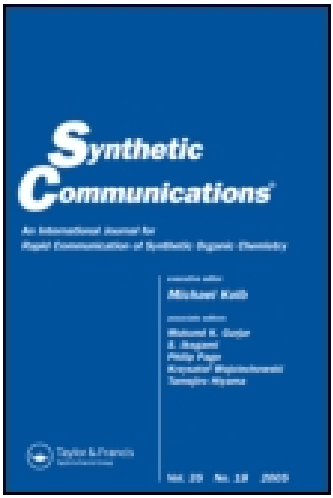

Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

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Published online: 22 Aug 2006.

To cite this article: M. Francis , S. Deepa , S. Sreekala & K. N. Rajasekharan (1997) Conversion of Alkylamines to Thiocarbamoylguanidines, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 27:19, 3463-3470, DOI: 10.1080/00397919708005648

To link to this article: http://dx.doi.org/10.1080/00397919708005648

SYNTHETIC COMMUNICATIONS, 27(19), 3463-3470 (1997)

CONVERSION OF ALKYLAMINES TO THIOCARBAMOYLGUANIDINES

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Abstract N-Alkyl-, N, N-dialkyl- or N-unsubstituted-N′-(arylthiocarbamoyl)guanidines are prepared in very good yield from amines and 1-(N-arylthiocarbamoyl)-amidino3,5-dimethylpyrazoles.

The synthesis of guanidines has attracted considerable attention recently and this has resulted in several new method for the conversion of amines to guanidines. The newly developed methods include: (i) the use of a sulfur abstracting agent such as a carbodiimide[1] or heavy metal salt to convert acyl or alkoxycarbonyl derivatives of thiourea[2] or S-methylisothiourea[3,4] to a reactive intermediate capable of *in situ* reaction with, (ii) the enhancement of the leaving group ability of the thiocarbonyl sulfur by S-alkylation[5], S-arylation[6] or S-oxidation[7,8] and (iii) the use of 1-amidinoazole–based amidine group transfer reagents such as the recently described 1-amidinopyrazole hydrochloride[9], bis-(N,N′-alkoxycarbonylamidino)pyrazoles[10,11], 1-(N-nitroamidino)-3,5-dimethylpyrazole[12], 1-amidino-1,2,3- benzotriazole tosylate[13] as well as the long established 1-amidino-3,5-dimethylpyrazole nitrate[14] for the preparation of simple and protected guanidines. We

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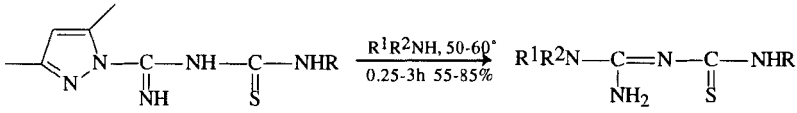
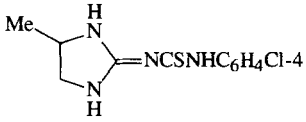
now show that functionalized guanidine derivatives may also be prepared by an azole-based methodology.



(1a - d) (2a - f, 3a - f, 4a - c)



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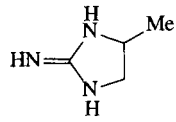

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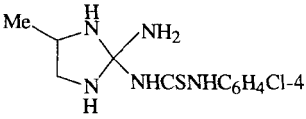

(7)

1	R
a	4-ClC$_6$H$_4$
b	C$_6$H$_5$
c	4-MeOC$_6$H$_4$
d	4-MeC$_6$H$_4$

2	R	R^1	R^2
a	4-ClC$_6$H$_4$	Me	H
b	C$_6$H$_5$	Me	H
c	C$_6$H$_5$	*n*-Pr	H
d	4-ClC$_6$H$_4$	*n*-Bu	H
e	4-MeOC$_6$H$_4$	Me	H
f	C$_6$H$_5$	c-C$_6$H$_{11}$	H

3	R	R^1	R^2
a	4-ClC$_6$H$_4$	(CH$_2$)$_4$	
b	4-ClC$_6$H$_4$	(CH$_2$)$_5$	
c	4-ClC$_6$H$_4$	(CH$_2$)$_2$O(CH$_2$)$_2$	
d	C$_6$H$_5$	(CH$_2$)$_5$	
e	4-MeC$_6$H$_4$	(CH$_2$)$_4$	
f	C$_6$H$_5$	Me	Me

4	R (R^1 = R^2 = H)
a	4-ClC$_6$H$_4$
b	C$_6$H$_5$
c	4-MeOC$_6$H$_4$

In connection with our interest in highly functionalized thiazoles[15], we required a variety of N-alkyl-, N,N-cycloalkyl and N,N-dialkyl-N′-(arylthiocarbamoyl)guani-

dines to be used as 2,4-diaminothiazole precursors. These may be prepared from aryl isothiocyanates and the appropriately substituted guanidines[16,17] which in turn are obtained by guanylation of amines. The aqueous solubility of alkylguanidines and their salts makes their isolation tedious. Also, the liberation of the free guanidine base requires strongly alkaline conditions. It appeared to us that an alternative could be the use of 1-(N-arylthiocarbamoyl)amidino-3,5-dimethylpyrazole (**1**)[18], which could serve as a common precursor and transfer a thiocarbamoylamidino group to amines.

Accordingly we studied the reaction of **1a-d** with primary alkylamines and found that the reaction yielded the required N-alkyl-N′-(arylthiocarbamoyl)guanidines (**2a-f**) in 55–86% yield. The reaction could be satisfactorily extended to secondary aliphatic amines, both cyclic and acyclic, to yield the N, N-disubstituted-N′-(arylthiocarbamoyl)guanidines (**3a-f**) in 70–84% yield. Simple 1-(N-arylthiocarbamoyl)guanidines (**4a-c**) were also obtained in 70–74% yield from ammonia. The reaction is generally complete in 0.25–3h at 50–60°C (within 1h in most cases) or in 18–36h at room temperature, with a 5–10 molar excess of the amine either without a solvent or in acetonitrile for the reactions using amines available as aqueous solutions. The simple work up involves removal of acetonitrile, trituration successively with petroleum ether and water followed by crystallization of the solid product.

The reaction of **1a** with 1,2-diaminopropane gave 1-(4-chlorophenyl)thiourea as the major product (64%) along with the cyclic guanidine derivative (**5**) in 15% yield and 2-iminoimidazolidine (**6**). It appears that the tentative tetrahedral intermediate (**7**) could collapse either by eliminating ammonia to give **5** or fragment into 1-arylthiourea and **6**. Attempts to improve the yield of **5** continue because these are attractive precursors for novel 5-acyl-4-[(ω-aminoalkyl)amino]-2-aminothiazoles.

We also observed that under the above conditions, simple arylamines didnot react. This is in accordance with the reported low reactivity of arylamines with the simple 1-amidinopyrazoles[9].

In summary, we now provide another instance of the use of 1-amidinopyrazole based guanylating agent for the conversion of alkylamines to guanidine derivatives. Our route to (N-substituted thiocarbamoyl)guanidines complements the recently described approaches to (thiocarbamoyl)guanidines[19,20] with no substituent on the thiocarbamoyl group. Our results are also noteworthy because N-acyl and N-alkoxycarbonyl derivatives of 1-amidinopyrazole are reported to be unreactive towards amines[11].

EXPERIMENTAL SECTION

The required 1-(N-arylthiocarbamoyl)amidino-3,5-dimethylpyrazoles (**1a-d**) were prepared from commercially available 1-amidino-3,5-dimethylpyrazole nitrate and aryl isothiocyanates by a single step procedure[18]. Elemental analyses were done at CDRI, Lucknow and spectra were recorded on Shimadzu 470 IR, Bruker WM-400 NMR, Varian-390 NMR and JEOL D-300 mass spectrometers. All new compounds gave satisfactory C, H and N analyses.

Reaction of 1-(N-arylthiocarbamoylamidino)-3,5-dimethylpyrazoles with aliphatic amines - General Procedure: The amidinopyrazole derivative (**1**, 0.001 mol) was added either to the neat amine (0.005-0.01 mol) or to acetonitrile (5 mL) containing concentrated aqueous solution of amine (0.01 mol). The mixture was kept at room temperature for 18–36h or kept at 50–60°C for 0.25–3h. The solvent was removed under reduced pressure and the syrupy residue was extracted by trituration with petroleum ether (60–90°C) to remove 3,5-dimethylpyrazole.

The residue was then triturated with water, and if necessary with little diethyl ether, to remove the excess amine. The crude solid obtained was then crystallized. Pyrrolidine required only 15 min is at 50–60°C to consume all of **1** whereas morpholine or dimethylamine required 3h and other amines, around 1h. The TLC analysis showed that during the preparation of **2d, 2f** and **3f**, some 1-alkyl- or 1,1-dialkyl-3-arylthioureas had formed as a side product (6–8% as determined by column separation on silica). Crystallization (twice in the above cases) from ethanol-water removed such side products. The melting points, yield and NMR data (δ) of N-arylthiocarbamoylguanidines prepared are given below. Spectra were run in DMSO-d_6 at 400 MHz unless otherwise mentioned.

2a: 128–130°C, (85%), ^{1}H NMR: 3.37 s, 3H); 7.20(d, 2H); 7.64 (d, 2H); 8.60 (b, 2NH); 9.35 (b, 1NH); 9.65 (b, 1NH)

2b: 138–140°C (85%), ^{1}H NMR: 3.34 (s, 3H); 6.93 (t, 2H); 7.20 (t, 2H); 7.68 (d, 2H); 8.56 (b, 2NH); 9.21 (b, 1NH); 9.52 (b, 1NH)

2c: 112–3°C (79%), ^{13}C NMR (100 MHz, $CDCl_3$): 11.32, 22.13, 43.16, 122.37, 123.98; 128.39, 160.37, 182.12

2d: 115–6°C (80%), ^{1}H NMR ($CDCl_3$): 0.95 (t, 3H), 1.43 (m, 2H); 1.62 (m, 2H); 3.19 (q, 2H); 6.34 (b, 2NH); 7.23 (d, 2H); 7.37 (d, 2H); 7.77 (b, 1NH); 9.40 (b, 1NH)

2e: 139–141°C (77%), ^{1}H NMR: 3.37 (s, 3H); 3.70 (s, 3H); 6.77 (d, 2H); 7.53 (d, 2H); 8.46 (b, 2NH); 9.14 (b, 1NH); 9.40 (b, 1NH).

2f: 158–9°C (55%), ^{1}H NMR (90 MHz, $CDCl_3$): 1.4–1.9 (m, 10H); 4.52 (m, 1H); 7.0–7.4 (m, 5H); 7.8 (b, 2NH); 8.4 (b, 1NH)

3a: 192–3°C (84%), ^{1}H NMR: 1.75–2.00 (m, 4H); 3.30–3.55 (m, 4H); 7.24 (d, 2H); 7.66 (d, 2H);

3b: 174–5°C (73%), ^{1}H NMR ($CDCl_3$): 1.53–1.81 (m, 6H); 3.45–3.63, (m, 4H); 7.19 (d, 2H); 7.48 (d, 2H); 8.48–8.65 (b,, 2NH); 8.73 (s, 1NH)

3c: 187–8°C (70%), ^{1}H NMR: 3.57 (t, 4H); 3.72 (t, 4H); 7.21 (d, 2H); 7.30 (d, 2H); 8.48 (b,, 1NH); 8.53 (b, 2NH)

3d: 166–7°C (82%) ^{1}H NMR ($CDCl_3$): 1.52–1.85 (m, 6H); 3.40–3.65 (m, 4H); 7.08 (t, 1H); 7.34 (t, 2H); 7.49 (t, 2H); 7.65–8.06 (b, 3NH)

3e: 194–5°C (80%) ^{13}C NMR (100 MHz, $CDCl_3$): 20.03, 25.17, 47.71, 121.93, 128.07, 137.03, 158.31, 190.82.

3f: 158–9°C (75%) ^{1}H NMR; 3.35 (s, 6H); 6.88, t, 1H); 7.22 (t, 2H); 7.60 (d, 2H); 8.62 (b, 1NH); 9.36 (b, 1NH): 9.65 (b, 1NH)

4a: 198–9°C (74%) Lit.[16] m.p. 182°C. ^{1}H NMR (90 MHz); 7.2 (d, 2H); 7.6 (d, 2H); 8.6 (b, 2NH); 9.2 (b, 2NH); 9.8 (b, 1NH)

4b: 175–6°C (70%) Lit.[16] m.p. 174°C, ^{1}H NMR, (90 MHz): 7.0–7.4 (m, 5H); 8.65 (b, 1NH); 9.1 (b, 2NH); 9.6 (b, 1NH)

4c: 150–1°C (72%) Lit.[16] m.p. 147–8°C, ^{1}H NMR (90 MHz): 3.7 (s, 3H); 6.8 (d, 2H); 7.3 (d, 2H); 8.7 (b, 2NH); 8.95 (b, 2NH); 9.6 (b, 1NH).

The reaction of **1**, (0.001 mol) with 1,2-diaminopropane (0.005 mol) was done in acetonitrile (5 mL) at 90°C. After triturations as described above, the solid product mixture was separated on a neutral alumina column to obtain 2-[(N-4-chlorophenylthiocarbamoyl)imino]-4-methylimidazolidine (**5**) m.p. 138°C (15%); ^{1}H NMR ($CDCl_3$): 1.32 (s, 3H of Me); 3.15 (t, 1H of CH_2); 3.72 (t, 1H of CH_2); 4.05 (apparent sextet, 1H of Me-CH); 7.21 (d, 2ArH); 7.38 (d, 2ArH); 7.7–7.9 (b, 2NH); 8.05–8.25 (b, 1NH); EIMS m/z(%) 270 (M+2, 10); 268 (M^+, 36) and 1-(4-chlorophenyl)thiourea, m.p. 182–3°C (64%). The filtrate obtained subsequent to trituration with water gave the picrate of 2-iminoimidazolidine (**6**), m.p. 193°C (29%). The latter two compounds were identified using authentically prepared samples.

REFERENCES

1. Poss, M. A.; Iwanowicz, E.; Reid, J. A.; Lin, J. and Gu, Z. *Tetrahedron Lett.*, **1992**, *33*, 5933.
2. Kim, K. S. and Qian, L., *Tetrahedron Lett.*, **1993**, *34*, 7677.
3. Chandrakumar, N. S., *Synth. Commun.*, **1996**, *26*, 2613.
4. Su, W., *Synth. Commun.*, **1996**, *26*, 407.
5. Rasmussen, C. R.; Villani, F. J.; Reynolds, B. E.; Plampin, J. N.; Hood, A. R.; Hecker, L. R.; Nortey, S. O.; Hanslin, A., Costanzo, M. J.; Howse, R. M. and Molinari, A. J., *Synthesis*, **1988**, 460.
6. Lammin, S. G.; Pedgrift, B. L. and Ratcliffe, A. J., *Tetrahedron Lett.*, **1996**, *37*, 6815.
7. Miller, A. E. and Bischoff, J. J. *Synthesis* **1986**, 777.
8. Maryanoff, C. A.; Stanzione, R. C.; Plampin, J. N. and Mills, J. E. *J. Org. Chem.*, **1986**, *51*, 1882.
9. Bernatowicz, M. S.; Wu, Y. and Matsueda, G. R., *J. Org. Chem.*, **1992**, *57*, 2497.
10. Drake, B.; Patek, M. and Lebl, M., *Synthesis*, **1994**, 579.
11. Bernatowicz, M. S.; Wu, Y. and Matsueda, G. R., *Tetrahedron Lett.*, **1993**, *34*, 3389.
12. Mitchinson, A.; Golding, B. T.; Griffin, R. J. and O'Sullivan, M. C., *J. Chem. Soc., Chem. Commun.*, **1994**, 2613.
13. Katritzky, A. R.; Parris, R. L. and Allin, S. M., *Synth. Commun.*, **1995**, *25*, 1173.
14. Bannard, R. A. B.; Casselman, A. A; Cockburn, W. F. and Brown, G. M., *Can. J. Chem.*, **1958**, *36*, 1541.

15. Rajasekharan, K. N.; Nair, K. P.; Jenardanan, G. C., *Synthesis*, **1986**, 353.

16. Ueda, T.; Takada, A; Takahashi, K. and Ueda, F.; *Chem. Pharm. Bull.* **1971**, 19, 1990.

17. Joshua, C. P. and Rajasekharan, K. N., *Aust. J. Chem.*, **1977**, *30*, 563.

18. Jenardanan, G. C.; Francis, M., Deepa, S. and Rajasekharan, K. N., *Synth. Commun*, **1997**, accompanying paper.

19. Tari, P. and Gajaray, A., *Org. Prep. Procedure Intl.*, **1995**, *27*, 697.

20. Reiter, L. A. and Brighty, K. E., *Synth. Commun.*, **1996**, *26*, 1423.

(Received in the UK 13 March 1997)