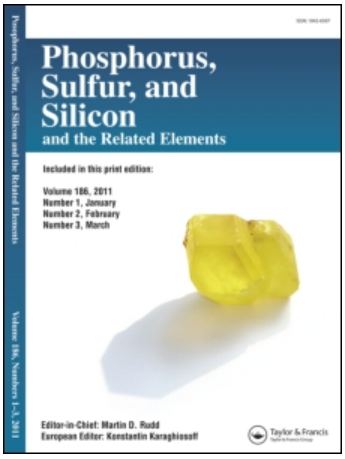

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Synthesis of Some of New Substituted 2-(Phenyl)-1,3-dimethyl- and -1,1,3,3-tetramethylguanidines

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SYNTHESIS OF SOME OF NEW SUBSTITUTED 2-(PHENYL)-1,3-DIMETHYL- AND -1,1,3,3-TETRAMETHYLGUANIDINES

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*A series of new 2-(phenyl)-1,3- and 2-(phenyl)-1,3,3-tetramethylguanidines (**a–k**) were synthesized by reaction of different substituted aniline and urea derivatives in the presence of phosphorus oxychloride. The yields of products following extraction from toluene without further purification were of the order of 50–70%. We have found that adjusting of the pH at 8-9 in the work up process increases the yield of products. IR, ^{1}HNMR, and also mass spectrscopies were used for identification of these compounds.*

Keywords: 1,3-Dimethyurea; dimethylguanidine; guanidine; *p*-bromoaniline; phosphorus oxychloride

Guanidines have been found in many natural products and are also known as critical part of certain biological processes.[1] Some of the guanidines act as antimamalarial agents.[2–4] Therefore guanidines have been subjected to a large variety of structural modifications in order to obtain derivatives with different properties and applications. Various synthetic approaches for the synthesis of different guanidines have been reported in several articles.[5–18] Most of these methods, which are nongeneral processes, are based on using new reagents for the preparation of protected and unprotected guanidines. A short review about recent developments in the guanidine chemistry has been reported by Yet.[19]

Here, due to versatile biological properties of guanidines, we have extended the more general synthetic method of Bredereck et al.[5] in order to synthesize some novel guanidines in high yield.

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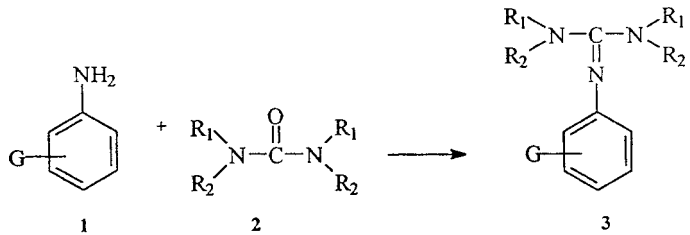
RESULTS AND DISCUSSION

The new substituted 2-(phenyl)-1,3- and 2-(phenyl)-1,3,3-tetramethylguanidines were synthesized easily by using a modification of Bredereck's general method.[5] Reaction of 1,3-dimethyurea or tetramethylurea with different substituted aniline in the presence of $POCl_3$ under reflux gave compounds **3(a–f)** and **3(g–k)** respectively. Adjusting the pH at 8–9 in the work-up process of these reactions is an important factor, which can transfer the unreacted starting material to the organic phase. This method is very clean and can be used with different substituted anilines depending on the group G to prepare various guanidines (Scheme 1).

Reactions were usually carried out for 7–8 h (Table I). Yields of the products were in the order of 40–57%; they are summarized in Table I. Based on the ^{1}H-NMR (500 MHz) spectra these products were of high purity. The ^{1}H NMR spectra of **3(a–f)** show two singlet signals at 2.0–2.6 and 5.2–5.6 ppm due to the resonance of two $-CH_3$ and two $-NH$ groups respectively. The multiplet signal at 6.6–7.2 ppm is assigned to the resonance of different aryl protons.

The ^{1}H NMR spectra of **3(g–k)** are very similar to those of **3(a–f)**. Two singlet signals at 2.3–2.80 are due to the resonance of four $-CH_3$ groups. The multiplet signal at 6.2–8.0 ppm is assigned to the resonance of different aryl protons. Compound **3i** has two singlet signals at 2.08 and 2.2 ppm attributable to two $-CH_3$ groups bonded to the phenyl ring. Such a resonance can be seen for **3e** at 2.0 and 2.2 ppm.



1 2 3

3a) G= 4-Br, $R_1 = CH_3$, $R_2 = H$
3b) G= 2-Cl, $R_1 = CH_3$ $R_2 = H$
3c) G= 2,4,5-trichloro, $R_1 = CH_3$ $R_2 = H$
3d) G= 3,4-dichloro, $R_1 = CH_3$ $R_2 = H$
3e) G= 2,4-dimethyl, $R_1 = CH_3$ $R_2 = H$
3f) G= H, $R_1 = CH_3$ $R_2 = H$
3g) G= 4-nitro, $R_1 = R_2 = CH_3$
3h) G=3-nitro, $R_1 = R_2 = CH_3$
3i) G= 2,4,5-trichloro, $R_1 = R_2 = CH_3$
3j) G= 4-Br, $R_1 = R_2 = CH_3$
k) G= H, $R_1 = R2 = CH_3$

SCHEME 1

TABLE I Reaction Time and Yields on the Formation of Guanidines

Entry	Reaction time (h)	Yield (%)
3a	7	40
3b	8	55
3c	8	45
3d	7	43
3e	7	49
3f	8	48
3g	8	42
3h	8	40
3i	7	49
3j	7	46
3k	7	57

In the IR spectra of compounds **3(g–k)** the absence of the absorption at 3200–3400 cm^{-1}, the characteristic absorption of the $-NH_2$ group of the starting material, is good evidence of the expected reactions. Additional evidence for the structure of the compounds was obtained from mass spectra. The molecular ion peak of the compounds could be seen clearly.

EXPERIMENTAL

Melting points were determined with an electrothermal digital melting point apparatus. IR spectra were recorded on a Galaxy series FT-IR 5000 spectrophotometer by using KBr pellets. HNMR spectra were recorded on Bruker 400 and 500 MHz spectrometers, using Me_4Si (TMS) as an internal standard. Mass spectra were measured with an EI (70 eV) + Q1MSLMR up LP spectrometer. Reaction courses and product mixtures were monitored by thin layer chromatography.

General Procedure for Preparation

1,3-Dimethyurea or tetra-methylurea (0.01 mmol) in dry toluene (50 ml) was stirred for 5 min. This solution was treated dropwise with a solution of phosphorus oxychloride (0.15 mmol) in 20 ml of dry toluene. The reaction mixture was stirred at room temperature for 10 h and then a solution of the appropriate substituted aniline (0.015 mmol) was added. The reaction mixture was refluxed for 7–8 h and the oily substance separated by a separator funnel. The residue was then dissolved in water and the pH adjusted to 8–9 with adding 2 N NaOH solution.

The resulting solution was washed several times with 20 ml portions of toluene. The pH was adjusted to about 14 by adding 2 N NaOH and extracted several times-with 20 ml portions of toluene. Evaporation of toluene on a rotary evaporator afforded the desired compound.

2-(4-Bromophenyl)-1,3-dimethylguanidine (3a)

m.p. 145–147°C. IR (KBr): $\upsilon = 3225$ (NH), 2900–3050 (CH arom and aliph), 1520–1620 (C=C and C=N conjugated), 1055 (C–N) cm^{-1}. ^{1}HNMR (DMSO-d_6): $\delta = 6.6$–7.2 (m, 4Harom), 5.4 (s, 2H, 2-NH), 2.6 (s, 6H, 2-CH_3) MS: (m/z %) = 242 (M^+, 98%), 241 (100%), 183 (84%), 170 (21%), 89 (37%).

2-(2-Chlorophenyl)-1,3-dimethylguanidine (3b)

m.p. 130–132°C. IR (KBr): $\upsilon = 3245$ (NH), 2900–3050 (CH arom and aliph), 1520–1620 (C=C and C=N conjugated), 1153 (C–N) cm^{-1}. ^{1}HNMR (DMSO-d_6): $\delta = 6.7$–7.2 (m, 4Harom), 5.2 (s, 2H, 2-NH), 2.6 (s, 6H, 2-CH_3).

2-(2,4,5-Trichlorophenyl)-1,3-dimethylguanidine (3c)

m.p. 162–164°C. IR (KBr): $\upsilon = 3240$ (NH), 2900–3045 (CH arom and aliph), 1520–1620 (C=C and C=N conjugated), 1150 (C–N) cm^{-1}. ^{1}HNMR (CD_3OD): $\delta = 7.5$ (s, 1Harom), 6.9 (s, 1Harom), 5.6 (s, 2H, 2-NH), 2.6 (s, 6H, 2-CH_3) MS: (m/z %) = 266 (M^+, 66%), 264 (80%), 236 (68%), 234 (80%), 194 (73%), 159 (40%), 123 (49%), 83 (45%).

2-(3,4-Dichlorophenyl)-1,3-dimethylguanidine (3d)

m.p. 111–113°C. IR (KBr): $\upsilon = 3267$ (NH), 2850–3050 (CH arom and aliph), 1500–1630 (C=C and C=N conjugated), 830 (C-Cl) cm^{-1}. ^{1}HNMR (DMSO-d_6): $\delta = 6.6$–7.2 (m, 3 Harom), 5.5 (s, 2H, 2-NH), 2.6 (s, 6H, 2-CH_3). MS: (m/z %) = 232 (M^+, 37%), 230 (100%), 202 (42%), 160 (76%), 71 (41%), 57 (52%).

2-(2,4-Dimethylphenyl)-1,3-dimethylguanidine (3e)

m.p. 95–97°C. IR (KBr): $\upsilon = 3225$ (NH), 2900–3100 (CH arom and aliph), 1520–1650 (C=C and C=N conjugated), 1147 (C–N) cm^{-1}. ^{1}HNMR (CD_3OD): $\delta = 6.6$–6.9 (m, 3Harom), 2.7 (s, 6H, 2N-CH_3), 2.2 (s, 3H, –CH_3), 2.0 (s, 3H, –CH_3). MS: (m/z %) = 199 (M^+, 100%), 176 (86%), 159 (24%), 105 (6%), 90 (6%).

2-Phenyl-1,3-dimethylguanidine (3f)

m.p. 112–114°C. IR (KBr): $\upsilon = 3265$ (NH), 2900–3100 (CH arom and aliph), 1500–1650 (C=C and C=N conjugated), 1149 (C–N) cm^{-1}. ^{1}HNMR (CD_3OD): $\delta = 6.6$–7.2 (m, 5Harom), 2.7 (s, 6H, 2N-CH_3). MS:

(m/z %) = 163 (M^+, 97%), 148 (15%), 133 (54%), 106 (100%), 91 (19%), 77 (6%).

2-(4-Nitrophenyl)-tetramethylguanidine (3g)

m.p. 83–85°C. IR (KBr): υ = 2900–3050 (CH arom and aliph), 1480–1550 (C=C and C=N conjugated), 1103 (C—N), 1280–1320 (NO_2) cm^{-1}. ^{1}HNMR (CD_3OD): δ = 6.6–8.0 (m, 4Harom), 2.8 (s, 12H, 4-N-CH_3).

2-(3-Nitrophenyl)-tetramethylguanidine (3h)

m.p. 233–235°C. IR (KBr): υ = 2850–3100 (CH arom and aliph), 1500–1600 (C=C and C=N conjugated), 1146 (C—N), 1348 (NO_2) cm^{-1}. ^{1}HNMR (CD_3OD): δ = 2.5 (s, 12H, 4-N-CH_3), 6.5–6.7 (m, 4Harom).

2-(2,4-Dimethylphenyl)-tetramethylguanidine (3i)

m.p. 228–230°C. IR (KBr): υ = 2900–3100 (CH arom and aliph), 1500–1700 (C=C and C=N conjugated), 1138 (C—N). ^{1}HNMR (CD_3OD): δ = 6.4–6.9 (m, 3Harom), 2.6 (s, 12H, 4-NCH_3), 2.2 (s, 3H, —CH_3), 2.08 (s, 3H, —CH_3).

2-(4-Bromophenyl)-tetramethylguanidine (3j)

m.p. 170–172°C. IR (KBr): υ = 2900–3100 (CH arom and aliph), 1500–1580 (C=C and C=N conjugated), 1141 (C—N), 642 (C-Br). ^{1}HNMR ($CDCl_3$): δ = 6.5–7.7 (m, 4Harom), 2.8 (s, 12H, 4-NCH_3).

2-Phenyl-tetramethylguanidine (3k)

m.p. 257–258°C. IR (KBr): υ = 2850–3100 (CH arom and aliph), 1500–1600 (C=C and C=N conjugated), 1146 (C—N). ^{1}HNMR ($CDCl_3$): δ = 6.2–6.9 (m, 5Harom), 2.3 (s, 12H, 4-NCH_3).

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