2-Metylthiazolium Salts as 1,4-Dinucleophiles. Thiazolo[3,2-*a*]pyridinium Salts from Westphal Condensation

C. Galera, J. J. Vaquero, J. L. Garcia Navio, J. Alvarez-Builla*

Departamento de Quimica Organica, Universidad de Alcalá de Henares,
Madrid Spain

Received February 25, 1985

Condensation of 2-methylthiazolium salts with 1,2-dicarbonyls in the presence of base, yielded thiazolo-[3,2-*a*]pyridinium derivatives. Results with different substrates are discussed.

J. Heterocyclic Chem., **23**, 1889 (1986).

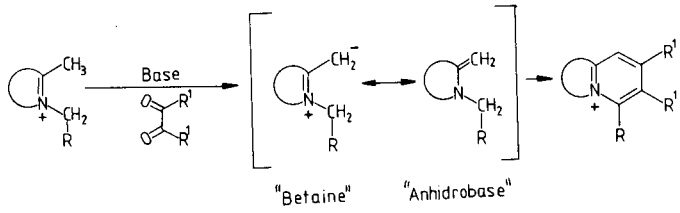
Westphal condensation [1,2] (Scheme 1) allows the synthesis of quinolizinium derivatives from *N*-substituted 2-methylpyridinium salts with 1,2-diketones. After additions from several authors [3-9] the method seems to be simple and extremely versatile. Extension of the general process is being studied by our group as the method could provide a way to straightforward preparation of quaternary nitrogen bridgehead heterocycles of great chemical and biological interest.

In addition to a previous communication from Westphal [10], our group tried the synthesis of thiazolo[3,2-*a*]pyridinium salts by building up the pyridinium moiety, instead of using the opposite traditional alternative [11].

2-Methylthiazolium salts used as starting materials were prepared by quaternization of 2-methylthiazole derivatives (Table 1) with phenacyl bromide and ethyl bromoacetate. Subsequent condensation of compounds **1** to **8** with 1,2-dicarbonyls such as diacetyl, benzyl, 3,3'-dinitrobenzyl, 9,10-fenantroquinone and 1,2-acenaphtoquinone allowed the desired thiazolo[3,2-*a*]pyridinium salts to be isolated, the best yields being obtained by using triethylamine as base under the reaction conditions indicated in Tables 2-5.

As it has been previously observed [9], aprotic solvents, as acetone or even acetone/ethanol mixtures, precluded the condensation of the bicyclic substrates as **7** or **8** due to the formation of the highly stabilised anhidrobase. More polar solvents, in contrast, increase the contribution of the betaine form with charge separation (Scheme 1).

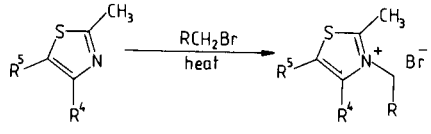
Scheme 1



In contrast to that previously observed for pyridinium substrates [8], 1-phenacyl derivatives did not show any trace of intramolecular cyclization product, as observed by ^{1}H nmr on the crude reaction mixture. Additional experiments, however, showed that intramolecular cyclization took place when compounds **1**, **3**, **5** and **7** were refluxed in ethanol in the presence of triethylamine without dicarbonyl, producing previously described pirrolo[2,1-*b*]thiazoles

Table 1

Substituted-2-methylthiazolium Salts

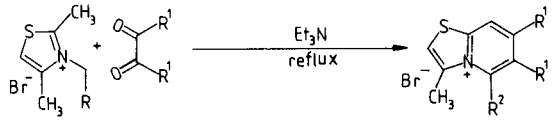


Compound	R	R^4	R^5	Reaction time (hours)	Yield (%) [a]	Mp (°C) [b]	Lit mp (°C)
1	COC_6H_5	CH_3	H	5	83	225-226	159-160, [c], 235 [d]
2	$CO_2C_2H_5$	CH_3	H	6	96	203-205	—
3	COC_6H_5	CH_3	CH_3	5	70	214-216	203-204 [c]
4	$CO_2C_6H_5$	CH_3	CH_3	7	50	170-171	—
5	COC_6H_5	C_6H_5	H	64	72	220-222	—
6	$CO_2C_2H_5$	H		No reaction after 72 hours			
7	COC_6H_5		-(CH=CH)$_2$-	21	57	223-224	
8	$CO_2C_2H_5$		-(CH=CH)$_2$-	22	50	199-201	190-191 [e]

[a] In isolated pure product. [b] Crystallization from ethanol-ether. [c] Described in ref [15]. [d] Described in ref [16]. [e] Described in ref [17].

Table 2

Thiazolo[3,2-*a*]pyridinium Salts from **1** and **2**

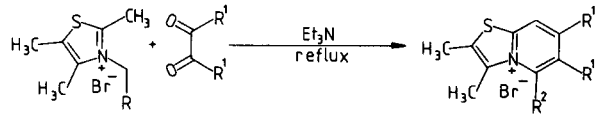


Compound	R	R¹	R¹	R²	Solvent	Reaction time (minutes)	Yield (%) [a]	Mp (°C, dec) [b]
9	COC_6H_5	CH_3	CH_3	H	Acetone	20	78	304-306
10	COC_6H_5	C_6H_5	C_6H_5	H	Acetone-ethanol	120	27	298-300
11	COC_6H_5	3-O_2N-C_6H_4	3-O_2N-C_6H_4	H	Acetone	60 [c]	70	317-319
12	COC_6H_5	naphth-1,8-diyl [e]		COC_6H_5	Acetone-ethanol	60	38	350
13	COC_6H_5	diphenyl-*o*,*o*'-diyl			Acetone-ethanol	No reaction after 120 minutes [d]		
14	$CO_2C_2H_5$	naphth-1,8-diyl [e]		$CO_2C_2H_5$	Acetone-ethanol	120	74	185

[a] In isolated pure product. [b] Compounds **9**, **10** and **14** were crystallized from ethanol and **11** from methanol-ether. [c] Reaction was carried out at room temperature. [d] Dicarbonyl compound was recovered unchanged in more than 85% yield. [e] Produces phenanthrene ring.

Table 3

Thiazolo[3,2-*a*]pyridinium Salts from **3** and **4**

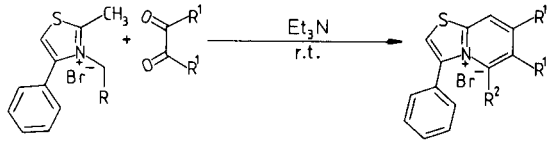


Compound	R	R¹	R¹	R²	Solvent	Reaction time (minutes)	Yield (%) [a]	Mp (°C, dec) [b]
15	COC_6H_5	CH_3	CH_3	H	Acetone	30	74	274-276
16	COC_6H_5	C_6H_5	C_6H_5	H	Acetone	20	22	328-331
17	COC_6H_5	3-O_2N-C_6H_4	3-O_2N-C_6H_4	H	Acetone	105 [c]	55	261-263
18	COC_6H_5	naphth-1,8-diyl [d]		COC_6H_5	Acetone-ethanol	30	38	314-317
19	$CO_2C_2H_5$	naphth-1,8-diyl [d]		$CO_2C_6H_5$	Acetone-ethanol	50	62	210

[a] In isolated pure product. [b] Crystallization from ethanol. [c] Reaction was carried out at room temperature. [d] Produces phenanthrene ring.

Table 4

Thiazolo[3,2-*a*]pyridinium Salts from **5**

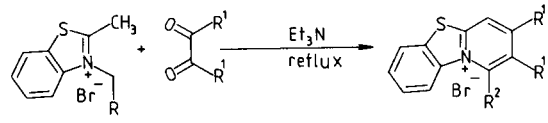


Compound	R	R¹	R¹	R²	Solvent	Reaction time (minutes)	Yield (%) [a]	Mp (°C, dec) [b]
20	COC_6H_5	C_6H_5	C_6H_5		Acetone	No reaction after 120 min at reflux [c]		
21	COC_6H_5	3-O_2N-C_6H_4	3-O_2N-C_6H_4	H	Acetone	120	23	322-325
22	COC_6H_5	diphenyl-*o*,*o*'-diyl			Acetone	No reaction after 120 min at reflux [c]		
23	COC_6H_5	naphth-1,8-diyl [d]		COC_6H_5	Acetone	60	25	> 350

[a] In isolated pure product. [b] Compound **21** crystallized from ethanol-ether and **23** from ethanol-water. [c] Dicarbonyl compound was recovered unchanged in more than 85% yield. [d] Produces phenanthrene ring.

Table 5

Benzothiazolo[3,2-*a*]pyridinium Salts from **7** and **8**

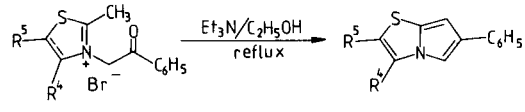


Compound	R	R¹	R¹	R²	Solvent	Reaction time (minutes)	Yield (% [a]	Mp (°C, dec) [b]
24	COC_6H_5	C_6H_5	C_6H_5		Ethanol	No reaction after 240 minutes [c]		
25	$CO_2C_2H_5$	C_6H_5	C_6H_5		Ethanol	No reaction after 240 minutes [c]		
26	COC_6H_5	3-O_2N-C_6H_4	3-O_2-C_6H_4	H	Ethanol	180	27	315-318
27	COC_6H_5	naphth-1,8-diyl [d]		COC_6H_5	Ethanol	240	32	> 350
28	$CO_2C_2H_5$	naphth-1,8-diyl [d]		H	Ethanol	240	32	> 350

[a] In isolated pure product. [b] Compound **26** crystallized from ethanol and **27**, **28** from acetic acid. [c] Dicarbonyl compound was recovered unchanged in more than 85% yield. [d] Produces phenanthrene ring.

Table 6

Pirrolo[2,1-*b*]thiazoles from Intramolecular Cyclization of **1**, **3**, **5** and **7**



Compound	R^4	R^5	Reaction time (minutes)	Yield (% [a]	M,p (°C) [b]	Lit Mp (°C) [c]
29	CH_3	H	180	71	70-71	71
30	CH_3	CH_3	120	97	122-133	120
31	C_6H_5	H	50	79	142-143	—
32	-(CH=CH)$_2$-		240	66	125-127	127-129

[a] In isolated pure product. [b] Crystallization from ethanol. [c] Compound **29** described in ref [18], **30** in [19] and **32** in [20].

with yields from 66-97% (Table 6). Novel compound **31** is described in the experimental.

Microanalytical and spectroscopic data of the compounds **1-28** are presented in Table 7.

EXPERIMENTAL

The melting points were determined in open capillary tubes and are uncorrected. Spectra were recorded with a Perkin Elmer 1310 grating ir spectrophotometer and with a Bruker WP 60 CW (60 MHz) ^{1}H nmr spectrometer. The 1,2-dicarbonyls were either from commercial sources or prepared from previously described methods as 3,3'-dinitrobenzil [11]. 2,4-Dimethylthiazole, 2,4,5-trimethylthiazole [12], 2-methyl-5-phenylthiazole [13] and 2-methylbenzothiazole [14] were also prepared by literature methods.

General Procedure for Preparation of 3-Substituted 2-Methylthiazolium Salts (Table 1, Compounds **1-8**).

A mixture of the corresponding thiazole (0.02 mole) and the halide (0.022 mole) was stirred at 50° (75° for compound **5**) in a water bath for the time indicated in Table 1. The salt was filtered off as a white powder and washed with ether. Finally, it was crystallized from ethanol-ether.

General Procedure for the Preparation of Thiazolo[3,2-*a*]pyridinium Salts (Tables 2-5, Compounds **9-28**).

To a mixture of the corresponding 2-methylthiazolium salt (1.5 mmoles), and the 1,2-dicarbonyl (1.5 mmoles) suspended in 15 ml of the solvent, as described in Tables 2-5, 0.16 g of triethylamine (1.6 mmoles) was added. Reflux was maintained for the time indicated. A precipitate appeared which was filtered, triturated with 3 ml of water and crystallized as described.

3,6-Diphenylpirrolo[2,1-*b*]thiazole (**29**).

To 1.12 g of 3-benzoylmethyl-2-methyl-4-phenylthiazolium bromide **5** (3 mmoles) suspended in 30 ml of ethanol, 0.32 g of triethylamine (3.22 mmoles) were added, and the mixture was refluxed for 50 minutes. Then, it was concentrated to the half of its volume, cooled to 0°, and the solid precipitate was filtered and crystallized from ethanol, yield 79%, mp 142-143°; ir (bromoform): 1595, 1480, 1455, 1435, 1390, 1280, 1060,

Table 7

Analytical and Spectroscopic Data from Compounds **1-28**

Compound	Molecular formula (Mw)	Microanalyses Found (%)/Required (%) C	H	N	IR (Bromoform) ν [cm^{-1}]	^{1}H-NMR δ [ppm]
1	$C_{13}H_{14}BrNOS$	49.78	4.74	4.56	2900, 1675, 1600, 1580,	2.40 (s, 3H), 2.93 (s, 3H), 6.42 (s, 2H), 7.5-7.8 (m, 3H), 7.96
	(312.2)	50.00	4.52	4.49	1450, 1220	(s, 1H), 8.0-8.3 (m, 2H)
2	$C_9H_{14}BrNO_2S$	38.66	5.44	5.24	1760, 1565, 1425, 1350	1.25 (t, 3H), 2.50 (s, 3H), 3.03 (s, 3H), 4.30 (q, 2H), 5.58
	(280.2)	38.58	5.04	5.00		(s, 2H), 8.00 (s, 1H)
4	$C_{10}H_{16}BrNO_2S$	40.93	5.78	5.03	2900, 1730, 1595, 1425	1.20 (t, 3H), 2.33 (s, 3H), 2.45 (s, 3H), 2.95 (s, 3H), 4.20
	(294.2)	40.82	5.48	4.76	1360, 1270, 1205	(q, 2H), 5.50 (s, 2H)
5	$C_{18}H_{16}BrNOS$	57.38	4.62	3.89	2900, 1680, 1590, 1570	3.10 (s, 3H), 6.20 (s, 2H), 7.3-8.1 (m, 10H), 8.30 (s, 1H)
	(374.3)	57.76	4.31	3.74	1470, 1440, 1335, 1220	
9	$C_{10}H_{12}BrNS$	46.11	5.05	5.21	1610, 1450, 1375, 1290	2.62 (s, 3H), 2.67 (s, 3H), 2.80 (s, 3H), 7.75 (s, 1H), 8.28
	(258.2)	46.51	4.69	5.42		(s, 1H), 8.72 (s, 1H)
10	$C_{20}H_{16}BrNS$	62.67	4.29	3.26	2900, 1600, 1450, 1425	2.86 (s, 3H), 7.35 (s, 10H), 7.90 (s, 1H), 8.50 (s, 1H), 8.86
	(382.3)	62.83	4.22	3.66	1375, 1285	(s, 1H)
11	$C_{20}H_{14}BrN_3O_4S$	50.51	3.00	8.66	1615, 1515, 1480, 1450	2.93 (s, 3H), 7.69 (s, 4H), 8.02 (s, 1H), 8.34 (s, 4H), 8.75
	(472.3)	50.86	2.99	8.90	1340, 1300	(s, 1H), 9.15 (s, 1H)
12	$C_{25}H_{16}BrNOS$	64.98	3.71	3.24	2920, 1655, 1605, 1585,	2.62 (s, 3H) 7.3-7.4 (m, 12H), 8.90 (s, 1H)
	(458.4)	65.44	3.52	3.06	1420, 1235, 1220	
14	$C_{21}H_{16}BrNO_2S\cdot 2H_2O$	54.13	4.22	2.93	2880, 1710, 1605, 1420	1.63 (t, 3H), 2.87 (s, 3H), 4.93 (q, 2H), 7.5-8.3 (m, 7H),
	(462.4)	54.55	4.36	3.03	1360, 1300, 1280, 1230	8.67 (s, H)
15	$C_{11}H_{14}BrNS$	48.38	5.48	4.83	2900, 1615, 1465, 1430,	2.58 (s, 3H), 2.67 (s, 9H), 8.15 (s, 1H), 8.60 (s, 1H)
	(272.2)	48.53	5.18	5.15	1380, 1275	
16	$C_{21}H_{18}BrNS$	63.29	4.78	3.47	2900, 1615, 1455, 1385,	2.73 (s, 6H), 7.30 (s, 10H), 8.38 (s, 1H), 8.75 (s, 1H)
	(396.3)	63.64	4.58	3.53	1220	
17	$C_{21}H_{16}BrN_3O_4S\cdot 2H_2O$	50.20	3.30	8.12	2890, 1615, 1510, 1480,	2.78 (s, 3H), 2.82 (s, 3H), 7.5-7.8 (m, 4H), 8.1-8.4 (m, 4H),
	(504.3)	50.01	3.60	8.33	1450, 1330	8.65 (s, 1H), 9.05 (s, 1H)
18	$C_{26}H_{18}BrNOS$	65.86	3.86	2.70	2940, 1655, 1610, 1590,	2.50 (s, 3H), 2.60 (s, 3H), 7.4-8.5 (m, 11H), 8.92 (s, 1H)
	(472.4)	66.10	3.84	2.97	1420, 1255, 1225	
19	$C_{22}H_{16}BrNO_2S$	59.68	4.25	3.48	1730, 1600, 1425, 1405,	1.60 (t, 3H), 2.70 (s, 3H), 2.73 (s, 3H), 4.80 (q, 2H), 7.6-8.5
	(440.3)	60.00	4.12	3.18	1300, 1245, 1220, 1200	(m, 6H), 8.80 (s, 1H)
21	$C_{25}H_{16}BrN_3O_4S$	55.86	3.05	7.57	1610, 1515, 1450, 1340,	7.72 (s, 8H), 7.92 (s, 1H), 8.1-8.7 (m, 5H), 8.85 (s, 1H), 9.05
	(534.4)	56.18	3.02	7.86	1290	(s, 1H)
23	$C_{30}H_{18}BrNOS$	68.88	3.61	2.92	2885, 1660, 1605, 1415,	7.4-8.6 (m, 17H), 9.10 (s, 1H)
	(520.4)	69.24	3.49	2.69	1250, 1225	
26	$C_{23}H_{14}BrN_3O_4S$	53.95	2.97	7.95	1620, 1520, 1450, 1345,	7.4-8.4 (m, 12H), 8.80 (s, 1H), 9.88 (s, 1H)
	(508.3)	54.34	2.78	8.27	1305, 1270	
27	$C_{28}H_{16}BrNOS$	68.09	3.20	2.85	2880, 1655, 1600, 1580,	7.4-8.6 (m, 15H), 9.10 (s, 1H)
	(494.4)	68.02	3.26	2.83	1410, 1310, 1260, 1205	
28	$C_{21}H_{12}BrNS$	64.19	3.12	3.62	2880, 1700, 1440, 1405,	7.2-8.3 (m, 11H), 9.30 (s, 1H)
	(390.3)	64.62	3.10	3.59	1270, 1200	

1015, 810, 760, 740, 715 cm^{-1}; pmr (hexadeuteriodimethylsulfoxide): δ 7.08-7.90 (m, 12H), 6.73 (s, 1H) ppm.

Anal. Calcd. for $C_{13}H_{14}BrNOS$: C, 50.00; H, 4.52; N, 4.49. Found: C, 49.78; H, 4.74; N, 4.56.

Acknowledgements.

Financial support from Comision Asesora de Investigación Cientifica y Técnica (C.A.I.C.Y.T., plan 1099) is gratefully acknowledged.

REFERENCES AND NOTES

[1] O. Westphal, K. Jahn and W. Heffe, *Arch. Pharm.*, **294**, 37 (1961).

[2] Dr. A. Wander A-G, British Patent 916,507, Jan. 23 (1963); *Chem. Abstr.*, **59**, 3900 (1963).

[3] Dr. A. Wander A-G, Swiss Patent 417,601, Feb. 15 (1967); *Chem. Abstr.*, **67**, 90696 (1967).

[4] F. Krohnke, H. Schnegelberg and W. Weis, *Chem. Ber.*, **97**, 3566 (1964).

[5] T. H. Hough and G. Jones, *J. Chem. Soc. (C)*, 1082 (1968).

[6] C. R. Costin, U. S. Patent 4,046,766, Sept. 6 (1977); *Chem. Abstr.*, **87**, 152907 (1977).

[7] G. Gonzalez Trigo, M. E. Fombella, J. Alvarez-Builla, B. del Castillo, A. Garcia de Marina and S. Avila, *An. Quim.*, **77C**, 225 (1981).

[8] J. Alvarez-Builla, G. Gonzalez Trigo, J. Ezquerra and M. E. Fombella, *J. Heterocyclic Chem.*, **22**, 681 (1985).

[9] J. Ezquerra and J. Alvarez-Builla, *J. Heterocyclic Chem.*, submitted.

[10] O. Westphal and A. Joos, *Angew. Chem., Int. Ed. Engl.*, **8**, 74 (1969).

[11] B. Kelein, *J. Am. Chem. Soc.*, **63**, 1474 (1941).

[12] R. P. Kurjy and E. V. Brown, *J. Am. Chem. Soc.*, **74**, 5778 (1952).

[13] J. P. Wetherill and R. M. Hann, *J. Am. Chem. Soc.*, **56**, 970 (1934).

[14] A. W. Hofmann, *Ber.*, **13**, 1230 (1887).

[15] V. K. Kibirev and F. S. Babichin; *Ukr. Khim. Zh.*, **30**, 488 (1964); *Chem. Abstr.*, **61**, 5629 (1964).

[16] C. T. Bahner, D. Pickeris and D. Bettisbales, *J. Am. Chem. Soc.*, **70**, 1652 (1948).

[17] I. Ciociou, C. H. Budeanu and I. Zugravesku, *Bul. Inst. Politech. Iasi, Sect. 2*, **24**, 109 (1978).

[18] H. Kondo and F. Nasagawa, *J. Pharm. Soc. Japan*, **57**, 308 (1937).

[19] T. Pyl, H. Gille and A. Nusch, *Ann. Chem.*, **676**, 139 (1964).

[20] F. Krohnke and R. Friedrich, *Chem. Ber.*, **96**, 1195 (1963).