HETEROCYCLES, Vol 27, No 11, 1988

THE LIGHT INDUCED CONVERSION OF THIENO[2,3-c]ISOTHIAZOLES INTO THIOPHENES

Antonino Corsaro,[a*] Francesco Guerrera,[b*] Maria C. Sarvà,[b] and Maria A. Siracusa[b]

[a] Dipartimento di Scienze Chimiche,[b] Istituto di Chimica Farmaceutica e Tossicologica, Università di Catania, Viale A. Doria 6, I-95125 Catania, Italy

Abstract - The sun light induced conversion of thieno[2,3-c]isothiazoles **1a-d** into thiophenes **2a-d** with loss of elemental sulfur is reported. A presumable mechanism for the thiophene nucleus formation is discussed to involve the opening of the two heterocyclic rings with formation of an open-chain valence bond isomer through the initial homolytic cleavage of the isothiazole N-S linkage.

The thieno[2,3-c]isothiazole bicyclic system, as well as the other positional isomers, has not received much attention until recently. Literature reports concern mainly the syntesis of series of its derivatives containing, in the most cases, amino, cyano, carbonyl and alkylthio functions as substituents.[1-5] The unsubstituted thieno[2,3-c]isothiazole was obtained by decarboxylation and deamination of 3-carboxylic acid and 3-amino derivative respectively by James and Krebs.[5] Two series of 4-amino-5-acyl substituted derivatives with an additionally functionalized 3-alkylthio substituent have been prepared also by us.[6,7] As regards its chemical properties, only reactions of the substituents have been reported,[3-5] but studies on the reactivity of the bicyclic rings are lacking.

Herein, we wish to report the sun light induced conversion of thieno[2,3-c]isothiazoles **1a-d** into thiophenes **2a-d** (Scheme 1) observed during the course of our experiments undertaken with the aim for obtaining isothiazolo[4',3':4,5]thieno[3,2-d]-1,2,3-triazine derivatives from **1a**.[8]

Scheme 1

1,**2**	X
a	CN
b	$CO_2C_2H_5$
c	$CONH_2$
d	$COCH_3$

Thus, in an optimization of the annellation reaction of compound **1a**, we found that **1a** in ethanolic solution was converted in the long run, with loss of elemental sulfur, into a new compound of molecular formula $C_7H_5N_3S_2$, mp 262-264°C, to which the structure of 2,4-dicyano-3-amino-5-methylthiothiophene **2a** was assigned on the basis of its analytical data and ir spectrum, and the complete conversion occurred within two days. Ir spectrum was characterized by two absorption bands at 3400 and 3344 cm^{-1} for the primary amino group, two bands at 2205 and 2183 cm^{-1} for the two cyano groups, the first of which lower in intensity, and a band at 1315 cm^{-1} for the methylthio moiety. The most intense band at 2183 cm^{-1} was associated with the nitrile function located at the 2-position, which suffers more efficently the 3-amino substituent electron-donor effect.[9] The structure of **2a** was confirmed by an unambigous synthesis starting from 2-methylthio-2-cyanomethylthio-1-cyanoacrylonitrile with a catalytic amount of sodium ethoxide following the Gompper procedure.[10]

Later on, compounds **1b-d** were also found to be converted into thiophenes **2b-d** and the 1⟶2 conversion proved to be a photochemical process independent from the used solvent, as shown in the Table.[11] In the dark, compounds **1a-d** dissolved in ethanol were found unchanged after a period of a month.

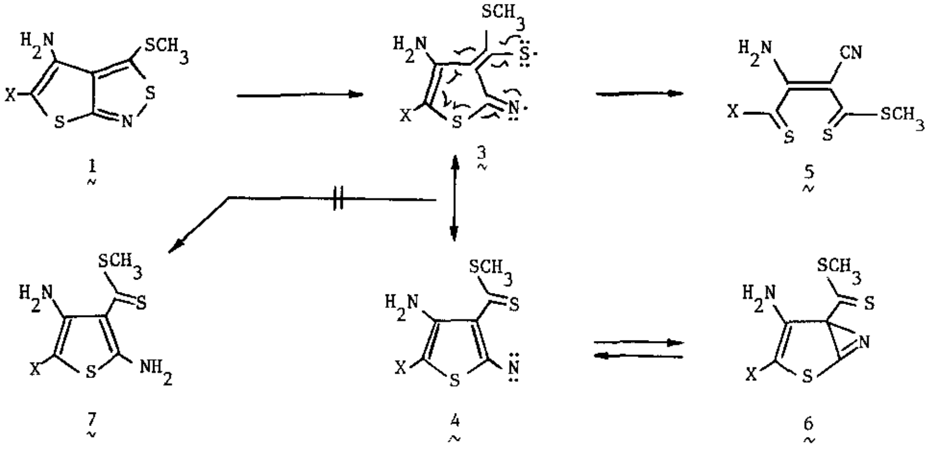
Table. Conversion time of thieno[2,3-c]isothiazoles **1a-d** into thiophenes **2a-d**[a]

Conversion	Solvent	Conversion time (days)[b]
1a ⟶ **2a**	Ethanol	2
	Acetic acid	4
	Ethyl acetate	3
	Dichloromethane	2
	Dioxane	2
	Benzene	4
1b ⟶ **2b**	Ethanol	4
1c ⟶ **2c**	Ethanol	5
1d ⟶ **2d**	Ethanol	7

a) Solutions of **1a-d** in the appropriate solvent were exposed contemporaneously to the sun light. b) Times were determined by checking up the disappearance of starting material.

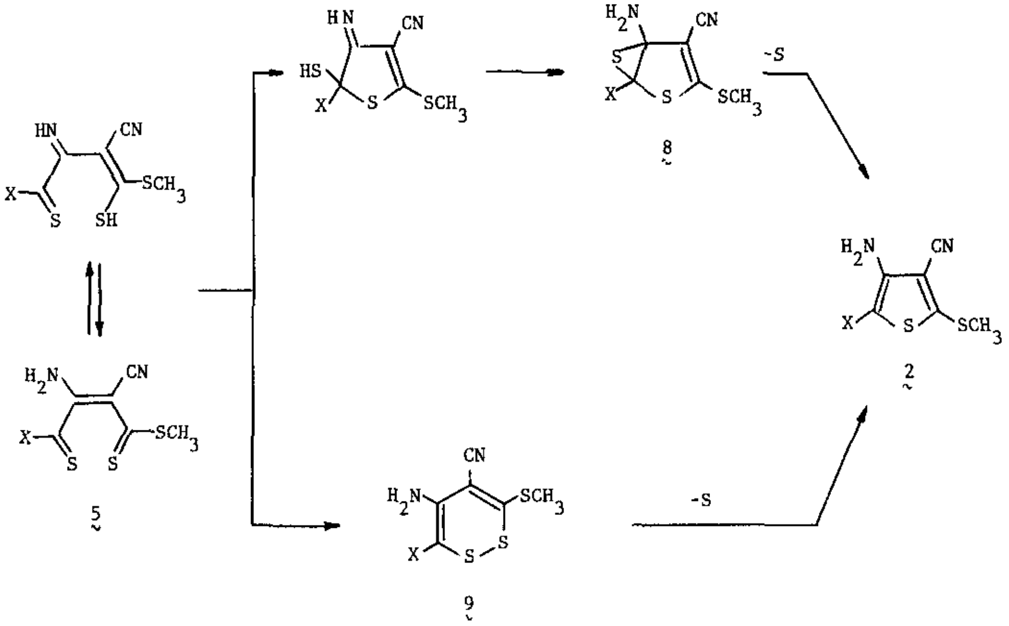
Substituents in 5-position and solvents showed to affect slightly only the photochemical process rate. The complete conversion of compounds 1b-d in ethanol required a period ranging between four days and a week. An examination of the solvent effect showed that in dichloromethane and dioxane the 1a ⟶ 2a conversion proceeds as in ethanol, while in acetic acid, ethyl acetate and benzene it is retarded (Table). In addition the 1a ⟶ 2a conversion was found to be strongly retarded by scavengers thus suggesting the involvement of radical species in the photochemical process. A 15 and 20% conversion of 1a into 2a was observed when an ethanolic solution of 1a was kept in the light in the presence of diphenyl disulfide and 2,4,6-tri-tert-butylphenol, respectively, for a period of time twice as long as required for achieving its complete conversion in the absence of the scavengers.

The mechanism of this ring degradation presumably involves the intermediary of the open-chain valence bond isomer 5 formed via an initial light induced homolytic cleavage of the nitrogen-sulfur linkage which is known to be the weakest single bond in the photochemically more reactive isothiazole nucleus[12] (Scheme 2).



Scheme 2

Cyclization of the enedithione 5 into the thiophene 2 can proceed through the formation of the bicyclic thiirane 8 which extrudes spontaneously sulfur[13,14] to give the push-pull stabilized thiophene 2. Indeed, it cannot be ruled out that the intermediate enedithione 5 undergoes a ready electrocyclic process with *formation* of an unstable 1,2-dithiin 9[15,16] which collapses in the most stable aromatic thiophene by extrusion of sulfur (Scheme 3).



Scheme 3

Attempts to obtain evidences for the postulated intermediates by ir and trapping studies were not however successfull. The monitoring of the conversion progress of 1d by ir in dichloromethane at two hours intervals over a four days period showed a decrease in intensity of the absorption band at 1527 cm^{-1} relative to the isothiazole ring stretching and a development of the band at 2200 cm^{-1} relative to the thiophene 4-nitrile substituent. No transitory ir absorption attributable to the intermediate enedithione 5 or dithiin 9, and no transitory shift of the isothiazole ring stretching band towards higher frequences indicative of the formation of the azirine 6, other conceivable intermediate,[17] was observed. No evidence of products deriving from hydrogen abstraction from solvent by diradical 3 or nitrene 4 was provided by experiments carried out by exposing terms 1a,b to the light in dioxane containing water (10:1,v/v), in methanol and in benzene containing aniline or diethylamine (10:1,v/v). In every case no isolable amounts of the expected thio esters **7**, or their transformation products were detected, but only thiophenes **2a,b** along with sulfur were recovered by solvent distillation after disappearance of the starting materials. The failure to detect trapping products is not however in conflict with the formation of the diradical **3** as intermediate, but instead it would suggest that the rate of the intramolecular rearrangement is much faster than the rate of the intermolecular trapping reaction with the solvent. The high sensitivity to the sun light of the isothiazole nitrogen-sulfur linkage in thieno[2,3-c]isothiazole structures **1a-d** was unexpected. It probably derives from the thieno[2,3-c]annellation, since no isothiazole ring opening was observed in isomeric thieno[3,2-d]isothiazoles containing the same substituents by exposure of their ethanolic solution to the light for long periods (three months). Isosteric 2,1-benzisothiazoles, as well as structurally related 3,4-benzoannellated isoxazoles and pyrazoles appear to be stable to the light too. Upon irradiation, however, they afford products derived from the cleavage of the only heterocyclic rings.[18-20] The synthesis and photochemical behaviour of thieno[2,3-c]annellated isoxazoles, pyrazoles, and dithioles are the objects of ongoing investigations.

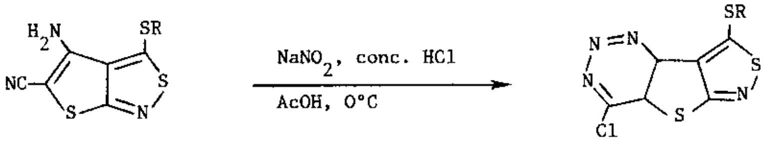
ACKNOWLEDGEMENTS

The authors are grateful to Professors G. Purrello and B. Tornetta for helpful discussions. This work was supported by grants from Ministero della Pubblica Istruzione.

REFERENCES AND NOTES

1. H. Eilingsfeld and R. Niess, D. B. P., 1972, 2,101,701; *Chem. Abstr.*, 1972, **77**, 400.
2. K. Gewald, M. Hentschel, and R. Heikel, *J. Prakt. Chem.*, 1973, **315**, 539.
3. K. Gewald, W. Radke, and U. Hain, *J. Prakt. Chem.*, 1980, **322**, 1021.
4. K. Clarke, W. R. Fox, and R. M. Scrowston, *J. Chem. Soc., Perkin Trans. I*, 1980, 1029.
5. F. C. James and H. D. Krebs, *Aust. J. Chem.*, 1982, **35**, 385.
6. B. Tornetta, G. Ronsisvalle, E. Bousquet, F. Guerrera, and M. A. Siracusa, *Gaz. Chim. Ital.*, 1980, **110**, 223.
7. E. Bousquet, M. A. Siracusa, B. Tornetta, and F. Guerrera, *Il Farmaco*, 1985, **40**, 347.
8. As a part of a research program devoted to the obtainment of biologically active tricyclic heterocycles incorporating a thiophene nucleus, we became

involved in the synthesis of a series of novel 4-chloro substituted isothiazolo[4',3':4,5]thieno[3,2-d]-1,2,3-triazines **10**. These were prepared by the route shown in the Scheme 4 according to Beck's method (J.R. Beck and J.A. Yahner, *J. Org. Chem.*, 1976, 41, 1733).



1a **10**

Scheme 4

9. K. Nakanishi, "Infrared Absorption Spectroscopy", Holden-Day, Inc., San Francisco, 1962.

10. R. Gompper, E. Kutter, and W. Topfl, *Liebig Ann. Chem.*, 1962, 659, 90.

11. Compounds **1a-d**[3] are known, while compounds 2a-d are new. These latter were identified on the basis of their microanalyses (C,H and N), which were in satisfactory agreement with the calculated values (within ± 0.4%) and ir spectra, and confirmed by independent synthesis. **2a**: mp 262-264°C; ir(ν,cm^{-1}): 3400, 3344, 2205, 2183, 1655; **2b**: mp 108-110°C; ir (ν,cm^{-1}): 3440, 3348, 2200, 1740, 1674,1620; **2c**: mp 223-225°C; ir (ν,cm^{-1}): 3424, 3400, 3316, 3260, 2208, 1660, 1622, 1594; **2d**: mp 197-199°C; ir (ν,cm^{-1}): 3380, 3290, 2202, 1630, 1605.

12. A. Padwa, "Rearrangements in Ground and Excited States", Vol. 3, ed. by P. de Majo, Academic. Press, Inc., London, 1980, pp 533-536.

13. W. J. Linn and E. Cicanek, *J. Org. Chem.*, 1969, **34**, 2146.

14. W. H. Mueller, *J. Org. Chem.*, 1969, **34**, 2955.

15. W. Schroth, H. Langguth, and F. Billig, *Z. Chem.*, 1965, **5**, 353.

16. W. Schroth, F. Billig, and G. Reinhold, *Angew. Chem. Int. Ed. Engl.*, 1967, **6**, 698.

17. F.W. Fowler, *Adv. Heterocycl. Chem.*, 1971, **13**, 45.

18. B. Jackson, H. Schmid, and H. J. Hansen, *Helv. Chim. Acta*, 1979, **62**, 391.

19. T. Dopper, H. Schmid, and H. J. Hansen, *Helv. Chim. Acta*, 1979, **62**, 304, and references cited in.

20. H. Tiefenthaler, W. Dorscheln, H. Goth, and H. Schmid, *Helv. Chim. Acta*, 1967, **50**, 2244.

Received, 5th July, 1988