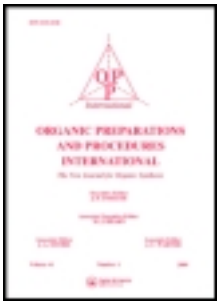


Organic Preparations and Procedures International: The New Journal for Organic Synthesis

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/uopp20

SYNTHESIS AND CYCLIZATION OF 1-(N-NITROAMIDINO)THIOUREAS TO 2,4-DIAMINOTHIAZOLES

R. Binu [a], K. K. Thomas [a], G. C. Jenardanan [a] & K. N. Rajasekharan [a]

[a] Department of Chemistry, University of Kerala, Kariavattom 695581, Trivandrum, INDIA

Version of record first published: 09 Feb 2009.

To cite this article: R. Binu, K. K. Thomas, G. C. Jenardanan & K. N. Rajasekharan (1998): SYNTHESIS AND CYCLIZATION OF 1-(N-NITROAMIDINO)THIOUREAS TO 2,4-DIAMINOTHIAZOLES, Organic Preparations and Procedures International: The New Journal for Organic Synthesis, 30:1, 93-96

To link to this article: http://dx.doi.org/10.1080/00304949809355265

REFERENCES

1. P. M. Borsenberger, H. C. Kan, E. H. Margin, and W. B. Vreeland, *J. Imaging Sci. Technol*, **39**, 6 (1995).

2. D. S. Acker and W. R. Hertler, *J. Am. Chem. Soc.*, **84**, 3370 (1962).

3. T. T. King and C. E. Newall, *J. Chem. Soc*, 974 (**1965**).

4. A. Rieker, *Chem. Ber.*, **103**, 656 (1970).

5. G. Jones, *Org. React.*, Vol. 15, p 204 (1967).

6. E. C. S. Jones and J. Kenner, *J. Chem. Soc.*, 1842 (**1931**).

7. C. R. H. I. De Jonge, H. J. Hageman, G. Hoentjen, and W. J. Mus, *Org. Synth.*, Coll. Vol. **6**, 413 (1988).

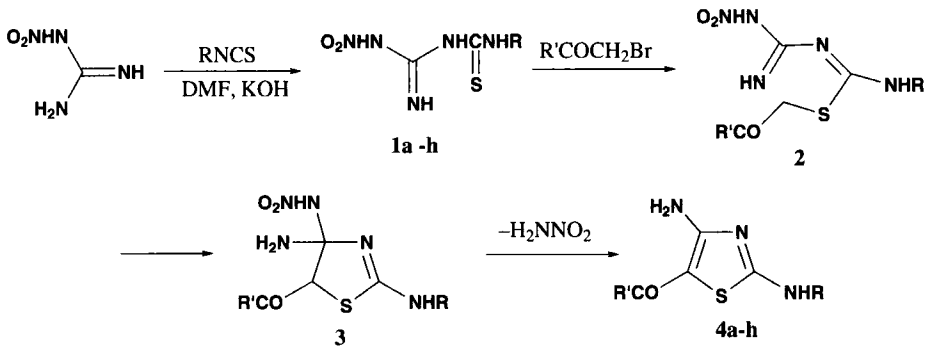
****

SYNTHESIS AND CYCLIZATION OF 1-(*N*-NITROAMIDINO)THIOUREAS TO 2,4-DIAMINOTHIAZOLES

Submitted by (03/18/97) R. Binu, K. K. Thomas, G. C. Jenardanan and K. N. Rajasekharan*

Department of Chemistry, University of Kerala
Kariavattom 695581, Trivandrum, INDIA

The Hantzsch synthesis of 2-aminothiazoles involves the reaction of a thiourea with a α-haloketone.[1] Despite being a century old, this classic reaction continues to be the mainstay of 2-aminothiazole synthesis and modifications and improvements are still appearing in the literature.[2-4] We have reported[5,6] that the use of 1-amidino-3-(substituted)thioureas in place of simple thioureas in the Hantzsch synthesis leads to 5-acyl-2,4-diaminothiazoles, the amidinothiourea derivative providing the C-N-C-S atoms of the thiazole ring and the remaining C atom arising from the 1α-haloketone. In continuation of this work, we decided to explore the reaction of (*N*-nitroamidino)thioureas (**1**) with α-haloketones. Based on our earlier work,[5,6] the formation of a tentatively assigned thiazoline intermediate (**3**) could be expected, from the initially generated S-alkyl intermediate (**2**), and the former could eliminate either ammonia or nitramine (Scheme). The expulsion of the former would lead to 2-amino-4-(*N*-nitroamino)thiazole derivatives which on reduction, could give hitherto unreported 2-amino-4-hydrazinothiazoles.



1a R = Me **1e** R = Ph
1b R = Et **1f** R = 4-MeC_6H_4
1c R = *n*-Pr **1g** R = 4-ClC_6H_4
1d R = *i*-Pr **1h** R = 4-$MeOC_6H_4$

4a R = Me, R' = 4-ClC_6H_4 **4e** R = R' = Ph
4b R = Et, R' = 4-ClC_6H_4 **4f** R = 4-MeC_6H_4, R' = Ph
4c R = *n*-Pr, R' = Ph **4g** R = Et, R' = Ph
4d R = *i*-Pr, R' = Ph **4h** R = 4-$MeOC_6H_4$, R' = Ph

Only two examples of **1** seem to have been described in literature and these were obtained[7] by the reaction of nitroguanidine with phenyl or *p*-tolyl isothiocyanates. In this procedure, the reactants were stirred in acetone containing suspended sodium. We now report that the reaction may be performed at room temperature in *N,N*-dimethylformamide using powdered potassium hydroxide, thus avoiding the use of sodium metal. Several 1-alkyl or aryl-3-(*N*-nitroamidino)thioureas (**1a-h**) were thus prepared.

The reaction of 1-methyl-3-(*N*-nitroamidino)thiourea (**1a**) with 4-chlorophenacyl bromide afforded 4-amino-5-(4-chlorobenzoyl)-2-methylaminothiazole (**4a**) as the sole product in 87% yield. It appears that in the eliminative-aromatization step leading to the thiazole, the -$NHNO_2$ group is a better leaving group, probably due to the greater stabilization of the developing negative charge. Thus the reaction did not provide any of the desired 4-(*N*-nitroamino)thiazoles, but led to 4-aminothiazoles (**4a-d**) which are also accessible from 1-alkyl-3-amidinothioureas.[6] However, the preparation of the required 1-alkyl-3-amidinothioureas is rather cumbersome since these water soluble compounds have to be isolated as nitrate, hydrogen carbonate or *p*-toluenesulfonate salts, some of which are hygroscopic. In contrast, 1-alkyl-3-(*N*-nitroamidino)thioureas are much less water soluble and are quite stable. In addition, the generally high yield of the 2,4-diaminothiazoles from nitroamidinothioureas encouraged us to prepare a few selected thiazoles (**4e**, **4f**, **4g** and **4h**) from the nitroamidinothioureas (**1e, 1f, 1b** and **1h**) respectively. These were chosen because we had obtained these thiazoles earlier[6] from amidinothioureas in ≥70% yield only. We now find that a consistent improvement in the yield (from 49-70% to 60-89%) resulted by switching to nitroamidinothioureas from amidinothioureas. In conclusion, we now show that nitroamidinothioureas (**1**) are excellent precursors of 2,4-diaminothiazoles (**4**).

EXPERIMENTAL SECTION

Nitroguanidine was obtained by treating guanidine nitrate with conc. sulfuric acid. Spectra were

recorded on Varian-390 and Bruker WM-400 NMR instruments and JEOL 300-D mass spectrometer. Elemental analysis was done at C. D. R. I. Lucknow, India. TLC were performed on Eastman Chromatogram plastic-backed silica gel sheets.

Preparation of 1-Alkyl or Aryl-3-(*N*-nitroamidino)thioureas (1a-h).- Nitroguanidine (5 mmol) was added to *N,N*-dimethylformamide (10 mL) containing powdered potassium hydroxide (10 mmol) and stirred at room temperature for 10 min. The isothiocyanate (5 mmol) in *N,N*-dimethylformamide (2 mL) was added dropwise over 20 min and stirring was continued for 90 min (30 min for aryl isothiocyanates) at room temperature. The reaction mixture was poured into ice-water (60 mL), filtered to remove any insolubles and acidified with hydrochloric acid (0.5N) to pH 3. The solid product obtained was collected, washed, dried and crystallized from methanol-water.

Reaction of *N*-Nitroamidinothioureas with α-Haloketones.- The 1-alkyl-3-(*N*-nitroamidino)-thioureas (**1a-d**) (1 mmol) in acetone (25 mL) were treated with the α-haloketone (1 mmol) and triethylamine (1.2 mmol). The pale yellow solution was stirred for 2 h and poured into ice-water (75 mL). The precipitate formed on keeping for 4-6 h was collected and crystallized from benzene. The aryl analogs were prepared from **1e-h** by refluxing the corresponding reactants (1 mmol each) and triethylamine (1.2 mmol) in 2-propanol (10 mL) for 1 h and working up as above. Benzene-methanol was used as the solvent for crystallization.

TABLE 1. Yields, mps. and Elemental Analyses of Compounds **1** and **4**

Compd	Yield (%) (Lit. yield)	mp. (°C) (Lit. mp.)	Analyses: Found (Calcd) C	H	N
1a	72	168-170	20.21 (20.33)	3.79 (3.98)	39.38 (39.53)
1b	71	158-160	25.34 (25.12)	4.61 (4.74)	36.39 (36.62)
1c	61	161-162	29.39 (29.26)	5.24 (5.40)	33.86 (34.13)
1d	73	162-163	29.11 (29.26)	5.29 (5.40)	33.90 (34.13)
1e	80 (58-68)[a]	160-161 (160-161)[a]	-	-	-
1f	84 (56-60)[a]	167-168 (168-170)[a]	-	-	-
1g	83	162-163	34.92 (35.10)	2.71 (2.95)	25.38 (25.59)
1h	82	145-146	40.26 (40.14)	4.01 (4.12)	25.74 (26.01)
4a	87	240-242	49.21 (49.34)	3.82 (3.76)	15.92 (15.70)
4b	90	155-156	51.02 (51.15)	4.34 (4.29)	15.02 (14.91)
4c	88	170-171	59.60 (59.74)	5.60 (5.79)	16.01 (16.08)
4d	86	153-154	59.56 (59.74)	5.60 (5.79)	16.17 (16.08)
4e	81 (61)[b]	186 (186)[b]	-	-	-
4f	88 (60)[b]	155-156 (155)[b]	-	-	-
4g	60 (49)[b]	180-181 (178-180)[b]	-	-	-
4h	89 (70)[b]	205-206 (206)[b]	-	-	-

a) Ref. 7. b) Ref. 6.

TABLE 2. ^{1}H NMR Spectral Data of Compounds **1** and **4**

Compd	^{1}H NMR (δ)
1a[a]	2.97 (d, *J* = 3Hz, 3H); 9.23 (s, 1H); 9.46 (s, 2H); 10.3 (s, 1H)
1b[a]	1.13 (t, *J* = 5Hz, 3H); 3.48 (quintet, *J* = 5Hz, 2H); 9.32 (s, 2H); 9.60 (s, 1H); 10.3 (s, 1H)
1c[a,c]	1.02 (t, *J* = 6Hz, 3H); 1.73 (sextet, *J* = 6Hz, 2H); 3.28 (m, 2H); 9.28 (s, 2H); 9.70 (s, 1H); 10.25 (s, 1H)
1d[a]	1.22 (d, *J* = 6Hz, 6H); 4.04-4.43 (m, 1H); 9.1-9.7 (s, 3H); 10.06 (s, 1H)
1g[a]	7.22 (d, *J* = 9Hz, 2H); 7.38 (d, *J* = 9Hz, 2H); 9.10-9.95 (s, 2H); 10.3 (s, 1H); 10.7s, 1H
1h[a]	3.77 (s, 3H); 6.82-7.32 (dd, 4H); 9.2-10.1 (s, 2H); 10.5 (s, 1H); 10.8 (s, 1H)
4a[b]	2.82 (d, *J* = 6Hz, 3H); 7.30-7.77 (dd, *J* = 8Hz, 4H); 8.05 (s, 2H); 9.96 (s, 1H)
4b[b,d]	1.26 (t, *J* = 6Hz, 3H); 3.30 (quintet, *J* = 6Hz, 2H); 5.92-6.18 (s, 2H); 7.38 (d, *J* = 9Hz, 2H); 7.8 (d, *J* = 9Hz, 2H)
4c[a]	0.88 (t, *J* = 6Hz, 3H); 1.2-1.9 (m, 2H); 3.15 (q, *J* = 6Hz, 2H); 7.2-7.7 (m, 5H)
4d[a]	1.31 (d, *J* = 6Hz, 6H); 3.4 (m, 1H); 7.2-7.7 (m, 5H)

a) ^{1}H NMR in DMSO-d_6. b) ^{1}H NMR in $CDCl_3$. c) ^{13}C NMR ($CDCl_3$, 100 MHz): δ 11.27 (Me); 21.24 (CH_2); 46.61 (CH_2); 159.07 (C=N); 188.07 (C=S). EIMS m/z (%): 191(M^+, 4); 144 (52); 129 (23); 127 (11); 103 (36); 96 (15); 87 (42); 74 (94); 71 (63); 64 (39); 44 (100). d) ^{13}C NMR ($CDCl_3$, 100 MHz): 13.71, 39.30, 127.78, 135.30, 140.02, 166.19, 172.06, 181.02. EIMS m/z (%): 283 (37); 281 (M^+, 100); 280 (60); 184 (11); 170 (26); 149 (8); 141 (19); 139 (48); 113 (20); 111 (47); 74 (10); 44 (48).

REFERENCES

1. A. Hantzsch and V. Traumann, *Ber.*, **21**, 938 (1888).

2. S. E. Bramley, V. Dupplin, D. G. C. Goberdhan and G. D. Meakins, *J. Chem. Soc. Perkin Trans. 1*, 639 (**1987**).

3. R. M. Moriarity, B. K. Vaid, M. P. Duncan, S. G. Levy, O. Prakash and S. Goyal, *Synthesis*, 845 (**1992**).

4. E. Aguillar and A. I. Meyers, *Tetrahedron Lett.*, **35**, 2473 (1994).

5. K. N. Rajasekharan and A. Sulekha, *Indian J. Chem.*, **20B**, 549 (1981).

6. K. N. Rajasekharan, K. P. Nair and G. C. Jenardanan, *Synthesis*, 353 (**1987**).

7. L. E. A. Godfrey and F. Kurzer, *J. Chem. Soc.*, 4566 (**1963**).

****