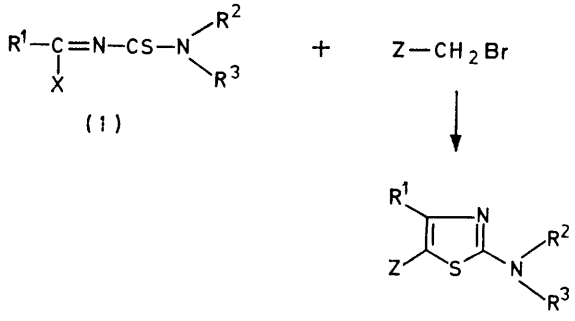
A General Synthesis of Thiazoles. Part 3.[1] Comparative Evaluation of Different Functionalised Thioureas as Precursors †

By Srinivasachari Rajappa,* Mohan D. Nair, Bhagwan G. Advani, Ramaswami Sreenivasan, and Jagdish A. Desai, CIBA-GEIGY Research Centre, Goregaon, Bombay 400 063, India

N-Acyl-*N'*-monosubstituted thioureas (9) react with phenacyl bromide to produce thiazolines (10) and not thiazoles (4), as claimed. The addition products of *N*-arylbenzamidines and phenyl isothiocyanate react with phenacyl bromide to give 2-anilino-5-benzoyl-4-phenylthiazole (4a). The adduct (11) of methyl benzimidate and phenyl isothiocyanate yields thiazoles (4a) and (12) by reaction with phenacyl bromide and bromonitromethane, respectively.

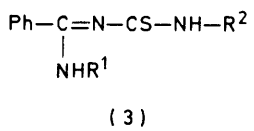
THIOUREA derivatives, *e.g.* (1), in which one of the nitrogen atoms is attached to a functionalised carbon atom have recently been utilised for the synthesis of novel thiazoles (2).[1-3] The thiourea moiety supplies two



(1) (2)

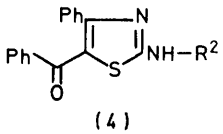
carbon atoms and both the heteroatoms of the resultant thiazole ring. The remaining carbon atom (C-5) is provided by the molecule $Z-CH_2Br$ in which Z is a group that activates the adjacent methylene for cyclisation. During the cyclisation, XH or XH_2^+ is eliminated. In the present article, we provide examples of this general synthesis, based on starting materials (1) in which X is an alkoxy or arylamino group. In addition, we prove that the acylthioureas (1; X = OH) are viable precursors for thiazoles only under certain circumstances.

The first such synthesis[2] utilised amidine–isothiocyanate adducts (1; X = NH_2; R_3 = H) as starting



(3)

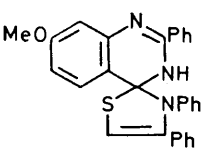
a; R^1 = H, R^2 = Ph
b; R^1 = H, R^2 = Ph–4–Cl
c; R^1 = R^2 = Ph
d; R^1 = Ph–3–OMe, R^2 = Ph
e; R^1 = Ph–4–OMe, R^2 = Ph



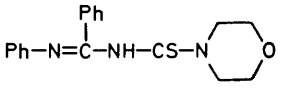
(4)

a; R^2 = Ph
b; R^2 = Ph–4–Cl

materials. For example, the benzamidine–phenyl isothiocyanate adduct (3a) reacted with phenacyl bromide to give the thiazole (4a). Later, we found[1] that when bromonitromethane is the active methylene component ($Z = NO_2$), it is preferable to start with *NN*-dialkylamidines; here the corresponding dialkylamine is eliminated during cyclisation. We now report that arylamines can also be effective leaving groups in this cyclisation. Thus the adducts (3c, d, and e) of *N*-arylbenzamidines and phenyl isothiocyanate react with phenacyl bromide in refluxing ethanol to yield the same product in essentially similar yields. Assuming that the first step in this reaction is *S*-alkylation, there are at least four subsequent nucleophile–electrophile interactions possible, leading to different cyclised products. Especially with the *m*-methoxyaniline derivative (3d), cyclisation on the benzene ring leading to the spirothiazoline (5) was considered a possibility. However, in all these cases, cyclisation occurred by attack of the active methylene on the amidine carbon atom with displacement of the aniline moiety, leading to the thiazole (4a).



(5)



(6)

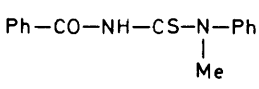
Ried and Kaiser[4] have published a similar synthesis recently. The starting material (6) for their synthesis is derived by adding a secondary amine (*e.g.* morpholine) to imidoyl isothiocyanates.

Subsequent to our original publication,[2] Liebscher and Hartmann reported[3] the formation of thiazoles from acyl thioureas (1; X = OH) by reaction with $Z-CH_2Br$. We now find that part of their claim is wrong.

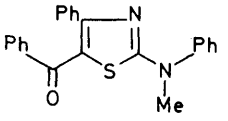
Thiazoles, *e.g.* (8), are undoubtedly formed when *N*-acyl-*N'N'*-disubstituted thioureas, *e.g.* (7), are condensed with phenacyl bromide. But when N' bears only one substituent, as in (9), reaction with phenacyl bromide produces the thiazoline (10) and *not* the isomeric thiazole (4) as claimed by Liebscher and Hartmann.[3] (This reaction has in fact been reported earlier.[5] Apparently, Liebscher and Hartmann were not aware of this report.) Our suspicion in this regard was initially aroused by the disparity in the u.v. spectra reported by those authors[3] for the thiazole (8) and the product claimed by them to be (4b). On the other hand, there was a great deal of similarity between the reported u.v.

† Contribution No. 517 from CIBA-GEIGY Research Centre.

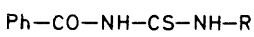
spectrum of (8) and that of the thiazole (4a) previously prepared by us [2] from benzamidine. We have now synthesised the two pairs of isomeric compounds [(4a, 10a) and (4b, 10b)] and compared their spectra with that of (8) (Table).



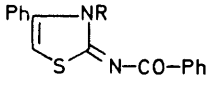
(7)



(8)

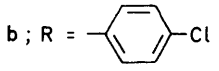


(9)



(10)

a ; R = Ph

b ; R = 

U.v. spectral characteristics of thiazoles and thiazolines

Compound	Absorptions
(4a)	$\lambda_{max.}$ 254 (4.36), $\lambda_{infl.}$ 275 (4.33), $\lambda_{max.}$ 382 (4.22)
(4b)	$\lambda_{infl.}$ 253 (4.36), $\lambda_{max.}$ 278 (4.38), $\lambda_{max.}$ 380 (4.27)
(8) *	$\lambda_{max.}$ 258 (4.23), $\lambda_{max.}$ 377 (4.01)
(10a)	$\lambda_{infl.}$ 235 (4.38), $\lambda_{max.}$ 337 (4.37)
(10b)	$\lambda_{infl.}$ 240 (4.35), $\lambda_{max.}$ 337 (4.33)
(10b) *	$\lambda_{infl.}$ 241 (4.34), $\lambda_{max.}$ 341 (4.31)

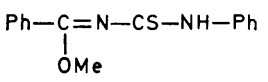
Wave-lengths in nm; log ε values in parentheses.

* Ref. 3.

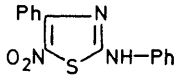
The assignment of thiazoline structures (10a and 10b) to the products from the acyl thioureas is further confirmed by their ^{1}H n.m.r. spectra. In $(CD_3)_2SO$ they exhibited one-proton singlets at δ 6.97 and 7.20, unchanged after addition of D_2O. The thiazole (4a), on the other hand, showed, apart from the expected signals due to the phenyl protons, an NH singlet at δ 10.8, disappearing on addition of D_2O.

It thus transpires that the two routes discussed above are complementary to each other. Amidine–isothiocyanate adducts can only lead to 2-monosubstituted aminothiazoles; on the other hand, *N*-acylthioureas yield thiazoles only when N′ is disubstituted, thereby generating aminothiazoles in which the exocyclic nitrogen carries two substituents.

We have also investigated the possibility of using imino-ethers as starting materials for the synthesis of these thiazoles. These react with isothiocyanates to form the adducts (1; X = OR; R^3 = H), which can then be condensed with Z–CH_2Br. Cyclisation, with elimination of a molecule of alcohol would lead to the thiazoles (2; R^3 = H). The thiourea derivative (11), obtained from methyl benzimidate and phenyl isothiocyanate, reacted with phenacyl bromide to produce the thiazole (4a) in 25% yield; it also reacted with bromonitromethane to give the 5-nitrothiazole (12) in 13.5% yield. The yields are thus lower in this case than when amidines are the starting materials. This is undoubtedly a consequence of the fact that protonated amines are better leaving groups than alcohols.



(11)



(12)

EXPERIMENTAL

U.v. spectra were measured for solutions in ethanol using a Beckman DK-2A machine. N.m.r. spectra were recorded on a Varian A60 or a Bruker WH90 spectrometer. Chemical shifts are quoted as δ values downfield from Me_4Si. Mass spectra were determined on a Varian MatCH-7 instrument at 70 eV utilising direct insertion.

5-Benzoyl-2-(4-chloroanilino)-4-phenylthiazole (4b).—Reaction of benzamidine hydrochloride (15.7 g) and *p*-chlorophenyl isothiocyanate (16.9 g) was carried out according to the method of Kurzer.[6] Crystallisation of the product from ethyl acetate–hexane gave the adduct (3b) (25 g), m.p. 160—162° (Found: C, 58.4; H, 4.5; N, 14.8. $C_{14}H_{12}ClN_3S$ requires C, 58.0; H, 4.2; N, 14.5%).

The above adduct (11.0 g) in isopropanol (100 ml) was refluxed for 1 h with phenacyl bromide (8.0 g). The solution was cooled, the product filtered, washed with water, and recrystallised from isopropanol to give the *thiazole* (4b) (9.5 g), m.p. 217—220°. (Found: C, 67.9; H, 4.1; N, 7.0. $C_{22}H_{15}ClN_2OS$ requires C, 67.6; H, 3.9; N, 7.2%), *m/e* 390 and 392 (M^+).

2-Benzoylimino-2,3-dihydro-3,4-diphenylthiazole [5] (10a).—A mixture of *N*-benzoyl-*N*′-phenylthiourea [7] (9a) (2.5 g) and phenacyl bromide (2.0 g) was refluxed in isopropanol (50 ml) for 2 h, the solvent removed, and water added to the residue. The product was extracted in ethyl acetate and crystallised from ethyl acetate–hexane to give the thiazoline (10a) (1.8 g), m.p. 209—210° (lit.,[5] 203—204°), *m/e* 356 (M^+). On admixture with the thiazole (4a),[2] the m.p. was depressed to 170—185° (Found: C, 74.3; H, 4.7; N, 7.8. Calc. for $C_{22}H_{16}N_2OS$: C, 74.1; H, 4.5; N, 7.9%).

2-Benzoylimino-3-(4-chlorophenyl)-2,3-dihydro-4-phenylthiazole (10b).—A mixture of *N*-benzoyl-*N*′-*p*-chlorophenylthiourea [7] (9b) (2.9 g) and phenacyl bromide (2.0 g) in isopropanol (80 ml) was refluxed for 2 h, cooled, and filtered. The solid was dissolved in ethyl acetate and washed with water. The solvent was removed and the product crystallised from ethyl acetate to give the thiazoline (10b) (1.0 g), m.p. 218—220° (lit.,[3] 215—216°), *m/e* 390 and 392 (M^+). On admixture with the thiazole (4b) above, the m.p. was depressed to 188—191°.

2-Anilino-5-benzoyl-4-phenylthiazole (4a).—(i) *By the iminoether route.* Methyl benzimidate (5.0 g) was mixed with phenyl isothiocyanate (5.0 g) and left at room temperature for 16 h. Hexane was then added, and the solid filtered off and recrystallised from ethyl acetate to give the adduct (11) (3.0 g), m.p. 128—132° (Found: C, 66.9; H, 5.5; N, 10.65. $C_{15}H_{14}N_2OS$ requires C, 66.65; H, 5.2; N, 10.4%).

This adduct (1.5 g) was mixed with phenacyl bromide (1.2 g) in isopropanol (80 ml) and refluxed for 2 h. The solvent was then removed and the residue digested with water. The product was extracted in ethyl acetate and crystallised from ethyl acetate–hexane to give the thiazole (4a) (0.5 g), m.p. and mixed m.p. with an authentic sample,[2] 196—

198° (Found: C, 74.3; H, 4.75; N, 7.7. Calc. for $C_{22}H_{16}N_2OS$: C, 74.1; H, 4.5; N, 7.9%), *m/e* 356 (M^+).

(ii) *By the* N-*arylbenzamidine route*. To a solution of *N*-phenylbenzamidine [8] (5.0 g) in dry toluene (100 ml) was added a solution of phenyl isothiocyanate (3.5 g) in dry toluene (20 ml). After stirring for 36 h, the mixture was left at room temperature for an additional 36 h, filtered, and the solid crystallised from ethyl acetate–hexane to give the adduct (3c) (4.0 g), m.p. 140—142°. The filtrate on concentration and cooling yielded more (2.0 g) of the adduct (Found: C, 72.8; H, 5.4; N, 12.6. $C_{20}H_{17}N_3S$ requires C, 72.5; H, 5.2; N, 12.7%).

To the above adduct (2.0 g) in ethanol (50 ml) was added phenacyl bromide (1.2 g), the mixture boiled under reflux for 16 h, cooled, and the solid filtered off and washed with ethanol to yield the product (0.5 g). The ethanol filtrate was concentrated to half its original volume and ether was added. Cooling of the mixture gave more (1.0 g) of the product. The combined solids were recrystallised from ethyl acetate–hexane to give the thiazole (4a) (1.0 g), m.p. 198—200°, undepressed on admixture with the sample obtained above (Found: C, 73.9; H, 5.0; N, 7.8; S, 9.0%); *m/e* 356 (M^+).

The adducts (3d) and (3e) were prepared similarly from the corresponding known *N*-arylbenzamidines.[9,10] The *m*-methoxyphenyl derivative (3d) was obtained in 66% yield, m.p. 120° (from benzene–hexane) (Found: C, 69.85; H, 5.5; N, 11.4. $C_{21}H_{19}N_3OS$ requires C, 69.8; H, 5.3; N, 11.6%). The *p*-methoxyphenyl derivative (3e) was obtained in 50% yield, m.p. 144—146° (from ethyl acetate–hexane) (Found: C, 69.9; H, 5.5; N, 11.65. $C_{21}H_{19}N_3OS$ requires C, 69.8; H, 5.3; N, 11.6%).

Both the adducts (3d) and (3e) reacted as before with phenacyl bromide in ethanol to produce the thiazole (4a), m.p. and mixed m.p. 198—200°.

2-*Anilino*-5-*nitro*-4-*phenylthiazole* (12).—The adduct (11) (2.7 g) was refluxed with bromonitromethane (1.4 g) in isopropanol (80 ml) for 2 h, then concentrated *in vacuo* and cooled. The solid was filtered off and recrystallised from acetone to give the 5-nitrothiazole (12) (0.4 g), m.p. and mixed m.p. with an authentic sample [1] 217—219° (Found: C, 60.7; H, 3.9; N, 14.0. Calc. for $C_{15}H_{11}N_3O_2S$: C, 60.6; H, 3.7; N, 14.1%).

We thank Dr. S. Selvavinayakam and his associates for the analytical and spectral data.

[8/905 *Received*, 16*th May*, 1978]

REFERENCES

[1] Part 2, S. Rajappa and R. Sreenivasan, *Indian J. Chem.*, 1978, **16B**, 749.
[2] S. Rajappa and B. G. Advani, *Indian J. Chem.*, 1970, **8**, 1145.
[3] J. Liebscher and H. Hartmann, *Z. Chem.*, 1974, **14**, 470.
[4] W. Ried and L. Kaiser, *Annalen*, 1976, 395.
[5] K. M. Murav'eva and M. N. Shchukina, *Zhur. obshchei Khim.*, 1960, **30**, 2327, 2334; T. S. Griffin, T. S. Woods, and D. L. Klayman in *Adv. Heterocyclic Chem.*, 1975, **18**, 110.
[6] F. Kurzer and W. Tertiuk, *J. Chem. Soc.*, 1959, 2851.
[7] E. Schroepl and R. Pohloudek-Fabini, *Pharmazie*, 1968, **23**, 484.
[8] F. C. Cooper and M. W. Partridge, *Org. Synth.*, 1963, Coll. Vol. IV, 769.
[9] Merck, B.P. 1,049,330 (*Chem. Abs.*, 1967, **66**, 65471).
[10] S. Robe, *Compt. rend. Acad. bulg. Sci.*, 1960, **13**, 159, (*Chem. Abs.*, 1961, **55**, 18,676).