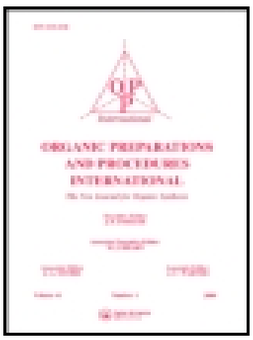

Organic Preparations and Procedures International

ISSN: 0030-4948 (Print) 1945-5453 (Online) Journal homepage: http://www.tandfonline.com/loi/uopp20

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To cite this article: M. Abdul-Ghan , Sh. N. Khattab , A. M. El-Massry , A. El-Faham & Adel Amer (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, DOI: 10.1080/00304940409355382

To link to this article: http://dx.doi.org/10.1080/00304940409355382

Published online: 09 Feb 2009.

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

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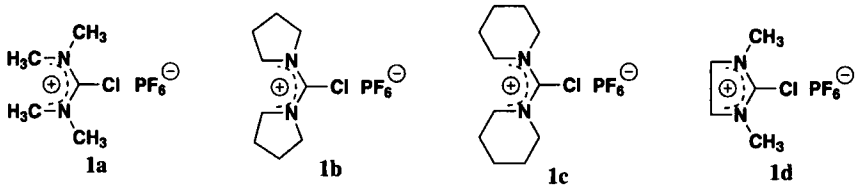
Guanidine functions are important motifs and often are present in natural products as well as in many compounds having therapeutic activity.[1,2] Consequently, a number of guanylating reagents in the literature and/or available commercial sources are known.[3-5] Direct synthetic approaches for the preparation 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]

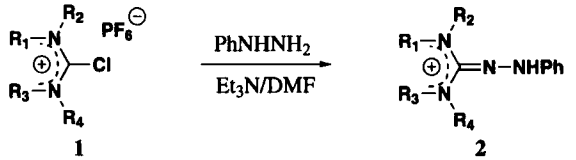
Salts **1a-d** have been used mainly as coupling reagents in peptide synthesis, in the presence or absence of an additive,[13] by activating the carboxyl group of the amino acid. However, during the much slower activation of hindered amino acids, protected peptide segments, or carboxylic acids involved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



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) $R_1 = R_3 = CH_2$; $R_2 = R_4 = CH_3$

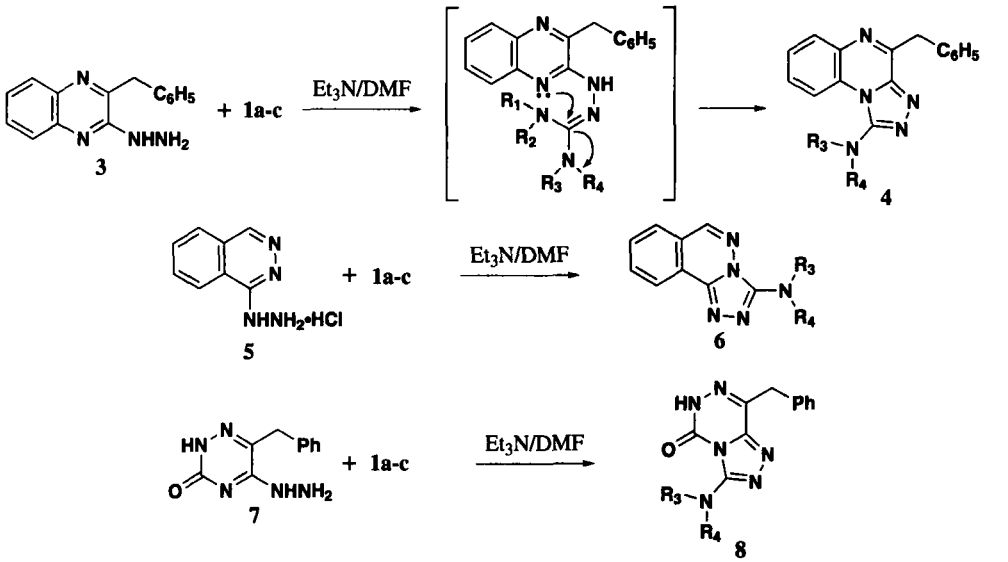
Scheme 1

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.

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