses obtained: C ±0.35, H ±0.30, N ±0.30.

The reaction takes place at room temperature and in the absence of strong bases (e.g. sodium hydride, lithium hydride) usually employed in the nucleophilic attack by 1,3-dianion of α-sulfonylketones.[5] The reaction seems to be applicable for the synthesis of a large number of new 1-ureido-3-sulfonylpyrroles **4** in good yield and without complicated procedures. The reagents used are readily available and relatively inexpensive (see experimental). The course of the reaction is easily monitored by TLC and the preliminary formation of the intermediate 1,4-adduct **3** is evidenced by ^{1}H-NMR spectroscopy, showing two characteristic doublets at δ = 4.00–4.20 ppm and δ = 6.37–6.57 ppm for the two CH vicinal protons, in accordance with our previous findings of related cases.[2] Afterwards, cyclization of the C=N nitrogen atom to ketonic carbonyl group in the presence of copper(II) chloride dihydrate produces the pyrrole ring system **4**. In the absence of the inorganic salt slower and incomplete reactions were observed.

The α-sulfonylketones **2** and copper(II) chloride dihydrate were commercial materials and were used without further purification. The aminocarbonylazoalkenes **1** were prepared as previously reported.[6]

Table 2. Spectral Data for 1-Ureido-3-sulfonylpyrroles **4**

Product	IR (Nujol)[a] ν(cm^{-1})	^{1}H-NMR (DMSO-d_6)[b] δ(ppm)
4ac	3460, 3330, 3250, 1705, 1675, 1605, 1305, 1150	2.23 (s, 3H, CH_3); 3.73 (s, 3H, OCH_3); 6.23 (br s, 2H, NH_2, D_2O exchange); 7.3–7.83 (m, 10H_{arom}); 9.2 (br s, 1H, NH, D_2O exchange)
4ad	3430, 3340, 3200, 1735, 1690, 1605, 1595, 1280, 1140	2.2 (s, 3H, CH_3); 2.37 (s, 3H, $ArCH_3$); 3.7 (s, 3H, OCH_3); 6.23 (br s, 2H, NH_2, D_2O exchange); 7.26–7.73 (m, 9H_{arom}); 9.2 (br s, 1H, NH, D_2O exchange)
4bc	3470, 3310, 3235, 1720, 1690, 1675, 1600, 1305, 1150	1.15 (t, 3H, J = 7.0 Hz, OCH_2CH_3); 2.23 (s, 3H, CH_3); 4.18 (q, 2H, J = 7.0 Hz, OCH_2CH_3); 6.3 (br s, 2H, NH_2, D_2O exchange); 7.27–7.93 (m, 10H_{arom}); 9.27 (br s, 1H, NH, D_2O exchange)
4bd	3630, 3330, 3210, 1705, 1695, 1610, 1600, 1290, 1150	1.2 (t, 3H, J = 7.0 Hz, OCH_2CH_3); 2.23 (s, 3H, CH_3); 2.38 (s, 3H, $ArCH_3$); 4.22 (q, 2H, J = 7.0 Hz, OCH_2CH_3); 6.28 (br s, 2H, NH_2, D_2O exchange); 7.3–7.8 (m, 9H_{arom}); 9.27 (br s, 1H, NH, D_2O exchange)
4cb	3280, 1745, 1655, 1610, 1605, 1315, 1145	2.27 (s, 3H, CH_3); 2.43 (s, 3H, $ArCH_3$); 2.53 (s, 3H, CH_3); 3.7 (s, 3H, OCH_3); 7.07–7.97 (m, 9H_{arom}); 9.63 (br s, 2H, 2NH, D_2O exchange)
4cd	3350, 3270, 1730, 1720, 1600, 1310, 1140	2.27 (s, 3H, CH_3); 2.37 (s, 3H, $ArCH_3$); 3.73 (s, 3H, OCH_3); 7.0–7.77 (m, 14H_{arom}); 9.23 (br s, 1H, NH, D_2O exchange); 9.5 (br s, 1H, NH, D_2O exchange)
4da	3590, 3280, 1715, 1690, 1625, 1600, 1290, 1140	1.3 (t, 3H, J = 7.0 Hz, OCH_2CH_3); 2.3 (s, 3H, CH_3); 2.37 (s, 3H, CH_3); 3.38 (s, 3H, SO_2CH_3); 4.27 (q, 2H, J = 7.0 Hz, OCH_2CH_3); 7.03–7.67 (m, 5H_{arom}); 9.5 (br s, 1H, NH, D_2O exchange); 9.6 (br s, 1H, NH, D_2O exchange)
4db	3290, 1720, 1655, 1610, 1605, 1310, 1145	1.17 (t, 3H, J = 7.0 Hz, OCH_2CH_3); 2.23 (s, 3H, CH_3); 2.4 (s, 3H, $ArCH_3$); 2.48 (s, 3H, CH_3); 4.17 (q, 2H, J = 7.0 Hz, OCH_2CH_3); 7.0–7.97 (m, 9H_{arom}); 9.57 (br s, 2H, 2NH, D_2O exchange)
4dc	3350, 3260, 1725, 1685, 1605, 1300, 1145	1.17 (t, 3H, J = 7.0 Hz, OCH_2CH_3); 2.3 (s, 3H, CH_3); 4.22 (q, 2H, J = 7.0 Hz, OCH_2CH_3); 7.0–7.93 (m, 15H_{arom}); 9.23 (br s, 1H, NH, D_2O exchange); 9.47 (br s, 1H, NH, D_2O exchange)
4dd	3610, 3320, 1705, 1665, 1600, 1310, 1150	1.23 (t, J = 7.0 Hz, 3H, OCH_2CH_3); 2.3 (s, 3H, CH_3); 2.4 (s, 3H, $ArCH_3$); 4.25 (q, 2H, J = 7.0 Hz, OCH_2CH_3); 7.1–7.8 (m, 14H_{arom}); 9.2 (br s, 1H, NH, D_2O exchange); 9.47 (br s, 1H, NH, D_2O exchange)

[a] Recorded on a Perkin-Elmer 298 Infrared spectrophotometer.
[b] Obtained on a Varian EM-360L spectrometer.

1-Ureido-3-sulfonylpyrroles 4; General Procedure:
The aminocarbonylazoalkene **1** (1 mmol) and α-sulfonylketone **2** (1 mmol) are dissolved in tetrahydrofuran (2 ml). The mixture is stirred at room temperature until the respective 1,4-adduct intermediate **3** is formed. Copper(II) chloride dihydrate (0.1 equiv with respect to **1**) is then added, and stirring is continued until the reaction is complete (monitored by TLC on Kieselgel plate). In most cases **(4ac–da)** the intermediate adduct **3** leads to a precipitate, that may be conveniently isolated by repeated suction, then dissolved in tetrahydrofuran (25 ml), and reacted by addition of copper(II) chloride dihydrate, thus affording a final product **4** of satisfactory purity. In general, the product can be further purified by recrystallization from dichloromethane/*n*-pentane (or petroleum ether b.p. 40–60 °C). Some time, prior purification of the reaction mixture by chromatography on a silica gel column may be necessary (Kieselgel, eluent: dichloromethane/ethyl acetate mixtures).

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(1) Suschitzky, H., Meth-Cohn, O., in: *Heterocyclic Chemistry*, Vol. 1–4, Royal Society of Chemistry, London, 1978–1985.
Hafez, E.A.A., Abed, N.N., Rifaat, M., Elmoghayer, H., El-Agamey, A.G.A. *Heterocycles* **1984**, *22*, 1821.
Katritzky, A.R., Rees, C.W., in: *Comprehensive Heterocyclic Chemistry*, Pergamon Press, London, 1984.
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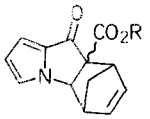
Patterson, J.M. *Synthesis* **1976**, 281.
Gossauer, A., in: *Die Chemie der Pyrrole*, Springer Verlag, Berlin, 1974.
(2) Attanasi, O., Caglioti, L. *Org. Prep. Proced. Int.* **1986**, *18*, 299, and references cited therein.
(3) Tests on the anticancer activity of these compounds is performed under the auspices of the Developmental Therapeutics Program, Division of Cancer Treatment, National Cancer Institute, Bethesda, Maryland, USA. Till now the substances tested revealed no significant activity.
(4) The screening of some other pharmaceutical and phytopharmaceutical properties of these compounds are presently in progress.
(5) See *inter alia*:
Magnus, P.D. *Tetrahedron* **1977**, *33*, 2019.
Sato, K., Inoue, S., Sakamoto, T. *Synthesis* **1981**, 796.
Scholz, D. *Chem. Ber.* **1981**, *114*, 909.
Tanikaga, R., Nozaki, Y., Tamura, T., Kaji, A. *Synthesis* **1983**, 134.
Hudson, A.T., Pether, M.J. *J. Chem. Res. (S)* **1983**, 56.
Grossert, J.S., Boyle, J., Hooper, D.L. *Tetrahedron* **1984**, *40*, 1135.
Tanikaga, R., Tamura, T., Nozaki, Y., Kaji, A. *J. Chem. Soc. Chem. Commun.* **1984**, 87.
Annunziata, R., Cinquini, M., Cozzi, F., Montanari, F., Restelli, A. *Tetrahedron* **1984**, *40*, 3815.
Cinquini, M., Manfredi, A., Molinari, H., Restelli, A. *Tetrahedron* **1985**, *41*, 4929, and references cited therein.
(6) Attanasi, O., Filippone, P., Mei, A., Santeusanio, S. *Synthesis* **1984**, 671.

Errata and Addenda 1987

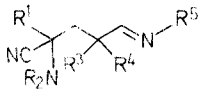
Hall, G., Sugden, J.K., Waghela, M.B.
Page 10. Line 3 of the Abstract should read: dropyrolizines ...
Page 14. The first word of Section 3.11. should be: Benzo[*b*]pyrrolizines.
Page 15. Formula **27** should be:



27

Page 15. The product referred to in Section 4.6., lines 4–5, should be: 10*H*-pyrrolizino[1,2-*b*]quinoline
Page 17. In Section 7., line 4 of the second paragraph should read: **34**.[182] ...

Ahlbrecht, H., von Daacke, A.
Page 24. Formula **8** should be:



8

Costisella, B., Keitel, I.
Page 45. In the heading of the experimental procedure, **6** should read **3** and **8** should read **7**.

Stoss, P., Merrath, P., Schlüter, G.
Page 174. Numbers 1 and 3 should be exhanged in formula **2a–f**.

Singh, G., Deb, B., Ila, H., Junjappa, H.
Page 286. Compounds **1** are 2-aroyl-2-arylthioketene dithioacetals.

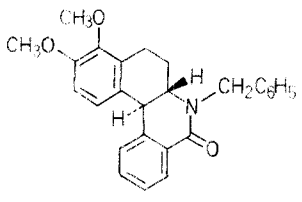
Asaad, F.M., Becher, J., Møller, J., Varma, K.S.
Page 301. Under the reaction scheme, the X group in compounds **3b,d** and **4b,d** should be $CO_2C_2H_5$.

Legrel, P., Baudy-Floc'h, M., Robert, A.
Page 306. The title should read: A One-Pot Synthesis of α-Halohydrazides from 2,2-Dicyanooxiranes.
Page 306. In the table under the reaction scheme, the second heading R^1 should be R^2.

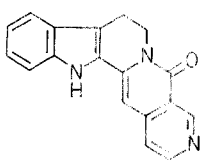
van der Goorbergh, J.A.M., van der Steeg, M., van der Gen, A.
Pages 314–317. The systematic names for the heterocycles involved are: 4,5-dioxo-3,4-dihydro-2*H*,5*H*-thiopyrano[3,2-*c*][1]benzopyrans **4** (RF 24756), 4,5-dioxo-2*H*,5*H*-thiopyrano[3,2-*c*][1]benzopyrans **7** (RF 24756), and 4,5-dioxo-1,3,4,4a,5,10b-hexahydro-2*H*-[1]benzopyrano[4,3-*b*]pyridines **8** (RF 24539).

Attanasi, O.A., Filippone, P., Santensanio, S., Serra-Zanetti, F.
Page 382. In the table under the reaction scheme, R^3 for **1b** should be $CO_2C_2H_5$ and R^3 for **1c** should be CO_2CH_3.

Campbell, A.L., Lenz, G.R.
Pages 428 and 446. Formulae **95** and **298** should be:



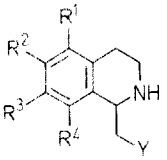
95



298

Page 437. The heading for Table 3 should be: Intermolecular ...

Pelletier, J.C., Cava, M.P.
Page 476. Formula **1a–m** should be:



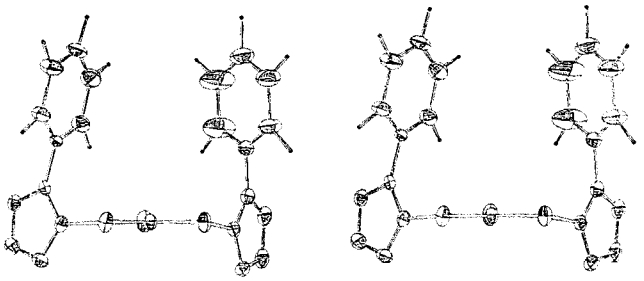
1a-m

L'abbé, G.
Page 528. Compound **45** should be named: 3-(2-pyridyl)-2,4-dithioxo-3,4-dihydro-2*H*-pyrido[1,2-*a*][1,3,5]triazine (RF 9177).

Evans, R.D., Schauble, J.H.
Page 551. Compounds **10** and **11** are tricyclo[2.2.1.$0^{2,6}$]heptane derivatives.

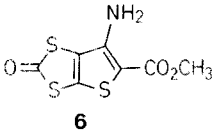
Takeda, K., Tsuboyama, K., Hoshino, M., Kishino, M., Ogura, H.
Page 559. The Y-group for **2g** and **2j** should be furfuryloxy.

Takeda, K., Tsuboyama, K., Takayanagi, H., Ogura, H.
Page 560. The following figure should appear after the 4th paragraph:



Eicher, T., Stapperfenne, U.
Page 625. Compounds **13a,b** are 6,7-dihydrofuro[2,3-*b*]pyridines (RF 7431), and compounds **15a,b** are 1,4-dihydrocyclopentimidazoles (RF 5892).

Dölling, W., Augustin, M., Ihrke, R.
Page 655. Formula **6** should be:



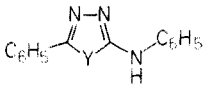
6

Mikołajczyk, M., Bałczewski, P.
Page 661. The second paragraph of ref. 21 should be ref. 22; refs. 22 and 23 should be 23 and 24, respectively.

Rösch, W., Regitz, M.
Page 692. Compounds **21a,b** are 2*H*-1,2,3-diazaphospholes.

Tietze, L.-F., Brumby, T., Pretor, M.
Page 702. Compounds **8** and **9** are 4a,10b-dihydro-4*H*,5*H*-pyrano[3,4-*c*][1]benzopyran-2-carboxylic esters.

Wamhoff, H., Zahran, M.
Page 877. Formula **18a,b** should be:



18a,b

Castaldi, G., Giordano, C.
Page 1039. The target compounds **3** are 1-bromoalkyl aryl ketones.