Synthesis of Highly Basic Hexasubstituted Biguanides by Environmentally Friendly Methods

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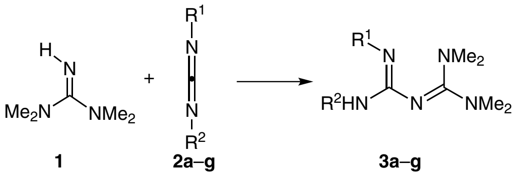
Abstract: A series of hexasubstituted biguanides was synthetized employing nonconventional and environmentally friendly methods. Their properties were studied computationally (basicity) and experimentally (basicity and catalytic properties in transesterification reaction).

Key words: guanidines, superbases, green chemistry, solid-phase synthesis, nucleophilic addition, catalysis

Guanidine derivatives occupy an important role in the design of strong nonionic organic bases, primarily due to their high catalytic potential in a number of synthetically important reactions,[1,2] to mention only the transesterification of vegetable oils, which is a key step in the production of biodiesel.[3,4] In the course of these studies, considerable attention, both experimentally and computationally, has been paid to molecular modifications of the parent molecule leading to an enhancement of its basicity. This was achieved through electronic effects by changing the nature and the site of attachment(s) of substituents at the guanidine moiety, substitution by flexible heteroalkyl chains which are capable of forming intramolecular hydrogen bonds (IMHB), implementing structural rigidity as in proton sponges,[5] enlargement of the guanidine framework leading to polyguanides, etc.[6] In contrast to guanidines, basicity of biguanides and their higher analogues has been less thoroughly explored. In the recent theoretical work it was shown that increasing the number of guanidine subunits in the molecule and the presence of bifurcation centers in the higher analogues significantly increases basicity relative to that of the parent guanidine, due to a pronounced increase in the resonance interaction in the corresponding conjugate acid.[7] In previous studies we have reported on the gas-phase basicity and pK_a values in acetonitrile of several guanidines with a special emphasis put on compounds capable of forming intramolecular hydrogen bonds upon protonation.[8] In the course of these studies, we became confronted with a lack of suitable reference bases which would allow precise determination of the proton affinity and/or pK_a values. We felt it, therefore worthwhile to extend a number of available bases starting with a series of biguanide derivatives described in this work. Our primary goal in undertaking this study was to explore possibility of applying different eco-friendly procedures for their preparation. Next, brief discussion on their gas-phase and solution basicities predicted by quantum chemical calculations are included. Finally, we compare catalytic ability of the newly prepared compounds in transesterification of vegetable oil with those of previously studied guanidine derivatives.

A series of seven biguanides **3a**–**g**[9] was prepared by reaction of tetramethylguanidine (**1**) to carbodiimides **2a**–**g** (Scheme 1). Reaction conditions were optimized for each carbodiimide and are listed in Table 1 and in the Supporting Information (Table S1).[10,11]



a $R^1 = R^2 =$ *i*-Pr, **b** $R^1 = R^2 =$ *c*-Hex, **c** $R^1 =$ Et, $R^2 = Me_2N(CH_2)_3$, **d** $R^1 = Me_2N(CH_2)_3$, **e** $R^1 = R^2 = MeO(CH_2)_3$, **f** $R^1 = Me_2N(CH_2)_3$, $R^2 =$ Ph, **g** $R^1 = Me_2N(CH_2)_3$, $R^2 = 4\text{-}MeOC_6H_4$

Scheme 1 Reaction of tetramethylguanidine (**1**) with carbodiimides

Table 1 Synthesis of Biguanides **3a**–**g**

Base	Method[a]	Conditions	Conv. (isolated yield, %)[b]
3a	MW[f]	120 °C, 40 min	>99 (56)
	HVSM-1[g]	ball (12 mm), 2 h	15
	HVSM-2[g]	50 balls (3 mm), 2 h	40
	HP	6 kbar, r.t., 96 h	66 (65)[c]
	US	50 °C, 2 h	53
	thermal		(94)[4]
3b	MW	120 °C, 90 min	95 (63)
		80 °C, 2.5 h, $Y(OTf)_3$	63
		80 °C, 2 h, $Yb(OTf)_3 \cdot H_2O$	62
	HVSM-2	50 balls (3 mm), 2 h	5
	HP	6 kbar, r.t., 24 h	n.r.[i]
	US	50 °C, 2 h	43
	thermal		(62)[4]

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Table 1 Synthesis of Biguanides **3a–g** (continued)

Base	Method[a]	Conditions	Conv. (isolated yield, %)[b]
3c	MW	120 °C, 5 min	>98 (89)
	HVSM-1	ball (12 mm), 30 Hz, 2 h	traces[d]
	HP	6 kbar, r.t., 24 h	traces[e]
	US	50 °C, 2 h	n/d[f] (44)
	thermal	90 °C, dry THF, 1 h	90 (77)
3d	MW	90 °C, 5 min	>98 (43)
	HSVM-1	ball (12 mm), 1 h	<5 polym.
	HP	6 kbar, r.t., 24 h	10
	US	50 °C, 1 h	50 (33)
	thermal	90 °C, dry THF, 1 h	98 (34)
3e	MW	90 °C, 10 min	>95 (80)
	HVSM-1	ball (12 mm), 1 h	44
	HP	6 kbar, r.t., 24 h	traces
	US	50 °C, 2 h	68 (18)
	thermal	90 °C, dry THF, 1 h	96 (54)
3f[h]	MW	90 °C, 5 min	98 (95)
	HVSM-1	ball (12 mm), 1 h	95 (82)
	HP	6 kbar, r.t., 24 h	80 (64)
	US	40 °C, 1 h	91(74)
	thermal	90 °C, dry THF, 2 h	99 (93)
3g[h]	MW	90 °C, 5 min	99 (92)
	HVSM-1	ball (12 mm), 1 h	94 (86)
	HP	6 kbar, r.t., 24 h	75 (57)
	US	40 °C, 1 h	86 (75)
	thermal	90 °C, dry THF, 2 h	99 (93)

[a] MW: microwave heating; HSVM: high-speed vibrational milling; HP: high pressure; US: ultrasound.
[b] Isolated yields are given in parentheses.
[c] n(TMG)/n(DIC) = 1:1.3; yields were determined from the crude product mixture and corrected for the presence of the reactants according to the GC analysis.
[d] Complete loss of EDCI was observed indicating polymerization or formation of some insoluble product.
[e] Solidification of material.
[f] Not determined.
[g] HSVM-1: MM 400 vibrational mill, 30 Hz, NaCl; HSVM-2: planetary mill (PM 200), 500 rpm, NaCl.
[h] Conditions for **3f**,**g**: Na_2SO_4: HSVM (1 equiv), other methods: 0.1 equiv.
[i] n.r. = no reaction.

Extent of conversion of the reactants into the products was determined by GC analysis. Isolation of the products included removal of the reactants under high vacuum, partitioning between CH_2Cl_2 and H_2O and (except for the biguanides **3f** and **3g**) distillation of the product under high vacuum. Details of the synthetic procedures are given in the Supporting Information.

The following nonclassical, environmentally friendly methods were employed: microwave heating,[12] high-speed vibrational milling,[13] high pressure,[14] and ultrasound.[15] Obtained results were compared with those obtained by classical thermal reactions carried out in the present work or taken from ref. 4. To the best of our knowledge, our work is the first account on the use of high pressure, mechanochemistry, and ultrasound for the synthesis of this type of compounds, while the reaction under microwave heating was used previously for the synthesis of biguanides from amine and guanidine.[16]

The inspection of results reveals that microwave reactions are the best in respect to reaction time and conversion into products. Isolated yields are moderate to high (56–92%), and in the most cases the reaction is completed within five minutes.[17] In all cases formation of some polymeric materials and unidentified side products was observed at the elevated temperatures (>90 °C). On the other hand, at the temperatures below 80 °C, reactions slowed down, but products were cleaner. Reaction conditions given in Table 1 represent a balance between minimizing amount of side products and shortening of the reaction time.

To avoid undesirable temperature effects we next performed reactions under high pressure, mechanochemical, and ultrasonic conditions at room temperature. However, condensations conducted at extremely high pressure (6 kbar) led only in few cases to satisfactory conversion into biguanides. The rest of carbodiimides afforded traces of products (**2b**, **2c**, and **2e**), while in the case of **2d** preferential formation of the polymeric unidentified material was observed. The best results were achieved for **3f** and **3g** (64 and 57% of the isolated yield, respectively). It is interesting to note that for both of these compounds the isolated yields were significantly lower than the extent of conversion, indicating that partial conversion of the carbodiimides to the undesired side products took place during the reaction and isolation of the products. In some cases, like, for example, in the reaction of carbodiimide **2a**, conversion into products could be improved by prolonged pressurization. Similar results were obtained in the solid-state reactions carried out in the ball mill. The best conversion was achieved in the synthesis of **3f** and **3g** (95 and 94%), while the other reactions were not successful. We also observed that in reactions of **2f** and **2g** the discrepancy between conversion and the isolated yields was smaller than in the corresponding high-pressure reactions. In preparation of **3a**, an attempt was also made to increase efficacy of mechanochemical reactions by increasing the number of stainless steel balls (see Supporting Information for details) in a planetary ball mill. It was found that the conversion of carbodiimide **2a** increased up to 40% when the 50 balls were used. Sonochemical syntheses of biguanides were also conducted at a temperature slightly above room temperature. Again, excellent conversions

(>90%) were achieved in the case of **2f** and **2g**, while the other carbodiimides were less reactive.

To summarize, under all experimental conditions applied, **2a** and **2b** showed the lowest reactivity and acceptable yields were obtained only under microwave-heating conditions at 120 °C. The GC analysis showed the formation of a large amount of the side products as evidenced by the largest difference between extent of conversion and the isolated yield. Attempts were also made to increase reactivity of **2b** at lower temperature under microwave conditions by addition of $Y(OTf)_3$ or $Yb(OTf)_3 \cdot H_2O$. Obtained results showed small if any improvement in comparison to the reaction under microwave heating carried out without catalysts.

Based on the above results we can classify reactions into three groups: first, in which carbodiimides of low reactivity (**2a** and **2b**) give significant amount of the target biguanides under prolonged heating; second: in which reactive carbodiimides **2f** and **2g** react smoothly and fast irrespectively of the method employed giving stable biguanides **3f** and **3g**; and the third group in which reactive carbodiimides (**2c**–**e**) give very good yields at the elevated temperature, but the concurrent side reactions take place. This particularly holds for the compound **2d** which gives the lowest yield under microwave heating and practically no product if the reactions are conducted at the room temperature (high pressure).

In the case of less reactive carbodiimides, microwave-heating reaction conditions were superior to thermally conducted reactions (conversion and yields), which are environmentally less friendly, since reactions are carried out in organic solvent and reaction times are much longer. Another 'green' aspect is the reduced use of organic solvent in reactions under microwave heating, which was needed only for product isolation.

Gas-phase basicities and proton affinities of biguanides **3a**–**g** were calculated at B3LYP/6-311+G-(2df,p)//B3LYP/6-31G(d) level of theory. Calculation of their pK_a in acetonitrile solution was conducted using either IPCM/B3LYP/6-311+G(2df,p)//B3LYP/6-31G(d) (M1[18]) or IEF-PCM/B3LYP/6-311+G(2df,p)//B3LYP/6-31G(d) (M2[19]) models which were proved to give very good agreement with the experimental data on structurally similar compounds in our previous papers.[18] The pK_a values of biguanides **3a**–**g** with exception for the most basic ones (**3b** and **3d**) were also measured by UV spectroscopy (in MeCN, Table 2).

All bases prepared in this study have much higher (20–30 kcal·mol^{-1}) proton affinities than a standard proton sponge (245 kcal·mol^{-1}) and thus belong to the superbase class.[1] Biguanide **3d** possesses the highest proton affinity and gas-phase basicity, as a consequence of stabilization of the protonated form by two intramolecular hydrogen bonds (Figure 1). The biguanides with substituents capable of forming only one intramolecular hydrogen bond are, as expected, less basic (**3e**–**g**). Absolute gas-phase basicities of the compounds are similar to the most basic representatives of recently measured series of heteroalkyl-substituted guanidines.[8d] These new biguanides fill the basicity scale between 256 and 266 kcal·mol^{-1} what until now was reserved for phosphazenes. Thus, the biguanides prepared in this work provide a suitable set of the reference bases for experimental measurements of pK_a values in the range of 25.5–27.0.

Table 2 Calculated Acid/Base Thermodynamic Properties of Biguanides **3a**–**g** in the Gas and the Solution Phase (MeCN)

Base	Proton affinity (kcal·mol^{-1})	Gas-phase basicities (kcal·mol^{-1})	pK_a (M1)[a]	pK_a (M2)[b]	pK_a (UV)
3a	264.9	257.3	27.8	28.4	26.2 (31.8)[4]
3b	267.9	261.3	29.1	29.7	(31.5)[4]
3c	268.6	260.4	27.9	27.8	27.0
3d	274.7	265.8	29.1	28.2	–
3e	269.7	260.6	26.3	25.5	26.6
3f	264.0	256.0	25.1	25.1	25.8
3g	266.9	259.4	26.2	26.3	26.4

[a] Using the equation pK_a = 0.545 $\Delta G_a{'}_{\mathrm{MeCN}}$ – 133.5, ref. 18.
[b] Using the equation pK_a = 0.608 $\Delta G_a{'}_{\mathrm{MeCN}}$ – 152.9, ref. 19.

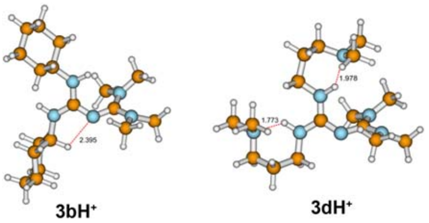
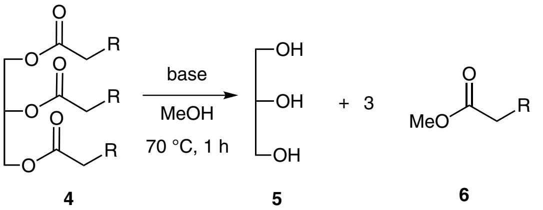


Figure 1 Optimized structures of the protonated forms of biguanides **3b** and **3d**

Biguanides **3b** and **3d** (Figure 1) are calculated to be the most basic and their estimated pK_a values go up to 29 pK_a units, what is comparable to the P_2-phosphazenes[20] and 1,8-bis(hexamethyltriaminophosphazenyl)naphthalene.[21] In acetonitrile, the basicity increase due to intramolecular hydrogen bonds is less pronounced than in the gas phase, and **3f** has the lowest pK_a. The measured pK_a values are in fair agreement with the computationally predicted values (differences are smaller than 0.7 pK_a units for **3f** and **3g**). It should be, however, stressed that our pK_a value for **3a** is significantly lower than the value reported previously in ref. 4. We assume that the reason for that could be ascribed to uncertainty of the method used earlier. The latter is corroborated with the fact that pK_a values of **3a** and **3b** are higher by ca. 2–3 pK_a units than our values predicted by M1 and M2 equations, and in the reverse relative order, while our experimentally determined pK_a value of **3a** is much closer to the calculated values. Furthermore, the measured pK_a value of **3a** is close to that of **3c** as predicted by calculations.

Catalytic activity of the prepared biguanides **3a**–**g** was explored in transesterification reaction of vegetable oil (Scheme 2), and the results are given in Table 3. Reactions were conducted using the reactant ratio and conditions as described in literature.[22] Detailed description of the procedure is given in the Supporting Information. For the sake of comparison catalytic activities of the known guanidine organic base triazabicyclodecene (TBD) and guanidines **Gu1**–**3**,[23] were also determined. Overall, all examined bases proved to be highly active at the 2% molar loading and within one hour reaction is nearly completed (>90%). At the low catalyst loading (0.5 mol%) differences in reactivities between bases are more pronounced – biguanide **3b** is the most active, while biguanides **3d** and **3f** are the least active. These differences are correlated with basicity in the case of **3b** and **3f**: biguanide **3b** is the most basic, while **3f** is the least basic in acetonitrile [pK_a (M1)]. On the other hand, **3d** is predicted to be equally basic as **3b** [pK_a (M1) = 29.1], but shows lower activity. The activity of most potent biguanide **3b** is comparable to that of TBD and significantly better than those of **Gu1**–**3**.



Scheme 2 Transesterification of vegetable oil with methanol

A small library of the biguanide was prepared using different eco-friendly methods and their performance critically examined. Their proton affinity, gas-phase basicity, and pK_a values were calculated and compared with the measured pK_a values of the selected representatives. All bases prepared in this study have significantly higher (20–30 kcal·mol^{-1}) basicities than N,N,N',N'-tetramethyl-1,8-naphthalenediamine (DMAN) proton sponge and could be classified as superbases. The calculated gas-phase basicity values fall in the range of 256–266 kcal·mol^{-1} making biguanides **3a**–**g** suitable reference bases for basicity measurements in this region. The importance of intramolecular hydrogen bonds in amplifying basicity is demonstrated computationally and experimentally. The prepared biguanides proved to be efficient catalysts in the transesterification reaction of the vegetable oil.

Acknowledgement

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Table 3 Transesterification of Vegetable Oil[a,b]

Base	Conv. (%)		
	Base 0.5 mol%	Base 1 mol%	Base 2 mol%
3a	55	77	93
3b	89	96	95
3c	72	93	95
3d	69	90	94
3e	75	93	97
3f	35	61	91
3g	61	80	93
TBD	95 (81)	99	94
Gu1[c]	54	91	95
Gu2[c]	74	91	96
Gu3[c]	74	94	92

[a] Conditions: 1 h, 70 °C, oil (8.0 g), MeOH (2.0 g), catalyst (0.5 mol).
[b] Obtained by ^{1}H NMR analysis.
[c] Gu = guanidine, **Gu1**: R^1 = R^2 = n-Pr; R^3 = 3-dimethylaminopropyl, **Gu2**: R^1 = R^2 = 3-dimethylaminopropyl; R^3 = n-Pr, **Gu3**: R^1 = R^2 = R^3 = 3-dimethylaminopropyl.23

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(9) Biguanides **3a** and **3b** are known compounds, see ref. 4.

(10) **General Procedures**

Microwave Reaction

The reactants were mixed in the nitrogen-flushed cuvette in the ratio **1**/**2** = 1:1.3 on the 2 mmol scale. The cuvette was heated under microwave irradiation for the desired reaction time (see Tables 1 and S1). Formed biguanides were isolated according to the procedure given below.

High-Speed Vibrational Milling Reaction

Reactants were mixed in a stainless steel jar and milled under conditions given in Tables 1 or S1. After milling for the desired period of time, CH_2Cl_2 was added, and the product mixture was filtered over Celite and charcoal and washed with CH_2Cl_2. Filtrate was evaporated to dryness, and the product was isolated as described below.

High-Pressure Reaction

The mixture of reactants in a molar ratio of **1**/**2** = 1:1.3 on the 1 mmol scale in the closed Teflon reaction vessel was subjected to the pressure of 6–8 kbar. After 24 h reaction the mixture was transferred into the flask, and the conversion was analyzed by GC.

Ultrasound Reaction

The reaction mixture was prepared in the same way as for the microwave-assisted reaction. The cuvette was immersed in the water bath preheated to 50 °C and agitated using ultrasound. Conversion of the carbodiimides into the products was determined by GC.

Thermal Reaction

The solution of reactants in dry THF (1 mL) was prepared in a microwave cuvette, closed, and immersed in an oil bath preheated to 90 °C. The progress of the reaction was followed by GC analysis after 1 or 2 h. The reaction mixture was then cooled, and the product was isolated as described below.

Isolation of the Products

The crude reaction mixture was transferred into the reaction flask, and the excess of **1** was removed via bulb-to-bulb distillation under reduced pressure. The obtained viscous material was dissolved in CH_2Cl_2 (7 mL) and washed with H_2O. The crude product was obtained either by evaporation of the water (**3b**–**e**) or dichloromethane layer (**3a**, **3f**, and **3g**). Biguanide **3b** was washed 7 times with 10 mL of H_2O until complete transfer into the water layer was achieved. In other cases, 3 × 7 mL H_2O portions were sufficient for the extractions. The hydrochloride salt of **3c** was deprotonated by dissolving the crude salt in dry MeOH (10 mL) containing NaOH (1 mol equiv). The solution was stirred for 30 min at r.t. and evaporated to dryness. The remaining material was mulled in CH_2Cl_2, and the solid was collected by filtration. The filtrate was evaporated to dryness and subjected to vacuum distillation. Biguanides **3a**–**e** were further purified by vacuum distillation at $2–5 \cdot 10^{-5}$ mbar (10^{-3} Pa) at the oil bath temperature of 150–180 °C.

(11) New compounds gave satisfactory physical and spectral data (^1H NMR, ^{13}C NMR, and HRMS spectra).

Selected Physical and Spectral Data

Compound **3c**: colorless viscous oil. ^1H NMR (600 MHz, CD_3CN): δ = 1.06 (t, J = 7.2 Hz, 3 H), 1.59 (q, J = 7.1 Hz, 2 H), 2.16 (s, 6 H), 2.27 (t, J = 7.2 Hz, 2 H), 2.73 (s, 12 H), 2.90–3.00 (m, 4 H). ^{13}C NMR (150 MHz, CD_3CN): δ = 16.4, 29.5, 38.9, 39.3, 43.2, 45.4, 58.6, 156.2, 159.9.

Compound **3d**: colorless viscous oil. ^1H NMR (300 MHz, DMSO-d_6): δ = 1.58 (q, J = 6.9 Hz, 2 H), 2.11 (s, 12 H), 2.23 (t, J = 7.0 Hz, 2 H), 2.75 (s, 12 H), 2.98 (t, J = 6.7 Hz, 2 H). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 27.8, 39.6, 45.6, 49.0, 57.3, 157.7, 161.6.

Compound **3e**: colorless viscous oil. ^1H NMR (600 MHz, CD_3CN): δ = 1.71 (q, J = 6.5 Hz, 4 H), 2.74 (s, 12 H), 2.99 (t, J = 6.5 Hz, 4 H), 3.32 (s, 6 H), 3.42 (t, J = 6.5 Hz, 4 H). ^{13}C NMR (150 MHz, DMSO-d_6): δ = 31.1, 39.1, 49.0, 58.2, 71.1, 156.0, 159.0.

Compound **3f**: brownish-yellow viscous oil. ^1H NMR (600 MHz, $CDCl_3$): δ = 1.74 (q, J = 7.0 Hz, 2 H), 2.20 (s, 6 H), 2.33 (t, J = 7.0 Hz, 2 H), 2.50 (s, 12 H), 3.31 (t, J = 7.0 Hz, 2 H), 3.71 (s, 3 H), 6.68 (d, J = 8.85 Hz, 2 H), 6.75 (d, J = 8.85 Hz, 2 H). ^{13}C NMR (150 MHz, $CDCl_3$): δ = 27.8, 38.6, 40.6, 45.6, 57.9, 120.3, 122.7, 128.1, 150.2, 155.7, 160.7.

Compound **3g**: brownish-yellow viscous oil. ^1H NMR (600 MHz, $CDCl_3$): δ = 1.74 (q, J = 7.0 Hz, 2 H), 2.20 (s, 6 H), 2.33 (t, J = 7.0 Hz, 2 H), 2.50 (s, 12 H), 3.31 (t, J = 7.0 Hz, 2 H), 3.71 (s, 3 H), 6.68 (d, J = 8.85 Hz, 2 H), 6.75 (d, J = 8.85 Hz, 2 H). ^{13}C NMR (150 MHz, $CDCl_3$): δ = 27.8, 38.7, 40.6, 45.5, 55.6, 57.9, 113.6, 123.4, 128.2, 154.0, 155.8, 160.4.

For further details see Supporting Information.

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(23) Substitution numbering (Figure 2).

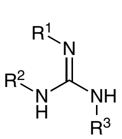

Figure 2