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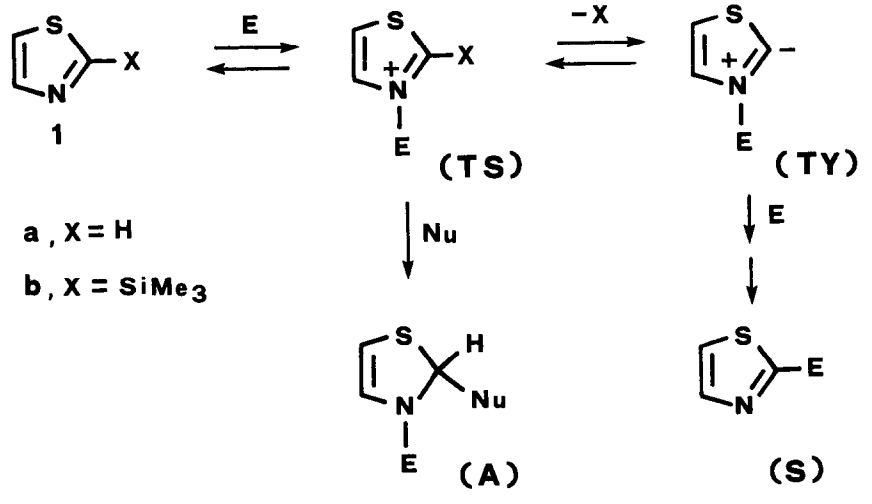
REGIOSELECTIVE CARBON-CARBON BOND FORMATION AT C_2 OF 1,3-THIAZOLE BY REACTION OF N-ETHOXYCARBONYLTHIAZOLIUM CHLORIDE WITH C-NUCLEOPHILES

Alessandro Dondoni,* Tiziano Dall'Occo, Giancarlo Fantin, Marco Fogagnolo and Alessandro Medici

Laboratory of Organic Chemistry, Faculty of Science, University of Ferrara, Ferrara, Italy

Summary : N-Ethoxycarbonylthiazolium chloride generated in situ from 1,3-thiazole and ethyl chloroformate, treated with lithium carbanions of esters, Grignard reagents, silyl enol ethers and esters, undergo nucleophilic addition at C_2 affording the corresponding 2-substituted N-ethoxycarbonylthiazolines.

We have recently described[1] the reactions of 1,3-thiazoles (1) (X = H, $SiMe_3$) with C-electrophiles (E), namely ketenes, acyl chlorides and aldehydes, to give the corresponding substitution product (S) at C_2. The reactions have been interpreted to occur via the N-thiazolium ylide (TY) (path a) in equilibrium with the N-thiazolium salt (TS) initially formed. In some cases the product (S) was accompanied by the adduct (A) derived from the coupling between (TS) and (TY). This indicated that the activation of 1 gained by quaternization of its nitrogen could



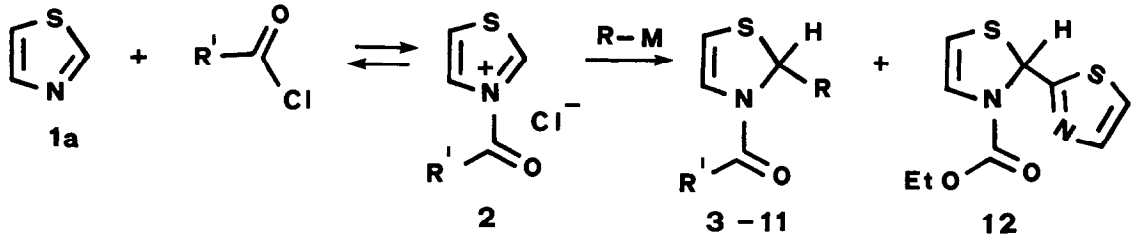
be exploited to perform reactions with either electrophiles (E) (path a) or nucleophiles (Nu) (path b) under proper conditions. We have therefore investigated

the reactivity of the in situ generated N-thiazolium salts with C-nucleophiles and we report here the results from selected examples.

Treatment of 1,3-thiazole (1a) in THF at 0°C with ethyl chloroformate produced N-ethoxycarbonyl-1,3-thiazolium chloride (2a) as a white precipitate.[2] Addition of lithium diethyl malonate in the same solvent and warming up to room temperature, gave N-ethoxycarbonyl-2-dicarbethoxymethan-1,3-thiazoline (3a) in good yield and the thiazol-2-yl thiazoline (12) as a by-product (Table 1). This indicates that lithium malonate adds selectively to C_2 of thiazolium salt 2a to give 3a whilst the thiazolium ylide (TY) inevitably present in the reaction mixture, by the same reaction leads to 12.

The reaction between 1a and lithium malonate appeared conditioned by the nature of the acyl chloride (R'COCl) employed for the quaternization.[3] In fact, using acetyl chloride (R' = Me) the yield of the corresponding N-acetylthiazoline (3b) lowered to 31%, while with dichloroacetyl (R' = CH_2Cl) and trichloroacetyl chloride (R' = CCl_3), no addition products of the malonate ion to the N--acylthiazolium salts (2c) and (2d) were isolated. In these cases the nucleophile attacks preferentially the carbonyl carbon of 2 with consequential displacement of 1,3-thiazole (1a).[4] This variation of the site of nucleophilic addition in 2 may be explained in terms of hard and soft centers in the reactants.[5]

The actual selectivity in favour of the attack at C_2 by the malonate ion in N-ethoxycarbonylthiazolium chloride (2a) pointed to ethyl chloroformate as the



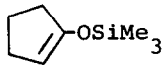
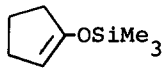
a, R' = OEt; b, R' = Me; c, R' = $CHCl_2$; d, R' = CCl_3

3a, R = $CH(CO_2Et)_2$; 3b, R = $CH(CO_2Et)_2$; 4a, R = $CH(COMe)CO_2Me$; 5a, R = $CH_2(CH_2)_4CH_3$; 6a, R = $CH{=}CH_2$; 7a, R = $C{\equiv}C(CH_2)_6CH_3$; 8a, R = CH_2COPh; 9a, R = cyclopentan-2-one; 10a, R = $CH(Me)CO_2Me$; 11a, R = $CH(Ph)CO_2Me$

activator of choice for the reaction of thiazoles with nucleophiles. The same criterium has been recently applied to pyridines and isoquinolines.[6] The results from the reactions of 2a with three types of organometallic reagents, namely li-

thium carbanion of esters, Grignard reagents, silyl enol ethers and esters, are collected in Table 1. Although the reaction conditions were not optimized, the yields of thiazolines 3a - 11a were satisfactory in all the cases examined. It is worth noting that the best results were obtained with silyl enol ethers and esters[7] in methylene dichloride as a solvent; therefore these silylated alkenes appear to be very convenient reactants toward 2a as stabilized equivalents of enolates and α-carboxylate anions.

TABLE 1. Reactions[a] of 1,3-thiazole (1a) with Organometallic Reagents (R-M) via N-Ethoxycarbonyl-1,3-thiazolium Chloride (2a)

R-M	(1a) : R-M	Time/h	Solvent	Products[b] (yield %)	
$(EtO_2C)_2CHLi$	1 : 1	3	THF	3a(59)	12(5)
$MeCO(MeCO_2)CHLi$	1 : 1	3	THF	4a[d](46)	12(4)
$CH_3(CH_2)_5MgBr$	1 : 1.5	1	THF	5a(41)	12[c]
$CH_2=CHMgBr$	1 : 1.5	1	THF	6a(15)	12[c]
$CH_3(CH_2)_4C\equiv CMgBr$	1 : 1.5	1	THF	7a(40)	12[c]
$CH_2=C(Ph)OSiMe_3$	1 : 1.2	4	Et_2O	8a (18)	
$CH_2=C(Ph)OSiMe_3$	1 : 1.2	2	CH_2Cl_2	8a[e](82)	
	1 : 1.2	4	Et_2O	9a[d](20)	
	1 : 1.2	2	CH_2Cl_2	9a[d,e](75)	
$MeCH=C(OMe)OSiMe_3$[f]	1 : 1.2	3	CH_2Cl_2	10a[d](80)	
$PhCH=C(OMe)OSiMe_3$[f]	1 : 1.2	3	CH_2Cl_2	11a[d](84)	

[a]All reactions were carried out by addition of R-M to 2a (from 1,3-thiazole (1a) and 1 equiv. of EtOCOCl at 0°C) followed by warming-up to room temperature. After washing with water and evaporation of the solvent, the products were isolated by chromatography. [b]All products were characterized by spectral data (IR, NMR, MS) and elemental analyses (C,H,N). [c]Detected by NMR. [d]Mixture of unseparated diastereomers in variable ratios. [e]A careful work-up of the reaction mixture allowed the isolation (5-20%) of an intermediate arising from the 1,2-addition of the thiazolium chloride (2a) to the silyl enol ether. [f]Prepared according to ref. 8.

The thiazolines 4a - 11a appear to be useful intermediates in thiazole chemistry. For instance the oxidative deacylation of 10a with o-chloranyl (CH_2Cl_2, 0°C, 1h) led to methyl 1,3-thiazol-2-yl-propionate (13) (oil, 40%). This constitutes a simple way for the introduction at C_2 of the thiazole ring of the α-pro-

pionic ester group, a well known functionality present in many non-steroidal antiinflamatory agents.[9] Therefore, we think that for the variety of nucleophiles which can be employed, the reaction described here is a new carbon-carbon bond forming process at C_2 of the thiazole ring which should enter in the current synthetic methodology.

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References and Notes

1. a) A. Medici, P. Pedrini, and A. Dondoni, J. Chem. Soc. Chem. Commun., 655 (1981). b) A. Medici, G. Fantin, M. Fogagnolo, and A. Dondoni, Tetrahedron Lett., 24, 2901 (1983). c) A. Medici, G. Fantin, M. Fogagnolo, P. Pedrini, and A. Dondoni, J. Org. Chem., 49, 590 (1984).
2. The isolation of 2a was not convenient because the salt was moisture sensitive.
3. Treatment of N-methylthiazolium iodide with lithium malonate (THF, 0°C, 3h) or with a silyl enol ester (O-trimethylsilyl,O-methyl-phenylketeneacetal) (CH_2Cl_2, 0°C, 3h) did not give reaction products.
4. For instance, from the salt 2d (R' = CCl_3) and lithium malonate generated from $(i\text{-Prop})_2NLi - CH_2(CO_2Et)_2$ the product observed (TLC) were 1a and the amide $R'CON(Prop\text{-}i)_2$; generation of the lithium malonate from BuLi - $CH_2(CO_2Et)_2$ gave 1a, unaltered diethylmalonate and several unidentified products.
5. R. Yamaguchi, Y. Nakazono, and M. Kawanisi, Tetrahedron Lett., 24, 1801 (1983).
6. K. Akiba, K. Araki, M. Nakatani, and M. Wada, Tetrahedron Lett., 24, 4961 (1983); ibid., 24, 5269 (1983).
7. The diastereoselectivity of these reactions was low and varied depending on the substituent (silyl enol ether) and/or the E,Z configuration (silyl enol esters). However, the reaction of 1a with O-trimethylsilyl,O-methyl-phenylketeneacetal, gave a 9:1 mixture of the two diastereomeric esters 11a.
8. C. Ainsworth, F. Chen, and Yu-N. Kuo, J. Organometal. Chem., 46, 59 (1972). Y. Kita, J. Haruta, J. Segawa, and Y. Tamura, Tetrahedron Lett., 44, 4311 (1979).
9. P. J. Piper, and J. R. Vane, Nature (London), 223, 29 (1969). W. Coyne in "Medicinal Chemistry", A. Burger, Ed. 3rd ed, Wiley, New York, N. Y. 1970, p. 953.

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