Thiomethoxymethylation of 5-aryloxytetrazoles via modified Swern reagents

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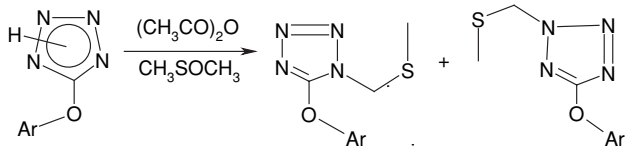
The modified Swern oxidation of 5-aryloxytetrazole (Ar- = 4-NO_2-C_6H_4-, C_6H_5-, 2,6-dimethoxy-C_6H_3-) rings is described using combination of dimethyl sulfoxide with dicyclohexylcarbodiimide (DCC), oxalyl chloride or trifluoroacetic anhydride. The product observed at 1- and/or 2-position of tetrazole rings and yield depends on the substrate, electronic effect of aryloxy group and reaction conditions. It was possible to introduce a thiomethoxymethyl group at 1 and 2-position of tetrazole via rearrangement of Swern intermediate.

Keywords: modified Swern oxidation, mechanism of thiomethoxymethylation, aryloxytetrazoles



Ar-	2 %	3 %
a (4- NO_2-C_6H_4-)	30	20
b (C_6H_5-)	26	16
c (2,6-dimethoxy-C_6H_3-)	14	8

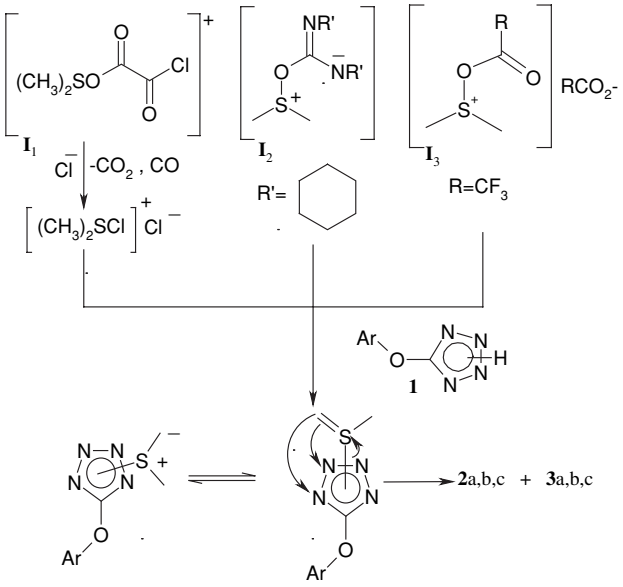
Scheme 1

Tetrazole derivatives possess various biological activities due to the fact that a tetrazole functional group serves successfully as a metabolically stable replacement for carboxylic acid. In most cases, the methods of preparation and biological activity have been the point of interest.[1-9] Tetrazoles have been widely used in various reactions such as: protection reactions,[10,11] methylation,[12] organometallic,[13,14] thermolysis and photolysis,[15-17] insertion reaction via nitrenes,[8] and more.[1-17]

Dabbagh and coworkers[4b-9] investigated the interconversion of the 1-, 2- and 5- substituted tetrazoles and showed that 1- and 2- alkoxycarbonyl tetrazoles and the imidoyl azides are in equilibrium. The equilibrium of tetrazoles and the azide depends on solvent, temperature and the electron–withdrawing nature of the functional group to which the tetrazole ring is fused. Recently, they reported the mechanism and kinetics of reactions of 1- and 2-alkoxycarbonyl-5-aryloxytetrazoles in solution and in solid phase.[6,9]

The development of the mild, but efficient, dimethyl sulfoxide (DMSO)-dicyclohexylcarbodiimide (DCC) method for the oxidation of hydroxyl groups and ortho thiomethoxymethylation of phenols and aniline opened the gates to the discovery of wide range of new reagents and reactions, today, known as Swern oxidation.[18-28]

Recently, numerous new and modified version of Swern oxidation is reported utilizing dodecyl methyl sulfide (Dod-S-Me),[29] DMSO-$Ph_3P.X_2$ complex,[30] fluorous Swern,[31] DMSO-oxalyl chloride,[32] Swern oxidation of tryptamine derivative[33], multi-polymer Swern oxidation reaction system,[34,35] efficient preparation of imidazole[1,2-*b*]pyridazines under Swern oxidation conditions,[36] use of a recyclable, polystyrene bound sulfoxide,[37] oxidation of carbamate-protected alkylhydrazines to the corresponding hydrazone,[38] and application to the synthesis of natural products.[39] Katritzky and coworkers introduced a novel and efficient method to functionalised ketones via 1-(benzotriazol-1-yl)alkyl methyl thioethers.[40,41]



Scheme 2

Recently, we developed a new method to prepare 1-thiomethoxymethyl-5-(4-nitro phenoxy) tetrazole (**2a**) by the direct thermal decomposition of 2-methoxycarbonyl-5-(4-nitrophenoxy) tetrazole in dimethyl sulfoxide with good yield. Alternatively, a mixture of **2a**, 2-thiomethoxy- methyl-5-(4-nitrophenoxy) tetrazole (**3a**), 1-thiomethoxymethyl-5-phenoxy tetrazole (**2b**), 2-thiomethoxymethyl-5-phenoxy tetrazole (**3b**), 1-thiomethoxymethyl-5-(2,6-dimethoxy-phenoxy) tetrazole (**2c**) and 2-thiomethoxymethyl-5-(2,6-dimethoxyphenoxy) tetrazole (**3c**) were produced by the reaction of tetrazoles **1a**, **1b** and **1c** (**a** = 4-NO_2–C_6H_4-, **b** = C_6H_5-, **c** = 2,6-dimethoxy-C_6H_3-) with acetic anhydride in the presence of dimethyl sulfoxide, Scheme 1.[4c]

In this work, oxidation of 5-aryloxytetrazole (**1**) rings is described using modified Swern regents (dimethyl sulfoxide with DCC, oxalyl chloride and trifluoroacetic anhydride). The introduction of a thiomethoxymethyl group at 1- and/or 2-position of tetrazole (**2a,b,c** and **3a,b,c**) via reaction and rearrangement of Swern intermediate ($\mathbf{I}_1$, $\mathbf{I}_2$ and $\mathbf{I}_3$) is sought, Scheme 2.

Experimental

Materials and general experimental procedure: 2,6-Dimethoxy phenol, phenol, 4-nitro phenol, bromine, sodium cyanide, DMSO, DCC, trifluoroacetic anhydride, oxalyl chloride, sodium azide and fuming nitric acid as starting materials obtained from commercial

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Table 1 Relative rate (%) of formation of 1- and 2- tetrazols in the thiomethoxymethylation reactions

Comp no.	Products	MCPNPT[b]	Ac_2O[c]	DCC[d]	DCC[e]	OC[f]	TFAA[g]
1a	**2a**	30	30	33	37	43	49
	3a	0	20	22	25	33	40
1b	**2b**	0	26	29	32	38	44
	3b	0	16	18	21	27	34
1c	**2c**	0	14	16	18	23	28
	3c	0	8	9	11	14	19

[a]Isolated yields. [b]2-Methoxycarbonyl-5-*p*-nitrophenoxy tetrazole, ref. 4c. [c]Acetic anhydride, at 55–60 °C, ref. 4c. [d]Dicyclohexylcarbodiimide, at room temperature. [e]At 50–55 °C. [f]Oxalyl chloride at dry ice–ethanol temperature. [g]Trifluoroacetic anhydride at dry ice–ethanol temperature.

Table 2 The total yields (%) obtained in the methylthiomethylation of tetrazols[a]

Comp no.	Products	MCPNPT[a]	Ac_2O[c]	DCC[d]	DCC[e]	OC[f]	TFAA[g]
1a	**2a,3a**	30	50	55	62	76	89
1b	**2b,3b**	0	42	47	53	65	78
1c	**2c,3c**	0	22	25	29	37	47

[a]See footnotes to Table 1.

sources were used without further purification. Cyanogen bromide[42] and phenyl cyanate[43] synthesised from related references in laboratory.[4b-9]

5-Aryloxytetrazoles [Ar = 4-NO_2-C_6H_4-, C_6H_5-, 2,6-$(CH_3O)_2$-C_6H_3-] were synthesised by the procedures reported earlier.[9,44,45]

Reaction of 5-(4-nitrophenoxy) tetrazole (1a) with DMSO in DCC

Typical procedure A. A solution of 1 g of DCC in 1 ml DMSO was added to a solution of 1 g of **1a** in 10 ml of CH_2Cl_2 during 20 min period. The mixture was stirred at room temperature for 24 h. The reaction mixture washed with water and diethyl ether, solvent was evaporated to produce a mixture of 1-thiomethoxymethyl-5-(4-nitrophenoxy) tetrazole (**2a**) and 2-thiomethoxymethyl-5-(4-nitrophenoxy) tetrazole (**3a**) which separated by silica gel column chromatography (solvent, 85:15, ethyl acetate/cyclohexane), Tables 1–4.

Typical procedure B. This procedure was identical with the procedure A except the temperature of the reaction mixture was kept at 50–55 °C (in an oil bath), Tables 1–4.

Conclusion

Triflouroacetic acid is the reagent with highest total yield (89%) for the oxidation of tetrazole carrying electron-withdrawing group (NO_2) with the least selectivity (**2a/3a** = 1.2). In contrast, aceticanhydride and DCC (at room temperature) show higher selectivity (**2c/3c** = 1.75 and 1.78, respectively) for the oxidation of tetrazole carrying electron-donating group (CH_3O) with the lowest yields (22% and 25%, respectively). 2-Methoxycarbonyl-5-*p*-nitrophenoxy tetrazole (**1a**) is the most selective reagent producing only 1-tetrazole **2a** (30% yield).

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Table 3 The fraction of 1-tetrazole over 2-tetrazole (adducts) obtained from Swern and modified Swern oxidations

Reagents	2a/3a	2b/3b	2c/3c
Ac_2O	1.50	1.63	1.75
DCC – RT	1.50	1.61	1.78
DCC – 55°C	1.48	1.52	1.64
OC	1.30	1.41	1.64
TFAA	1.23	1.29	1. 47
MCPNPT	[b]	[c]	[c]

[a]See footnotes to Table 1. [b]Only 1-tetrazol was produced. [c]No tetrazole was produced.

Table 4 Melting point and mass spectroscopy analysis of methylthiomethylated tetrazols

Products	M.p./°C	Mass(EI) *m/z*(relative intensity%)[a]
2a	67–68	269 ([M^++2] (10), 267 [M^+] (47), 192 (75), 122 (28), 101(90), 76 (33), 61 (100).
3a	92–94	269 [M^++2] (2.6), 267 [M^+] (65), 192 (36), 191 (40), 22(30), 75 (28), 61 (100).
2b	Viscous	224 [M^++2] (0.64), 222 [M^+] (14), 147 (70), 101 (79), 77 (100), 74 (23), 61 (58)
3b	64–66	224 [M^++2] (0.64), 222 [M^+] (14), 176 (27), 147 (16), 101 (22), 77 (67), 61 (100).
2c	78	284 [M^++2] (1.7), 282 [M^+] (43), 207 (34), 179 (27), 165 (70), 122 (52), 107 (88), 101 (100), 61 (68).
3c	90	284 [M^++2] (0.6), 282 [M^+] (15), 281 (20), 236 (100), 151 (73), 140 (39), 107 (59).

[a]See footnotes to Table 1 and Schemes of 1 and 2. For further characterisation see ref. 4c.

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