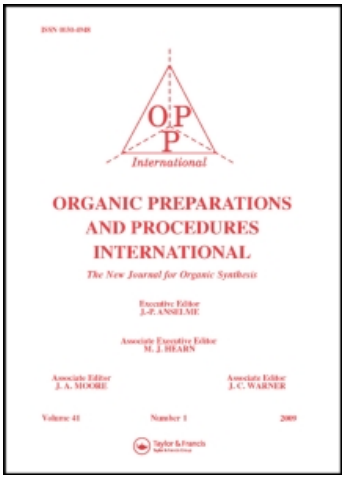


Organic Preparations and Procedures International
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t902189982

A NOVEL AND DIRECT METHOD FOR THE PREPARATION OF 4-AMINO-1,1,3,3-TETRASUBSTTTUTED GUANIDINES AND OF [1,2,4]TRIAZOLO-FUSED HETEROCYCLIC DERIVATIVES

M. Abdul-Ghan[a]; Sh. N. Khattab[b]; A. M. El-Massry[b]; A. El-Faham[a]; Adel Amer[b]
[a] Department of Chemistry, Faculty of Science, Beirut Arab University, Beirut, LEBANON [b] Department of Chemistry, Faculty of Science, Alexandria University, Alexandria, EGYPT

To cite this Article Abdul-Ghan, M. , Khattab, Sh. N. , El-Massry, A. M. , El-Faham, A. and Amer, Adel(2004) 'A NOVEL AND DIRECT METHOD FOR THE PREPARATION OF 4-AMINO-1,1,3,3-TETRASUBSTTTUTED GUANIDINES AND OF [1,2,4]TRIAZOLO-FUSED HETEROCYCLIC DERIVATIVES', Organic Preparations and Procedures International, 36: 2, 121 — 127
To link to this Article: DOI: 10.1080/00304940409355382
URL: http://dx.doi.org/10.1080/00304940409355382

ORGANIC PREPARATIONS AND PROCEDURES INT., 36 (2), 121-127 (2004)

A NOVEL AND DIRECT METHOD FOR THE PREPARATION OF 4-AMINO-1,1,3,3-TETRASUBSTITUTED GUANIDINES AND OF [1,2,4]TRIAZOLO-FUSED HETEROCYCLIC DERIVATIVES

M. Abdul-Ghani,[†] Sh. N. Khattab,[††] A. M. El-Massry,[††] A. El-Faham,*[†] and Adel Amer[††]

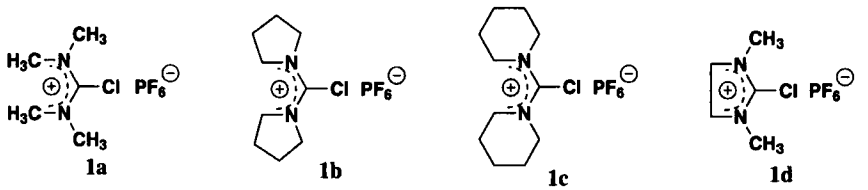
[†]*Department of Chemistry, Faculty of Science*
Beirut Arab University, P. O. Box 11-5020, Beirut, LEBANON

[††]*Department of Chemistry, Faculty of Science*
Alexandria University, Alexandria, EGYPT
E-mail: Aymanel_faham@hotmail.com

Guanidine functions are important motifs and often are present in natural products as well as in many compounds having therapeutic activity.[1,2] Consequently, a number of guanylating reagents in the literature and/or available commercial sources are known.[3-5] Direct synthetic approaches for the preparation of guanidine-derived products in high yields under mild conditions are of great interest in medicinal chemistry. Although fully substituted guanidines are not common, their presence can facilitate binding to complex receptors and therefore can be of key importance for the development of bioactive molecules.[6,7] Due to their strongly basic character,[8,9] guanidines can be considered as super bases and chiral guanidines are of potential use as asymmetric reagents. Their limited utilization[10] in asymmetric synthesis as chiral auxiliaries is mainly due to the absence of simple preparative methods. Although several methods have been described for the preparation of functionalized guanidines, either in solution[11] or by solid-phase methods,[1f-h, 6c,7c,12] they do not allow the formation of pentasubstituted guanidines. The present work reports a novel and an efficient procedure for preparation of 4-amino-1,1,3,3-tetrasubstituted guanidines in solution under very mild conditions, which involves the use of chloroformamidinium salts **(TCFH, 1a), (BTCFH, 1b), (BPCFH, 1c)** and the chloroimidazolidinium salt **(CIP, 1d)**. These salts **1a-d** were prepared as described previously.[13]

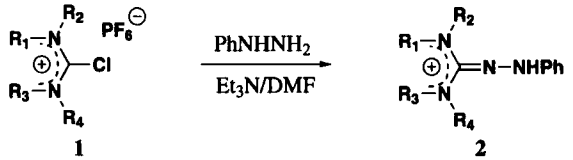
Salts **1a-d** have been used mainly as coupling reagents in peptide synthesis, in the presence or absence of an additive,[13] by activating the carboxyl group of the amino acid. However, during the much slower activation of hindered amino acids, protected peptide segments, or carboxylic acids involved in cyclization, the formamidinium salts may undergo reaction with the

amino component to give the corresponding guanylated derivatives.[14] We have taken advantage of this side-reaction and used it for the synthesis of 4-amino-1,1,3,3-tetrasubstituted guanidines as well as [1,2,4]triazolo derivatives.



1a **1b** **1c** **1d**

Treatment of **1a-d** (1 mmol) with phenylhydrazine (1 mmol) in DMF, in the presence of triethylamine (2 equiv.), afforded the guanidine derivatives **2a-d**. The reaction was complete at room temperature within several hours, and the side-products were removed by successive washing with water and saturated NaCl. Although the crude products were usually sufficiently pure for further use, recrystallization afforded the guanidine derivatives in high yields and purity as observed from their spectroscopic data and elemental analyses (*Scheme 1, Table 1, 2*).



a) $R_1 = R_2 = R_3 = R_4 = CH_3$
b) $R_1, R_2 = R_3, R_4 = (CH_2)_4$
c) $R_1, R_2 = R_3, R_4 = (CH_2)_5$
d) $R_1 = R_3 = CH_2$; $R_2 = R_4 = CH_3$

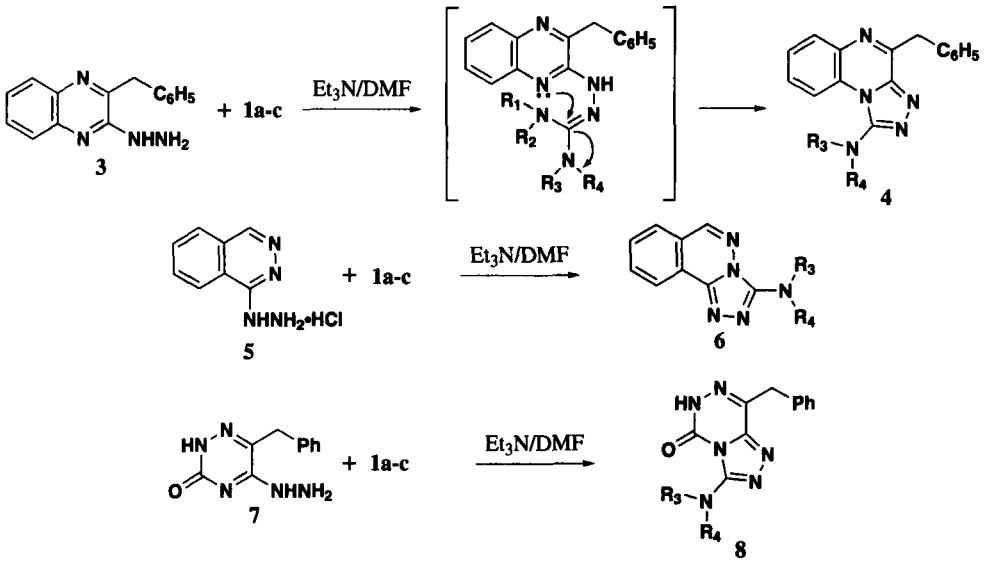
Scheme 1

Table 1. Yields, Color, Mps., Mass Spectra, and Elemental Analyses of Compounds **2, 4, 6, 8.**

Cmpd	Yield (%)	Color	mp (°C)	MS (m/z)	Elemental Analysis (Found) C	H	N
2a	81	White[a]	89-91	206	64.05 (63.83)	8.79 (8.99)	27.16 (27.35)
2b	84	White[a]	110(dec)	258	69.76 (69.93)	8.53 (8.76)	21.69 (21.88)
2c	86	White[a]	119-121	286	71.29 (71.41)	9.09 (9.36)	19.58 (19.85)
2d	83	White[a]	112-114	204	64.71 (64.93)	7.84 (7.69)	27.45 (27.37)
4a	89	Yellow[b]	169-170	303	71.29 (71.05)	5.61 (5.60)	23.10 (22.92)
4b	71	Beige[b]	144-146	329	72.93 (72.71)	5.80 (5.69)	21.28 (21.33)
4c	83	Red[b]	130-131	343	73.47 (73.31)	6.12 (6.28)	20.44 (20.58)
6a	66	Beige[b]	230-232	213	61.97 (61.71)	5.16 (5.33)	32.86 (33.01)
6b	81	Beige[b]	239-340	239	65.27 (65.03)	5.44 (5.61)	29.29 (29.44)
6c	78	Yellow[b]	246-248	253	66.40 (66.19)	5.93 (6.13)	27.66 (27.89)
8a	83	White[b]	185-186	270	57.77 (57.48)	5.22 (5.45)	31.09 (30.98)
8b	71	White[b]	194-196	296	60.80 (61.03)	5.44 (5.63)	28.36 (28.65)
8c	71	White[b]	199-202	310	61.19 (61.44)	5.81 (5.67)	27.10 (27.37)

a) From CH_2Cl_2/hexane *b*) from ethanol

Interestingly, compounds such as 3-benzyl-2-hydrazinoquinoxaline (**3**), 1-hydrazino phthalazine hydrochloride (**5**), and 6-benzyl-5-hydrazino-2*H*-[1,2,4]triazin-3-one (**7**), which are considered biologically active compounds,[15] reacted with **1a-c** in a different manner under the same conditions. No guanidines were observed in these cases. Apparently, there was a strong tendency toward *in situ* heterocyclization and substitution[16] of one of the dialkylamino groups to give the new [1,2,4]triazolo derivatives **4, 6, 8** in high yields and purity as observed from their spectroscopic data and elemental analyses (*Scheme 2, Table 1, 2*).



a) $R_3 = R_4 = CH_3$; b) $R_3, R_4 = (CH_2)_4$; c) $R_3, R_4 = (CH_2)_5$

Scheme 2

In summary, we have successfully demonstrated the versatility of **1a-c** as useful reagents for the synthesis of guanidine derivatives as well as heterocyclic derivatives. Additional applications of **1a-d** both in solution and in the solid-phase are underway in our laboratory.

Table 2. ^1H and ^{13}C NMR Data of Compounds **2, 4, 6, 8.**

Cmpd	^1H NMR (δ) ppm	^{13}C NMR (δ) ppm
2a[a]	2.95 (2s, 12H, $4CH_3$), 6.93-6.85 (m, 3H, aromatic), 7.25-7.37 (m, 2H, aromatic), 8.25 (s, 1H, NH)	40.36, 40.64, 113.10, 113.20, 120.53, 129.35, 129.51, 147.63, 162.12
2b[a]	1.95-2.01 (m, 4H, $2CH_2$), 3.36-3.65 (m, 4H, $2CH_2$), 6.95-7.03 (m, 3H, aromatic), 7.37-7.70 (m, 2H, aromatic), 8.45 (s, 1H, NH)	24.88, 49.67, 112.63, 112.79, 120.73, 128.96, 129.35, 146.63, 155.66
2c[a]	1.85-2.10 (m, 6H, $3CH_2$), 3.65-3.83 (m, 4H, $2CH_2$), 6.95-7.03 (m, 3H, aromatic), 7.37-7.70 (m, 2H, aromatic), 8.25 (s, 1H, NH)	23.85, 24.88, 49.67, 112.63, 112.79, 121.37, 128.69, 129.04, 146.63, 156.56

Table 2. Continued...

Cmpd	^{1}H NMR (δ) ppm	^{13}C NMR (δ) ppm
2d[a]	3.14 (s, 6H, $2CH_3$), 3.63 (s, 4H, $2CH_2$), 6.85-7.03 (m, 3H, aromatic), 7.30-7.60 (m, 2H, aromatic), 8.75 (s, 1H, NH)	33.11, 48.69, 113.03, 117.10, 122.53, 128.64, 129.02, 146.33, 157.76
4a[b]	3.04 (s, 6H, 2 CH_3), 4.61 (s, 2H, CH_2), 7.19-7.29 (m, 3H, aromatic), 7.52-7.74 (m, 4H, aromatic), 8.04 (d, 1H, aromatic), 8.45 (2d, 1H, aromatic)	40.68, 43.40, 116.37, 126.43, 127.20, 127.38, 128.86, 130.20, 136.76, 137.08, 143.37, 154.98, 157.18
4b[b]	1.96-2.07 (m, 4H, 2 CH_2), 3.51-3.56 (m, 4H, 2 CH_2), 4.57 (s, 2H, CH_2), 7.17-7.28 (m, 3H, aromatic), 7.45-7.58 (m, 4H, aromatic), 7.99 (d, 1H, aromatic), 8.37 (d, 1H, aromatic)	24.75, 40.24, 51.91, 116.00, 126.73, 127.47, 128.15, 128.41, 129.76, 136.44, 136.70, 142.89, 154.50, 155.50
4c[b]	1.98-2.07 (m, 6H, 3 CH_2), 3.33-3.51 (m, 4H, 2 CH_2), 4.57 (s, 2H, CH_2), 7.17-7.28 (m, 3H, aromatic), 7.45-7.58 (m, 4H, aromatic), 8.09 (d, 1H, aromatic), 8.36 (d, 1H, aromatic)	21.88, 22.81, 40.35, 50.68, 117.00, 125.93, 126.77, 128.35, 128.61, 130.76, 136.44, 136.70, 142.89, 154.50, 155.50
6a[a]	3.35 (s, 6H, 2 CH_3), 7.95-8.01 (m, 2H, aromatic), 8.08 (d, 1H, aromatic), 8.39 (d, 1H, aromatic), 8.99(s, 1H, aromatic)	40.45, 119.27, 120.35, 121.83, 123.73, 129.18, 130.71, 134.38, 140.77, 146.78, 153.68
6b[a]	2.02-2.1 (m, 4H, 2 CH_2), 3.83-3.96 (m, 4H, 2 CH_2), 7.97-8.02 (m, 2H, aromatic), 8.08 (d, 1H, aromatic), 8.32 (d, 1H, aromatic), 8.99 (s, 1H, aromatic)	22.88, 47.75, 119.28, 120.52, 121.49, 122.49, 130.83, 132.88, 137.21, 143.54, 146.46, 156.46
6c[a]	1.62-1.68 (m, 6H, 3 CH_2), 3.43-3.52 (m, 4H, 2 CH_2), 7.77-7.96(m, 2H, aromatic), 8.06 (d, 1H, aromatic), 8.39 (d, 1H, aromatic), 8.82 (s, 1H, aromatic)	21.83, 22.80, 46.91, 119.48, 120.30, 121.32, 126.79, 128.37, 130.85, 131.98, 138.45, 144.49, 150.79
8a[b]	3.04 (s, 6H, 2 CH_3), 4.11 (s, 2H, CH_2), 7.18-7.69 (m, 5H, aromatic), 12.93 (br, 1H, NH)	36.50, 43.02, 126.97, 128.71, 129.49, 136.86, 138.74, 143.92, 148.53, 167.42
8b[b]	1.99-2.05 (m, 4H, 2 CH_2), 3.57-3.64 (m, 4H, 2 CH_2), 4.21 (s, 2H, CH_2), 6.96-7.09 (m, 5H, aromatic), 9.86(s, 1H, NH)	24.63, 35.92, 46.69, 126.17, 127.61, 128.49, 134.46, 139.04, 142.60, 147.03, 164.48
8c[b]	1.61-1.86 (m, 6H, 3 CH_2), 3.54-3.63 (m, 4H, 2 CH_2), 3.94 (s, 2H, CH_2), 6.90-7.09 (m, 5H, aromatic), 10.75 (s, 1H, NH)	24.64, 25.67, 35.42, 48.75, 126.50, 128.53, 129.05, 137.70, 138.31, 144.33, 148.44, 161.80

a) DMSO-d_6 *b*) $CDCl_3$

EXPERIMENTAL SECTION

Melting points were obtained in open capillary tubes using a Gallen Kamp apparatus and are uncorrected. NMR spectra were recorded using a Brucker 300 MHz instrument with TMS as

internal standard. MS were recorded using a Shimadzu Gas Chromatograph Mass Spectrometer (GCMS-QP 5050). Elemental analyses were carried out at the University of Cairo, Microanalytical Laboratories. All solvents were HPLC grade or of equivalent purity and used without further purification.

General Procedure for Reaction of 1a-d with Hydrazine Derivatives.- The salt **1a-d** (1 mmol) was added to a solution of the hydrazine derivative (1 mmol) and Et_3N (2 mmol) in DMF (5 mL) and the reaction mixture was stirred overnight at room temperature. The reaction mixture was poured into water (30 mL), extracted with methylene chloride (2 x 15 mL), washed with water (2 x 10 mL), saturated NaCl (2 x 10 mL), dried ($MgSO_4$), filtered and the solvent was removed under vacuum. The residue was obtained as colorless viscous oil, which slowly solidified to give pale yellow crystals, which were recrystallized from the indicated solvent.

Abbreviations used:

TCFH = Tetramethylchloroformamidinium hexafluorophosphate

BTCFH = *bis*(Tetramethylene)chloroformamidinium hexafluorophosphate

BPCFH = *bis*(Pentamethylene)chloroformamidinium hexafluorophosphate

CIP = 2-Chloro-1, 3-dimethyl imidazolidiniumhexafluorophosphate

DMF = Dimethylformamide

Et_3N = Triethylamine

Acknowledgment.- Professor L. A. Carpino is thanked for his support and advice. We are indebted to the National Council for Scientific Research (CNRS-48-08-03) for support of the work in Lebanon.

REFERENCES

* **Correspondence author:** on leave of absence, Faculty of Science, Department of Chemistry, Alexandria University, Alexandria, Egypt.

1. (a) L. Heys, C. G. Moore and P. J. Murphy, *Chem. Soc. Rev.*, **29**, 57 (2000). (b) I. J. McAlpine and R. W. Armstrong, *Tetrahedron Lett.*, **41**, 1849 (2000). (c) V. D. Lee and C. H. Wang, *J. Org. Chem.*, **65**, 2399 (2000). (d) K. Feichtinger, C. Zapf, H. L. Sings and M. Goodman, *J. Org. Chem.*, **63**, 3804 (1998). (e) K. Feichtinger, H. L. Sings, T. J. Baker, K. Mathews and M. Goodman, *J. Org. Chem.*, **63**, 8432 (1998). (f) D. S. Dodd and O. B. Wallace, *Tetrahedron Lett.*, **39**, 5701 (1998). (g) P. C. Kearney, M. Fernandez and J. A. Flygare, *Tetrahedron Lett.*, **39**, 2663 (1998). (h) P. Lin. Ganesan, *Tetrahedron Lett.*, **39**, 9789 (1998). (i) D. S. Dodd and A. P. Kazawski, *Tetrahedron Lett.*, **35**, 977 (1994).

2. L. Y. Hu, J. Guo, S. S. Magar, J. B. Fischer, K. J. Burke-Howie and J. G. Durant, *J. Med. Chem.*, **40**, 421 (1997).

3. Chloroformamidinium salts were used by Barton *et al* for prepartion of sterically hindered guanidine bases in a strategy similar to that the described in this work. D. H. R. Barton J. D. Elliot and J. D. Gero, *J. Chem. Soc., Perkin Trans. I*, 2085 (1982).

4. M. Lipton, *Tetrahedron Lett.*, **40**, 53(1999).

5. A. R. Katritzky, B. V. Rogovoy, C. Chassaing and V. Vvedensky, *J. Org. Chem.*, **65**, 7080 (2000).

6. (a) B. R. Linton, A. J. Carr, B. P. Orner and A.D. Hamilton, *J. Org. Chem.*, **65**, 1566 (2000). (b) B. Linton and A. D. Hamilton, *Tetrahedron*, **55**, 6027 (1999). (c) S. E. Schneider, P. A. Bishop, M. A. Salazar, O. A. Bishop and E.V. Anslyn, *Tetrahedron*, **57**, 15063 (1998). (d) F. A. Cotton, V. W. Day, E. E. Jr. Hazen and S. Larsen, *J. Am. Chem. Soc.*, **95**, 4834 (1973).

7. (a) M. Frederic, D. Scherman and G. Byk, *Tetrahedron Lett.*, **41**, 675 (2000). (b) L. J. Wilson, S. R. Klopfenstein and M. Li, *Tetrahedron Lett.*, **40**, 3999 (1999). (c) J. M. Ostresh, C. C. Schoner, V. T. Hamashhin, A. Nefzi, J. P. Meyer and R. A. Houghten, *J. Org. Chem.*, **63**, 8622 (1998). (d) D. H. Drewry, C. W. Gerritz and J. A. Linn, *Tetrahedron Lett.*, **38**, 3377 (1997).

8. Y. Yamamato and S. Kojima, "*The Chemistry of Amidines and Imidates*" Editors S.Patai and Z.Rappoport, *John Wiley & Sons*, Inc. New York, **Vol. 2**, pp. 485 (1991).

9. (a) T. Isobe, K. Fukuda and T. Ishikawa, *J. Org. Chem.*, **65**, 7770 (2000). (b) M. Costa , G. P. Chiusoli, D. Taffurelli and G. Dalmonego, *J. Chem. Soc., Perkin. Trans. I*, 1541 (1998).

10. (a) K. Hada, T. Watanabe, T. Isobe and T. Ishikawa, *J. Am. Chem.*, **123**, 7705 (2001). (b) T. Isobe, K. Fukuda, K. Yamaguche, H. Seki, T. Tokunaga and T. Ishikawa, *J. Org. Chem.*, **65**, 779 (2000). (c) A. Howard-Jones, P. J. Murphy, D. A. Thomas and P. W. R. Caulkett, *J. Org. Chem.*, **64**, 1039 (1999). (d) E. J. Corey and M. Gorgan, *Org. Lett.*, **1**. 157 (1999). (e) M. S. Iyer, K. M. Gigstad, N. D. Namdev and M. Lipton, *J. Am. Chem. Soc.*, **118**, 4910 (1996). (f) R. Chinchilla, C. Najera and P. Sanchez-Agullo, *Tetrahedron: Asymmetry*, **5**, 1393 (1994).

11. (a) Z. Szekely, S. Zakhariev, C. Guaranallia, N. Antcheva and S. Ponger, *Tetrahedron Lett.*, **40**, 4439 (1999). (b) S. Y. Ko, J. Lerpiniere and A. M. Christofi, *Synlett.*, 815 (1995). (c) K. S. Kim and L. Qian, *Tetrahedron Lett.*, **34**, 7677 (1993). (d) M. A. Poss, A.Iwanowicz, J. A. Reid and J. Lin, Z. Gu, *Tetrahedron Lett.*, **33**, 5933 (1992).

12. (a) C. W. Zapf and M. Goodman, *J. Org. Chem.*, **68**, 10092 (2003). (b) M. Bonnat, M. Bradley and J. D. Kilburn, *Tetrahedron Lett.*, **37**, 5409 (1996).

13. (a) A. El-Faham, *Chemistry Lett.*, 671 (1998). (b) A. El-Faham, *Org. Prep. Proced. Int.*, **30**, 477 (1998). (c) L. A. Carpino and A. El-Faham, *J. Am. Chem. Soc.*, **117**, 5401 (1995).

14. (a) M. Del Frenso, A. El-Faham, L. A. Carpino, M. Royo and F. Albericio, *Org. Lett.*, **2**, 3539 (2000). (b) J. Jordi, G. Barany, F. Albericio and S. Kates, *Lett. Pept. Sci.*, **6**, 243 (1999). (c) F. Albericio, J. M. Bofill, A. El-Faham and S. A. Kates, *J. Org. Chem*, **63**, 9678 (1998). (c) H. Gausephohl, U. Pieles and R. W. Frank, J. A. Smith and J. R. Rivier (Eds) *Peptide, Chemistry and Biology: Proceedings of the 12th American Peptide Symposium*, ESCOM, Leiden, The Notherland, 1992, pp-523-524.

15. A. El-Faham, A. M. El Massry, A. Amer and Y. Goher, *Lett. Pept. Sci.*, **9**, 49 (2002).

16. E. W. Douglas and S. Hamilton, *J. Org. Chem.*, **67**, 7553 (2002).

(Received November 10, 2003; in final form January 24, 2004)