The Preparation of 1,2,3-Trisubstituted Guanidines

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Submitted to honor the 85th birthday of *Rolf Huisgen:* inspiring chemist and good friend

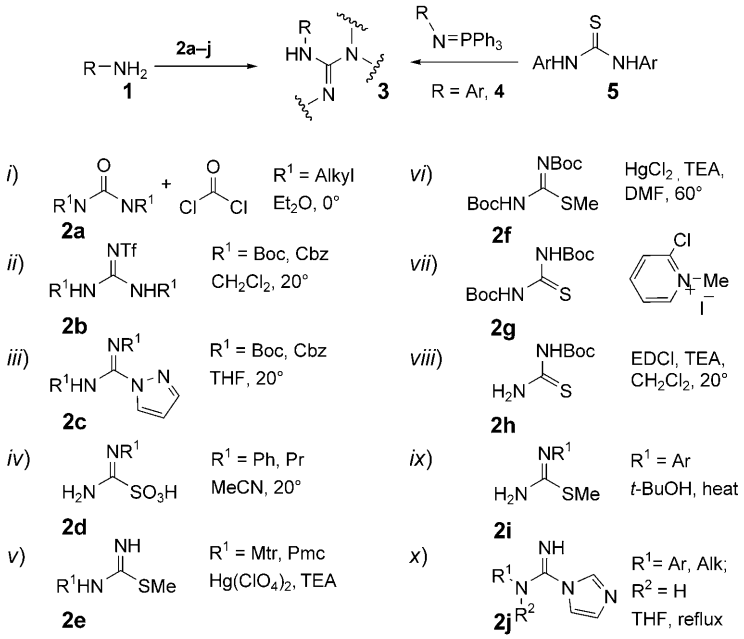
An operationally straightforward and efficient benzotriazole-based method for the guanylation of diverse amines by use of the new reagent classes (bis-benzotriazol-1-yl-methylene)amines **13a**–**13f** and benzotriazole-1-carboxamidines **17a**–**17i** is described. The preparation is described for a variety of both acyclic and cyclic 1,2,3-trisubstituted guanidines in high yields.

Introduction. – A wide variety of structurally diverse molecules that incorporate guanidine units have been isolated from many microorganisms and higher plants [1]. Guanidines are core features of many therapeutically active compounds [2–7], and guanidine alkaloids exhibit antiviral, antifungal, and antitumor activities [1]. Thus, procedures for the preparation of guanidines [8] are of great interest in medicinal chemistry, and much effort has been directed towards efficient syntheses of these compounds (see, *e.g.*, [9]).

The synthesis of guanidines **3** is complicated by their high basicity and nucleophilicity. Many syntheses utilize intermediates with easily removed protective groups. Common methods for the preparation of guanidines **3** involve attack of an amine **1** on various activated guanidinylating reagents **2a**–**2j** (*Scheme 1*). Primary amines react smoothly and efficiently with these reagents, whereas sterically more demanding secondary or electronically deactivated aromatic amines face various difficulties.

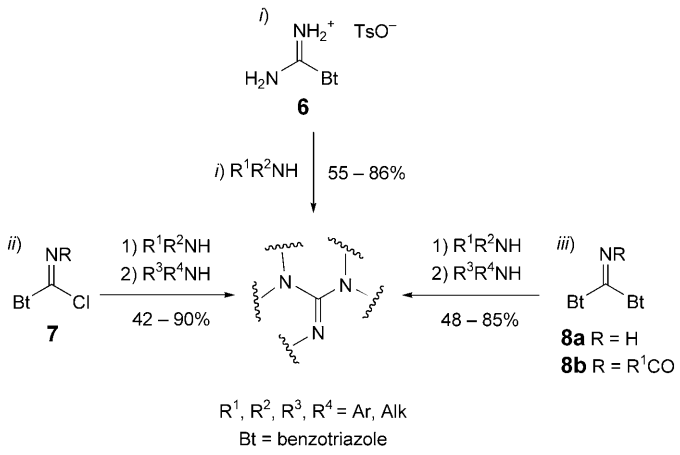
Methods for the preparation of guanidines **3** (*Scheme 1*) include: *i*) reaction of various ureas **2a** with phosgene then treating the resultant *Vilsmeier* salt with amines **1** [10]; *ii*) using triflicguanidines **2b** as guanidinylating reagents [11], or *iii*) guanylpyrazole **2c** as guanidinylating reagents [12]. Several common routes to **3** involve the treatment of amines with electrophilic species **2d**–**2i** generated from thioureas: *iv*) sulfonic acids **2d** derived from *N*-alkyl-substituted thioureas [13]; *v*) *S*-methyl(aryl)-sulfanylisothioureas **2e** [14], in the presence of Hg salts; *vi*) bis-Boc-isothioureas **2f** and $HgCl_2$ [15–18]; *vii*) bis-Boc-thioureas **2g** and *Mukaiyama*'s Reagent to form a carbodiimide subsequently treated with amines [19]; *viii*) acylthioureas **2h** and amines in the presence of the water-soluble carbodiimide, EDCI (=1-ethyl-3-[3-(dimethylamino)propyl]carbodiimide hydrochloride), [20]; *ix*) *S*-methylisothiourea **2i** in refluxing *t*-BuOH with aryl amines [21][22]; or *x*) other guanidinylating reagents including 1*H*-imidazole-1-carboxamidines **2j** [23], and 1,3-diarylthioureas **5** with iminophosphoranes **4** to form trisubstituted guanidines **3** [24].

Scheme 1



Our group introduced benzotriazole-based guanylating reagents: *i*) 1*H*-benzotriazole-1-carboxamidinium *p*-toluenesulfonate **6** [25], *ii*) (1*H*-benzotriazolyl)carboximidoyl chlorides **7** [26], and *iii*) bis(1*H*-benzotriazolyl)carboximidamides **8a** and **8b** (*Scheme 2*) [27]. Reagents **6**–**8** guanylate primary and secondary amines under mild conditions in high yields (*Scheme 2*). 1*H*-Benzotriazole-1-carboxamidinium *p*-tolu-

Scheme 2



enesulfonate **6** affords mono- and *N,N*-disubstituted guanidines (55–86%). Stable, odorless (1*H*-benzotriazolyl)carboximidoyl chlorides **7** allow the preparation of unsymmetric polysubstituted guanidines (45–92%). Bis(1*H*-benzotriazolyl)carboximidamide **8a** enables the synthesis of tri- and tetra-substituted-guanidines from a wide variety of amines. Bis(1*H*-benzotriazolyl)carboximidamides **8b** are efficient for the preparation of acylguanidines (48–85%) [28].

To provide for the facile preparation of polysubstituted guanidines (*cf. Scheme 3*, and *Tables 1* and *3*), we have now introduced convenient 1*H*-benzotriazole-based guanylation using novel [bis(1*H*-benzotriazol-1-yl)methylidene]amines **13** and 1*H*-benzotriazole-1-carboxamidines **17**.

Results and Discussion. – [Bis(1*H*-benzotriazol-1-yl)methylidene]amines **13a**–**13f** were prepared from bis(1*H*-benzotriazol-1-yl)methanethione (**15**) and triphenylphosphine imides **14a**–**14f** in toluene at 70° for 3 h and purified by column chromatography (*Scheme 3*). Known triphenylphosphine imides **14a**–**14g** were synthesized in quantitative yields from the reaction of the corresponding organic azides with Ph_3P in EtOH at reflux for 2 h [29]. Melting points and spectral data for **14a**–**14g** were identical to reported values (see the *Exper. Part*). The structures of novel **13a**–**13e** were supported by their ^{1}H- and ^{13}C-NMR spectra, and elemental analysis data (see the *Exper. Part*). Known **13f** was previously been synthesized by a different method [28].

Syntheses of symmetric guanidines **11a**–**11e** from **13a**–**13e** and aliphatic primary amines were accomplished in high yields on refluxing in toluene for 1 h (*Scheme 3* and *Table 1*). Compound **11a** was prepared earlier [30]; novel **11b**–**11e** were fully characterized on the basis of ^{1}H- and ^{13}C-NMR spectroscopy, and elemental analysis. However, we failed to prepare symmetric guanidines corresponding to **11** from **13a**–**13e** and secondary amines; possibly because, with secondary amines, carbodiimide **10** formation [31] by elimination of 1*H*-benzotriazole from an intermediate analogous to **9** is not possible (*Scheme 3*).

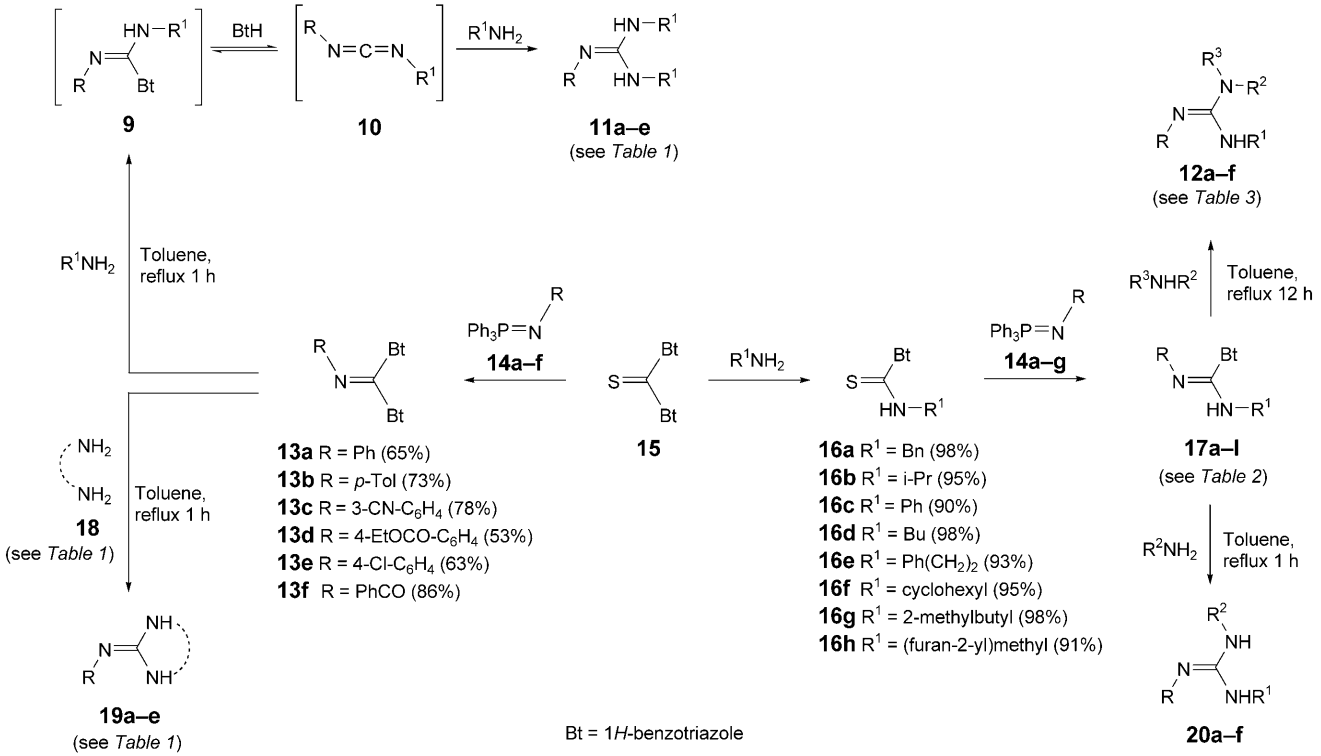
Table 1. *Preparation of Symmetric and Cyclic Trisubstituted Guanidines* **11a**–**11e** *and* **19a**–**19e**

13	R	Product	R^1	Yield [%]	**13**	R	Diamine **18**	Product	Yield [%]
13a	Ph	**11a**	Cyclohexyl	79	**13b**	*p*-Tol	$NH_2(CH_2)_3NH_2$	**19a**	95
13b	*p*-Tol (4-Me–C_6H_4)	**11b**	Bu	83	**13b**	*p*-Tol	$NH_2(CH_2)_2NH_2$	**19b**	95
13c	3-CN–C_6H_4	**11c**	i-Pr	87	**13e**	4-Cl–C_6H_4	$(NH_2CH_2)_2CMe_2$	**19c**	96
13d	4-EtOCO–C_6H_4	**11d**	PhCH(Me)	91	**13a**	Ph	$NH_2(CH_2)_3NHMe$	**19d**	89
13e	4-Cl–C_6H_4	**11e**	Bn	85	**13f**	PhCO	$NH_2(CH_2)_3NH_2$	**19e**	77

Reagents **13a** and **13b** and **13f** also successfully guanylated diamines **18** to give cyclic trisubstituted guanidines **19a**–**19e** in high yields (*Scheme 3* and *Table 1*). The structures of novel **19a**, **19c**, and **19d** were supported by their ^{1}H- and ^{13}C-NMR spectra, and elemental-analysis data. For known **19b** [32] and **19e** [33], the ^{1}H- and ^{13}C-NMR spectra data are now given, they were previously unreported (see the *Exper. Part*).

Preparation of intermediates **16a**–**16h** was achieved by a simple one step reaction of bis(1*H*-benzotriazol-1-yl)methanethione (**15**) and appropriate primary amines in CH_2Cl_2 at 20° (*Scheme 3*) [34]. Melting points for known **16a**, **16f**, and **16h** were found

Scheme 3


BtH
R1NH2
9
10
11a–e
(see Table 1)
Toluene, reflux 1 h
Ph3P=N
14a–f
13a R = Ph (65%)
13b R = p-Tol (73%)
13c R = 3-CN-C6H4 (78%)
13d R = 4-EtOCO-C6H4 (53%)
13e R = 4-Cl-C6H4 (63%)
13f R = PhCO (86%)
15
16a R1 = Bn (98%)
16b R1 = i-Pr (95%)
16c R1 = Ph (90%)
16d R1 = Bu (98%)
16e R1 = Ph(CH2)2 (93%)
16f R1 = cyclohexyl (95%)
16g R1 = 2-methylbutyl (98%)
16h R1 = (furan-2-yl)methyl (91%)
14a–g
12a–f
(see Table 3)
R3NHR2
Toluene, reflux 12 h
17a–l
(see Table 2)
R2NH2
Toluene, reflux 1 h
20a–f
18
(see Table 1)
19a–e
(see Table 1)
Bt = 1H-benzotriazole

to be identical to reported values (see the *Exper. Part*). Novel **16b**–**e**, and **16g** were characterized by ^{1}H- and ^{13}C-NMR spectra, and elemental analyses (see the *Exper. Part*). Synthesis of **17a**–**17l** was achieved from the reaction of **16a**–**16h** with triphenylphosphine imides **14a**–**14g** in refluxing toluene for 1 h (*Scheme 3* and *Table 2*). Novel 1*H*-benzotriazole-1-carboximidamides **17a**–**17l** were identified by ^{1}H- and ^{13}C-NMR spectra, and elemental analyses (see the *Exper. Part*). Attempts to prepare bis(1*H*-benzotriazol-1-yl-methylene)amines **17** by the reaction of **16a** and **16b** with **14** when R Ts or 4-NO_2–C_6H_4 failed, apparently due to the strong electron-withdrawing nature of these groups (*Scheme 3*). In addition, our efforts to prepare analog of **17** from **16b** (R^1 = i-Pr) also failed to give the corresponding *N*,*N*′-substituted thiourea.

Table 2. *Preparation of Guanylating Reagents* **17a**–**17l**

Reactants **16** + **14**	R^1	R	Product **17**	Yield [%]
16a + **14a**	Bn	Ph	**17a**	91
16a + **14b**	Bn	*p*-Tol	**17b**	96
16b + **14b**	i-Pr	*p*-Tol	**17c**	92
16b + **14e**	i-Pr	4-Cl–C_6H_4	**17d**	67
16c + **14g**	Ph	Mesityl	**17e**	80
16d + **14d**	Bu	4-EtOCO–C_6H_4	**17f**	53
16d + **14g**	Bu	Mesityl	**17g**	84
16e + **14c**	Ph(CH_2)$_2$	3-CN–C_6H_4	**17h**	95
16f + **14e**	Cyclohexyl	4-Cl–C_6H_4	**17i**	40
16g + **14b**	2-Methylbutyl	*p*-Tol	**17j**	82
16h + **14e**	(Furan-2-yl)methyl	4-Cl–C_6H_4	**17k**	93
16d + **14e**	Bu	4-Cl–C_6H_4	**17l**	87

Secondary amines (see R^2 and R^3 for amines in *Table 3*) underwent efficient guanylation using reagents **17a**, **17b**, **17f**, **17g**, **17h**, and **17i** in toluene under reflux for 12 h to afford unsymmetric guanidines **12a**–**12f** (*Scheme 3* and *Table 3*). The 1*H*-benzotriazole group in **17a**–**17c**, **17e**, **17j**, and **17k** was displaced by primary alkylamines in refluxing toluene in just 1 h to form unsymmetric guanidines **20a**–**20f** in high yields (*Scheme 3* and *Table 3*). The 1*H*-benzotriazole formed as a by-product was removed by washing with saturated aqueous Na_2CO_3. Novel compounds **12a**–**12f** and **20a**–**20f** were fully characterized by ^{1}H- and ^{13}C-NMR spectroscopy, and elemental analyses. The hydroscopic nature of guanidines **12a**–**12f** and **20a**–**20f** caused difficulties in obtaining the elemental analyses. For this reason, compounds **12c** and **12d**, and **20e** and **20f** were characterized by elemental analyses of the corresponding hydrochlorides (see the *Exper. Part*).

In summary, new routes for the guanylation of a series of structurally varied primary and secondary amines have been reported. [Bis(1*H*-benzotriazol-1-yl)methylidene]-amines **13a**–**13f** and 1*H*-benzotriazole-1-carboxamidines **17a**–**17l** are stable, crystalline guanylating reagents that can be stored at room temperature for many weeks with no apparent loss of activity. The preparation of reagents of type **13** and **17** is facile and should find widespread use in the synthesis of guanidines. An attractive feature of this methodology is that 1*H*-benzotriazole, which is generated as a by-product, can be easily

Table 3. *Preparation of Substituted Unsymmetrical Guanidines* **12a**–**12f** *and* **20a**–**20f**

17	R	R^1	R^2	R^3	Product	Yield [%]
17a	Ph	Bn	i-Pr	i-Pr	**12a**	67
17b	*p*-Tol	Bn	$-(CH_2)_2O(CH_2)_2-$		**12b**	90
17f	4-EtOCO–C_6H_4	Bu	Pr	Pr	**12c**	96
17i	4-Cl–C_6H_4	Cyclohexyl	$-CH(Me)(CH_2)_3CH(Me)-$		**12d**	93
17h	3-CN–C_6H_4	$Ph(CH_2)_2$	$-(CH_2)_4-$		**12e**	91
17g	Mesityl	Bu	Et	Et	**12f**	93
17a	Ph	Bn	Bu	–	**20a**	99
17b	*p*-Tol	Bn	Pentyl	–	**20b**	93
17c	*p*-Tol	i-Pr	PhCH(Me)	–	**20c**	71
17e	Mesityl	Ph	i-Pr	–	**20d**	96
17j	*p*-Tol	2-Methylbutyl	Bn	–	**20e**	85
17k	4-Cl–C_6H_4	(Furan-2-yl)methyl	Bu	--	**20f**	91

removed from the reaction mixture by washing with aqueous Na_2CO_3, followed by short column chromatography to give the desired guanidines.

Experimental Part

General. M.p.: hot-stage apparatus; uncorrected. NMR Spectra: in $CDCl_3$, or (D_6)DMSO with TMS as the internal standard for ^{1}H- (300 MHz) or a solvent as the internal standard for ^{13}C-NMR (75 MHz). Column chromatography (CC): on silica gel (200–425 mesh) or on basic alumina (60–325 mesh). *Bis(1*H*)benzotriazol-1-yl)methanethione* (**15**) was prepared according to a previously reported procedure. M.p. 171–172°, yield 98%, ([35]: M.p. 170–171°, yield 90%).

General Procedure for the Preparation of Compounds **14a**–**14g** [29]. Compounds **14a**–**14g** were prepared by adding Ph_3P to an ethereal solution of the corresponding azide. After the soln. was heated under reflux for 2 h, the solvent was removed under reduced pressure, and the residue was crystallized from abs. EtOH.

(Phenylimino)(triphenyl)phosphorane (**14a**). White microcrystals from EtOH (100%). M.p. 134–135° ([29]: 133–134°).

[(4-Methylphenyl)imino](triphenyl)phosphorane (**14b**). Yellow microcrystals from EtOH (99%). M.p. 136–137° ([29]: 136–137°).

3-[(Triphenyl-λ^5-phosphanylidene)amino]benzonitrile (**14c**). White microcrystals from EtOH (96%). M.p. 159–160° ([29]: 157–158°).

Ethyl 4-[(Triphenyl-λ^5-phosphanylidene)amino]benzoate (**14d**). White microcrystals from EtOH (85%). M.p. 136–137° ([36]: 136°).

[(4-Chlorophenyl)imino](triphenyl)phosphorane (**14e**). White microcrystals from EtOH (71%). M.p. 161–162° ([29]: 160–161°) [29].

N-*(Triphenyl-λ^5-phosphanylidene)benzamide* (**14f**). White microcrystals from EtOH (98%). M.p. 194–195° (Lit. M.p. 195–196°) [37].

[(2,4,6-Trimethylphenyl)imino(triphenyl)phosphorane (**14g**). White microcrystals from EtOH (77%). M.p. 146–147° ([38]: 146–146.5°).

General Procedure for the Preparation of Compounds **13a**–**13f**. To a stirred soln. of **15** (0.007 mol) in toluene (12 ml), the appropriate **14a**–**14f** (0.007 mol) was added at r.t., and the resulting mixture was heated at 60° for 4 h. Completion of the reaction was monitored by TLC. Then, the mixture was concentrated under reduced pressure, and the residue purified by gradient CC (AcOEt/hexanes) on silica gel to give **13a**–**13f**.

N-*[Bis(1*H*-benzotriazol-1-yl)methylidene]aniline* (**13a**). White microcrystals from AcOEt/hexanes (76%), M.p. 155–156°. ^{1}H-NMR ($CDCl_3$): 8.4 (*d*, *J* = 8.4, 1 H); 8.21 (*d*, *J* = 8.1, 1 H); 8.13–8.12 (*m*, 1 H); 7.75 (*t*, *J* = 7.4, 1 H); 7.60 (*t*, *J* = 7.7, 1 H); 7.41–7.38 (*m*, 2 H); 7.20–7.03 (*m*, 4 H); 6.8 (*d*, *J* = 8.2, 2 H). ^{13}C-NMR ($CDCl_3$): 143.4; 130.2; 129.3; 129.2; 126.4; 126.3; 125.0; 121.2; 120.6; 114.3; 110.1. Anal. calc. for $C_{19}H_{13}N_7$: C 67.25, H 3.86, N 28.89; found: C 67.49, H 4.01, N 28.50.

N-*[Bis(1*H*-benzotriazol-1-yl)methylidene]-4-methylaniline* (**13b**). White microcrystals from AcOEt/hexanes (73%). M.p. 165–166°. ^{1}H-NMR ($CDCl_3$): 8.41 (*d*, *J* = 8.2, 1 H); 8.18 (*d*, *J* = 8.2, 1 H); 8.14–8.11

(*m*, 1 H); 7.75–7.70 (*m*, 1 H); 7.59–7.54 (*m*, 1 H); 7.41–7.38 (*m*, 2 H); 7.13–7.10 (*m*, 1 H); 6.96 (*d*, *J* = 9.0, 2 H); 6.73 (*d*, *J* = 9.0, 2 H). ^{13}C-NMR ($CDCl_3$): 146.6; 144.8; 140.7; 136.3; 133.9; 132.4; 131.8; 130.1; 129.8; 129.3; 126.2; 125.0; 121.3; 120.5; 114.2; 110.1; 20.9. Anal. calc. for $C_{20}H_{15}N_7$: C 67.98, H 4.28, N 27.74; found: C 67.81, H, 4.22, N 27.43.

*3-{[Bis(1*H*-benzotriazol-1-yl)methylidene]amino}benzonitrile* (**13c**). Yellow microcrystals from AcOEt/hexanes (79%). M.p. 205–206°. ^{1}H-NMR ($CDCl_3$): 8.38 (*d*, *J* = 8.1, 1 H); 8.22 (*d*, *J* = 8.1, 1 H); 8.14 (*d*, *J* = 7.6, 1 H); 7.81–7.76 (*m*, 1 H); 7.63–7.59 (*m*, 1 H); 7.51–7.45 (*m*, 2 H); 7.37 (*d*, *J* = 7.7, 1 H); 7.30–7.24 (*m*, 2 H); 7.10 (*d*, *J* = 7.6, 1 H); 6.99 (*d*, *J* = 8.1, 1 H). ^{13}C-NMR ($CDCl_3$): 146.8; 144.8; 144.6; 132.5; 131.5; 130.6; 130.2; 129.9; 129.4; 126.7; 125.5; 125.2; 124.9; 120.8; 117.8; 114.2; 113.4; 109.9. Anal. calc. for $C_{20}H_{12}N_8$: C 65.17, H 3.32, N 30.11; found: C 64.71, H 3.20, N 29.83.

*Ethyl 4-{[Bis(1*H*-benzotriazol-1-yl)methylidene]amino}benzoate* (**13d**). Yellow microcrystals from AcOEt/hexanes (53%). M.p. 197–198°. ^{1}H-NMR ($CDCl_3$): 8.46–8.36 (*m*, 1 H); 8.26–8.08 (*m*, 2 H); 7.88 (*d*, *J* = 8.5, 2 H); 7.81–7.71 (*m*, 1 H); 7.62 (br. *s*, 2 H); 7.43 (br. *s*, 1 H); 7.12 (br. *s*, 1 H); 6.92 (*d*, *J* = 8.5, 2 H); 4.31 (*q*, *J* = 7.1, 2 H); 1.35 (*t*, *J* = 7.1, 3 H). ^{13}C-NMR ($CDCl_3$): 165.7; 147.6; 135.4; 130.8; 130.4; 127.9; 126.6; 125.3; 120.9; 120.7; 114.2; 110.0; 61.0; 14.22. Anal. calc. for $C_{22}H_{17}N_7O_2$: C 64.23, H 4.16, N 23.83; found: C 64.12, H 4.11, N 23.88.

*[Bis(1*H*-benzotriazol-1-yl)methylidene](4-chlorophenyl)amine* (**13e**). White microcrystals from AcOEt/hexanes (58%). M.p. 167–168°. ^{1}H-NMR ($CDCl_3$): 8.39 (*d*, *J* = 8.1, 1 H); 8.20 (*d*, *J* = 8.2, 1 H); 8.16–8.13 (*m*, 1 H); 7.78–7.73 (*m*, 1 H); 7.62–7.57 (*m*, 1 H); 7.45–7.42 (*m*, 2 H); 7.16–7.09 (*m*, 3 H); 6.79 (*d*, *J* = 8.7, 2 H). ^{13}C-NMR ($CDCl_3$): 146.7; 144.8; 142.0; 135.0; 131.8; 130.3; 129.6; 129.4; 126.5; 125.2; 122.6; 120.7; 114.2; 110.0. Anal. calc. for $C_{19}H_{12}ClN_7$: C 61.05, H 3.24, N 26.23; found: C 60.95, H 3.11, N 26.02.

N-*[Bis(1*H*-benzotriazol-1-yl)methylidene]benzamide* (**13f**) [28]. White needles from AcOEt/hexanes (86%). M.p. 108–109°. ^{1}H-NMR ($CDCl_3$): 8.40 (*d*, *J* = 8.2, 1 H); 8.23–8.16 (*m*, 4 H); 7.74–7.68 (*m*, 3 H); 7.61–7.56 (*m*, 4 H). ^{13}C-NMR ($CDCl_3$): 166.7; 145.7; 133.6; 132.3; 131.7; 131.4; 130.4; 128.4; 126.3; 120.2; 114.8; 109.6.

General Procedure for the Preparation of Compounds **16a**–**16h**. 1-Thiocarbamoyl-1*H*-benzotriazoles **16a**–**16h** were synthesized by the reaction of compound **15** (2 mmol) and the appropriate primary amine (2 mmol) in CH_2Cl_2 at r.t. for 18 h according to the procedure in [34]. M.p. and spectral data were used to characterize known **16a**, **16f**, and **16h**, and were found to be identical to reported values: **16a**: m.p. 108–109° ([38]: 108–109); **16f**: m.p. 72° ([38]: 72–73°); **16h**: m.p. 117° ([38]: 117–119°).

N-*Isopropyl-1*H-*benzotriazole-1-carbothioamide* (**16b**). White powder (95%). M.p. 107.7°. ^{1}H-NMR ($CDCl_3$): 8.84 (*d*, *J* = 8.5, 2 H); 8.00 (*d*, *J* = 8.2, 1 H); 7.57–7.52 (*m*, 1 H); 7.41–7.36 (*m*, 1 H); 4.67 (*sept.*, *J* = 7.0, 1 H); 1.36 (*d*, *J* = 6.4, 6 H). ^{13}C-NMR ($CDCl_3$): 173.1; 147.0; 132.4; 130.1; 125.5; 120.1; 116.1; 47.0; 21.5. Anal. calc. for $C_{10}H_{12}N_4S$: C 54.52, H 5.49, N 25.43; found: C 54.55, H 5.49, N 25.27.

N-*Phenyl-1*H-*benzotriazole-1-carbothioamide* (**16c**). White powder (90%). M.p. 98.5°. ^{1}H-NMR ($CDCl_3$): 10.74 (*s*, 1 H); 8.94 (*d*, *J* = 8.5, 1 H); 8.13 (*d*, *J* = 8.4, 1 H); 7.77 (*d*, *J* = 8.0, 2 H); 7.70–7.65 (*m*, 1 H); 7.54–7.46 (*m*, 2 H); 7.38–7.32 (*m*, 1 H); 7.29–7.20 (*m*, 1 H). ^{13}C-NMR ($CDCl_3$): 179.7; 137.1; 129.5; 129.4; 127.2; 126.9; 125.6; 125.1. Anal. calc. for $C_{13}H_{10}N_4S$: C 63.40, H 3.96, N 18.33; found: C 63.85, H 4.33, N 18.54.

N-*Butyl-1*H-*benzotriazole-1-carbothioamide* (**16d**). White powder (98%). M.p. 92.3°. ^{1}H-NMR ($CDCl_3$): 9.10 (br. *s*, 1 H); 8.92 (*d*, *J* = 8.5, 1 H); 8.09 (*d*, *J* = 8.2, 1 H); 7.64 (*t*, *J* = 7.7, 1 H); 7.47 (*t*, *J* = 7.87, 1 H); 3.85 (*dd*, *J* = 12.8, 7.0, 2 H); 1.83–1.75 (*m*, 2 H); 1.54–1.47 (*m*, 2 H); 1.01 (*t*, *J* = 7.3, 3 H). ^{13}C-NMR ($CDCl_3$): 174.1; 147.0; 132.4; 130.2; 125.6; 120.2; 116.0; 44.8; 30.1; 20.2; 13.7. Anal. calc. for $C_{11}H_{14}N_4S$: C 56.38, H 6.02, N 23.81; found: C 56.74, H 6.40, N 23.47.

N-*(2-Phenethyl)-1*H-*benzotriazole-1-carbothioamide* (**16e**). White powder (93%). M.p. 110.2°. ^{1}H-NMR ($CDCl_3$): 9.18 (*s*, 1 H); 8.91 (*d*, *J* = 8.5, 1 H); 8.07 (*d*, *J* = 8.2, 1 H); 7.65–7.60 (*m*, 1 H); 7.48–7.43 (*m*, 1 H); 7.36–7.22 (*m*, 5 H); 4.10 (*t*, *J* = 7.1, 2 H); 3.11 (*t*, *J* = 7.1, 2 H). ^{13}C-NMR ($CDCl_3$): 174.4; 147.0; 137.8; 132.3; 130.2; 128.8; 128.6; 126.9; 125.6; 120.2; 116.0; 46.1; 34.0. Anal. calc. for $C_{15}H_{14}N_4S$: C 63.80, H 5.00, N 19.84; found: C 63.92, H 4.98, N 19.59.

N-*(2-Methylbutyl)-1*H-*benzotriazole-1-carbothioamide* (**16g**). White powder (98%). M.p. 96°. ^{1}H-NMR ($CDCl_3$): 9.06 (*s*, 1 H); 8.91 (*d*, *J* = 8.5, 1 H); 8.10 (*d*, *J* = 8.2, 1 H); 7.64 (*t*, *J* = 7.5, 1 H); 7.47 (*t*, *J* = 7.4, 1 H); 1.97–1.93 (*m*, 1 H); 1.38–1.26 (*m*, 2 H); 1.06 (*d*, *J* = 6.7, 3 H); 1.01–0.99 (*m*, 3 H); 0.96–0.86 (*m*, 2 H). ^{13}C-NMR ($CDCl_3$):174.3; 146.9; 132.2; 130.1; 125.5; 120.0; 115.9; 50.6; 33.8; 27.1; 17.3; 11.1. Anal. calc. for $C_{12}H_{16}N_4S$: C 58.04, H 6.49, N 22.56; found: C 57.92, H 6.45, N 22.37.

General Procedure for the Preparation of Compounds **11a**–**11e**. To a soln. of **13a**–**13e** (see *Table 1*; 0.85 mmol) in toluene (10 ml), the amine of choice (2.5 mmol) was added with stirring. The mixture was heated under reflux until full conversion of starting materials (1–2 h). Upon completion, the solvent was evaporated under reduced pressure. The crude product was dissolved in CH_2Cl_2, washed twice with sat. aq. Na_2CO_3, dried

($MgSO_4$), and filtered. The solvent was removed under reduced pressure. The desired guanidines were isolated by flash CC on basic alumina (first AcOEt to remove impurities and MeOH to elute guanidine) to give **11a**–**11e**.

1,3-Dicyclohexyl-2-phenylguanidine (**11a**) [30]. Yellow oil (79%). ^{1}H-NMR ($CDCl_3$): 7.24–7.19 (*m*, 2 H); 7.03–6.98 (*m*, 3 H); 3.16–3.09 (*m*, 2 H); 1.91 (*s*, 2 H); 1.83–1.80 (*m*, 4 H); 1.61 (br. *s*, 4 H); 1.48 (br. *s*, 2 H); 1.23–1.15 (*m*, 5 H); 1.11–1.05 (*m*, 5 H). ^{13}C-NMR ($CDCl_3$): 179.6; 153.6; 129.4; 124.2; 122.6; 52.2; 33.2; 25.0; 24.8; 24.7.

1,3-Dibutyl-2-(4-methylphenyl)guanidine (**11b**). Yellow oil (83%). ^{1}H-NMR ($CDCl_3$): 7.08 (*d*, J = 8.2, 2 H); 6.95 (*d*, J = 8.2, 2 H); 3.04 (*t*, J = 7.0, 4 H); 2.30 (*s*, 3 H); 1.95 (*s*, 2 H); 1.51 (*quint.*, J = 7.4, 4 H); 1.26 (*sext.*, J = 7.4, 4 H); 0.84 (*t*, J = 7.3, 6 H). ^{13}C-NMR ($CDCl_3$): 179.2; 155.9; 134.5; 129.9; 122.1; 43.2; 31.3; 20.8; 19.8; 13.5. Anal. calc. for $C_{16}H_{27}N_3$: C 73.52, H 10.41, N 16.07; found: C 73.28, H 10.39, N 16.38.

2-(3-Cyanophenyl)-1,3-diisopropylguanidine (**11c**). Yellow oil (87%). ^{1}H-NMR ((D_6)DMSO): 8.81 (*s*, 1 H); 7.94 (*s*, 1 H); 7.57 (*dd*, J = 8.3, 1.0, 1 H); 7.42 (*t*, J = 8.0, 1 H); 7.31 (*d*, J = 7.6, 1 H); 6.33 (*d*, J = 7.4, 1 H); 3.76 (*sept.*, J = 6.7, 2 H); 1.1 (*d*, J = 6.7, 12 H). ^{13}C-NMR ((D_6)DMSO): 154.3; 141.5; 130.0; 124.3; 122.1; 119.9; 119.0; 111.4; 41.0; 22.8. Anal. calc. for $C_{14}H_{20}N_4$: C 73.74, H 8.25, N 22.93; found: C 73.89, H 8.30, N 23.54.

Ethyl 4-({Bis[(1-phenylethyl)amino]methylidene}amino)benzoate (**11d**). Yellow oil (91%). ^{1}H-NMR ($CDCl_3$): 7.86–7.83 (*m*, 3 H); 7.34–7.21 (*m*, 3 H); 7.19–7.15 (*m*, 3 H); 6.96–6.93 (*m*, 4 H); 6.80 (*d*, J = 8.2, 1 H); 4.78 (*q*, J = 6.4, 1 H); 4.52 (*q*, J = 6.2, 1 H); 4.30–4.22 (*m*, 4 H); 1.40 (*d*, J = 6.7, 2 H); 1.33–1.27 (*m*, 7 H). ^{13}C-NMR ($CDCl_3$): 166.3; 147.1; 143.4; 143.3; 131.0; 129.0; 128.8; 127.8; 127.5; 125.9; 125.6; 124.6; 122.3; 120.7; 60.7; 52.2; 23.6; 23.1; 14.3. Anal. calc. for $C_{26}H_{29}N_3O_2$: C 70.75, H 7.03, N 9.41; found: C 70.27, H 6.80, N 8.95.

1,3-Dibenzyl-2-(4-chlorophenyl)guanidine (**11e**). Yellow oil (85%). ^{1}H-NMR ($CDCl_3$): 7.24–7.22 (*m*, 6 H); 7.2 (*d*, J = 8.6, 2 H); 7.08–7.05 (*m*, 4 H); 6.81 (*d*, J = 8.6, 2 H); 4.18 (*s*, 4 H); 1.80 (*s*, 2 H). ^{13}C-NMR ($CDCl_3$): 179.8; 154.6; 137.1; 129.4; 129.1; 128.8; 127.7; 127.0; 123.7; 46.5. Anal. calc. for $C_{21}H_{20}ClN_3$: C 68.09, H 5.76, N 10.21; found: C 68.41, H 5.94, N 10.50.

General Procedure for the Preparation of Compounds **19a**–**19e**. To a soln. of appropriate **13** (see *Table 1*; 0.70 mmol) in toluene (10 ml), the corresponding diamine **18** (0.7 mmol) was added with stirring. The mixture was heated to reflux and kept at that temp. until the full conversion of starting materials (1–2 h). Upon completion, the solvent was evaporated under reduced pressure; crude product was dissolved in CH_2Cl_2, washed twice with sat. aq. Na_2CO_3, dried ($MgSO_4$), and filtered. The solvent was removed under reduced pressure. Desired guanidines were isolated by flash CC on basic alumina (first AcOEt to remove impurities and MeOH to elute guanidine) to give **19a**–**19e**.

4-Methyl-N-*(3,4,5,6-tetrahydro-1*H*-pyrimidin-2-ylidene)benzenamine* (**19a**). Colorless oil (95%). ^{1}H-NMR ($CDCl_3$): 7.2 (*d*, J = 8.2, 2 H); 7.07 (*d*, J = 8.2, 2 H); 3.37–3.33 (*m*, 4 H); 2.32 (*s*, 3 H); 11.98 (*s*, 2 H); 1.98–1.93 (*m*, 2 H). ^{13}C-NMR ($CDCl_3$): 152.7; 136.5; 132.7; 130.5; 125.2; 38.4; 24.2; 20.9; 20.2. Anal. calc. for $C_{11}H_{15}N_3$: C 69.81, H 7.99, N 22.20; found: C 70.01, H 8.25, N 22.27.

N-*(Imidazolidin-2-ylidene)-4-methylbenzenamine* (**19b**) [32]. Yellow oil (95%). ^{1}H-NMR ($CDCl_3$): 7.13 (*d*, J = 8.2, 2 H); 7.06 (*d*, J = 8.2, 2 H); 3.66 (*s*, 4 H); 2.31 (*s*, 3 H); 1.94 (*s*, 2 H). ^{13}C-NMR ($CDCl_3$): 159.6; 136.0; 134.1; 130.2; 123.1; 42.9; 20.8.

4-Chloro-N-*[3,4,5,6-tetrahydro-5,5-dimethyl-1*H*-pyrimidin-2-ylidene]aniline* (**19c**). Yellow oil (96%). ^{1}H-NMR ($CDCl_3$): 7.26 (*d*, J = 8.6, 2 H); 7.08 (*d*, J = 8.6, 2 H); 2.97 (*s*, 4 H); 1.91 (*s*, 2 H); 1.02 (*s*, 6 H). ^{13}C-NMR ($CDCl_3$): 152.0; 134.1; 132.2; 130.1; 126.3; 50.1; 27.2; 24.1. Anal. calc. for $C_{12}H_{16}ClN_3$: C 60.63, H 6.78, N, 17.68; found: C 60.78, H 6.55, N 17.77.

N-*[3,4,5,6-Tetrahydro-1-methyl-1*H*-pyrimidin-2-ylidene]benzenamine* (**19d**). Yellow oil (89%). ^{1}H-NMR ($CDCl_3$): 7.31–7.26 (*m*, 2 H); 7.08–7.03 (*m*, 1 H); 7.00 (*d*, J = 7.8, 2 H); 3.42–3.33 (*m*, 4 H); 2.75 (*s*, 3 H); 2.11–2.03 (*m*, 2 H); 1.99 (*s*, 1 H). ^{13}C-NMR ($CDCl_3$): 154.4; 139.9; 129.4; 123.7; 121.1; 48.5; 39.6; 38.5; 21.8. Anal. calc. for $C_{11}H_{15}N_3$: C 69.81, H 7.99, N 22.20; found: C 69.98, H 7.75, N 22.57.

N-*(3,4,5,6-Tetrahydro-1*H*-pyrimidin-2-ylidene)benzamide* (**19e**) [33]. White microcrystals from AcOEt/hexanes (77%). M.p. 132–133°. ^{1}H-NMR ($CDCl_3$): 7.80 (*d*, J = 7.1, 2 H); 7.41–7.32 (*m*, 5 H); 3.41–3.49 (*m*, 4 H); 1.78–1.62 (*m*, 2 H). ^{13}C-NMR ($CDCl_3$): 183.3; 168.2; 134.2; 131.5; 128.5; 127.0; 36.2; 29.8.

General Procedure for the Preparation of Compounds **17a**–**17l**. To a stirred soln. of **16a**–**16h** (0.01 mol) in toluene (12 ml), the corresponding **14** (0.01 mol; see *Table 2*) was added at room temperature and the resulting mixture was heated at 110° for 1 h. Completion of the reaction was monitored by TLC. Upon completion, the reaction mixture was concentrated under reduced pressure and residue purified by gradient CC (AcOEt/hexanes) on silica gel to give **17a**–**17l**.

N-*Benzyl*-N′-*phenyl-1*H-*benzotriazole-1-carboximidamide* (**17a**). White microcrystals from AcOEt/hexanes (91%). M.p. 129–130°. ^{1}H-NMR ($CDCl_3$): 8.14 (br. *s*, 1 H); 8.06 (*d*, J = 8.2, 1 H); 7.51–7.46 (*m*,

1 H); 7.42–7.37 (*m*, 1 H); 7.32–7.22 (*m*, 7 H); 7.03–6.94 (*m*, 3 H); 6.53 (br. *s*, 1 H); 4.31 (*s*, 2 H). ^{13}C-NMR ($CDCl_3$): 146.5; 141.0; 137.4; 131.6; 129.0; 128.9; 128.7; 127.8; 127.5; 125.0; 122.9; 121.6; 119.8; 114.5; 47.8. Anal. calc. for $C_{20}H_{17}N_5$: C 73.37, H 5.23, N 21.39; found: C 73.78, H 5.25, N 21.27.

N-*Benzyl*-N′-*(4-methylphenyl)-1*H-*benzotriazole-1-carboximidamide* (**17b**). Yellow oil (96%). ^{1}H-NMR ($CDCl_3$): 8.06 (*d*, *J* = 8.1, 1 H); 7.51–7.46 (*m*, 1 H); 7.42–7.37 (*m*, 1 H); 7.33–7.24 (*m*, 6 H); 7.05 (*d*, *J* = 7.1, 2 H); 6.86 (*d*, *J* = 7.1, 2 H); 6.45 (br. *s*, 1 H); 4.31 (*s*, 2 H); 2.30 (*s*, 3 H). ^{13}C-NMR ($CDCl_3$): 143.9; 137.5; 134.6; 132.3; 131.7; 129.5; 129.2; 129.0; 128.7; 127.7; 127.5; 125.0; 121.4; 119.7; 115.3; 47.9; 20.8. Anal. calc. for $C_{21}H_{19}N_5$: C 73.88, H 5.61, N 19.90; found: C 73.83, H 5.96, N 19.85.

N-*Isopropyl*-N′-*(4-methylphenyl)-1*H-*benzotriazole-1-carboximidamide* (**17c**). Yellow oil (92%). ^{1}H-NMR ($CDCl_3$): 7.97 (*d*, *J* = 8.2, 1 H); 7.67–7.60 (*m*, 1 H); 7.45–7.28 (*m*, 2 H); 7.00 (*d*, *J* = 7.0, 2 H); 6.82 (*d*, *J* = 7.0, 2 H); 5.82 (br. *s*, 1 H); 3.61 (br. *s*, 1 H); 2.22 (*s*, 3 H); 1.08 (*d*, *J* = 6.2, 6 H). ^{13}C-NMR ($CDCl_3$): 144.3; 132.3; 132.1; 131.7; 129.5; 128.8; 128.5; 128.4; 124.8; 121.1; 119.6; 44.5; 23.0; 20.8. Anal. calc. for $C_{17}H_{19}N_5$: C 69.60, H 6.53, N 23.87; found: C 69.40, H 6.38, N 23.62.

N′-*(4-Chlorophenyl)*-N-*isopropyl-1*H-*benzotriazole-1-carboximidamide* (**17d**). Yellow oil (67%). ^{1}H-NMR ($CDCl_3$): 8.06 (*d*, *J* = 8.2, 2 H); 7.51–7.46 (*m*, 1 H); 7.42–7.37 (*m*, 1 H); 7.20 (*d*, *J* = 8.2, 2 H); 6.90 (*d*, *J* = 8.0, 2 H); 6.02 (br. *s*, 1 H); 3.69 (br. *s*, 1 H); 1.19 (*d*, *J* = 6.3, 6 H). ^{13}C-NMR ($CDCl_3$): 146.3; 145.6; 141.3; 131.5; 129.0; 128.9; 127.8; 125.0; 122.6; 119.8; 114.1; 44.6; 22.8. Anal. calc. for $C_{16}H_{16}ClN_5$: C 61.24, H 5.14, N 22.32; found: C 61.43, H 5.11, N 21.95.

N-*Phenyl*-N′-*(2,4,6-trimethylphenyl)-benzotriazole-1-carboximidamide* (**17e**). Yellow microcrystals from AcOEt/hexanes (80%). M.p. 140–141°. ^{1}H-NMR ($CDCl_3$): 8.42–8.40 (*m*, 1 H); 8.10 (*d*, *J* = 8.4, 1 H); 7.87 (br. *s*, 1 H); 7.59–7.54 (*m*, 1 H); 7.48–7.43 (*m*, 1 H); 7.02–6.85 (*m*, 3 H); 6.76–6.70 (*m*, 2 H); 6.66 (*s*, 1 H); 6.59 (*s*, 1 H); 2.23 (*s*, 3 H); 2.15 (*s*, 6 H). ^{13}C-NMR ($CDCl_3$): 135.0; 132.3; 132.2; 131.5; 129.2; 128.7; 128.5; 128.4; 128.2; 127.7; 125.1; 123.1; 122.3; 120.5; 119.8; 20.6; 18.4 (2C). Anal. calc. for $C_{22}H_{21}N_5$: C 74.34, H 5.95, N 19.70; found: C 74.15, H 6.03, N 19.44.

*Ethyl 4-{[(1*H-*benzotriazol-1-yl)(butylamino)methylidene]amino}benzoate* (**17f**). Yellow oil (53%). ^{1}H-NMR ($CDCl_3$): 8.00 (*d*, *J* = 8.2, 1 H); 7.96 (*d*, *J* = 8.2, 1 H); 7.87 (*d*, *J* = 8.4, 2 H); 7.42–7.37 (*m*, 1 H); 7.33–7.28 (*m*, 1 H); 6.91 (*d*, *J* = 8.2, 2 H); 6.40–6.30 (*m*, 1 H); 4.25 (*q*, *J* = 7.1, 2 H); 3.00 (*q*, *J* = 6.3, 2 H); 1.44 (*quint.*, *J* = 7.3, 2 H); 1.29 (*t*, *J* = 7.1, 3 H); 1.23 (*sext.*, *J* = 7.5, 2 H); 0.77 (*t*, *J* = 7.3, 3 H). ^{13}C-NMR ($CDCl_3$): 166.4; 151.5; 146.3; 141.3; 131.4; 130.4; 129.1; 125.0; 124.4; 121.3; 119.7; 114.2; 60.6; 43.4; 31.5; 19.6; 14.2; 13.5. Anal. calc. for $C_{20}H_{23}N_5O_2$: C 65.73, H 6.34, N 19.16; found: C 65.63, H 6.77, N 18.90.

N-*Butyl*-N′-*(2,4,6-trimethylphenyl)-1*H-*benzotriazole-1-carboximidamide* (**17g**). Yellow oil (84%). ^{1}H-NMR ($CDCl_3$): 8.40 (*d*, *J* = 8.3, 1 H); 8.02 (*d*, *J* = 8.2, 1 H); 7.48–7.43 (*m*, 1 H); 7.38–7.33 (*m*, 1 H); 6.78 (*s*, 2 H); 6.28 (br. *s*, 1 H); 2.78 (*q*, *J* = 6.7, 2 H); 2.20 (*s*, 3 H); 2.11 (*s*, 6 H); 1.34 (*quint.*, *J* = 7.1, 2 H); 1.16 (*sext.*, *J* = 7.1, 2 H); 0.73 (*t*, *J* = 7.3, 3 H). ^{13}C-NMR ($CDCl_3$): 146.7; 141.8; 139.5; 131.9; 131.7; 128.9; 128.2; 128.1; 124.9; 119.6; 115.5; 42.2; 32.1; 20.7; 19.7; 18.6 (2C); 13.4. Anal. calc. for $C_{20}H_{25}N_5$: C 71.61, H 7.51, N 20.53; found: C 71.90, H 7.80, N 20.19.

N′-*(3-Cyanophenyl)*-N-*(2-phenylethyl)-1*H-*benzotriazole-1-carboximidamide* (**17h**). Yellow oil (95%). ^{1}H-NMR ($CDCl_3$): 8.02 (*d*, *J* = 8.2, 1 H); 7.91 (br. *s*, 1 H); 7.50–7.45 (*m*, 1 H); 7.41–7.36 (*m*, 1 H); 7.32–7.24 (*m*, 5 H); 7.21–7.20 (*m*, 1 H); 7.12–7.10 (*m*, 3 H); 6.47 (br. *s*, 1 H); 3.45–3.43 (*m*, 2 H); 2.87 (*t*, *J* = 7.0, 2 H). ^{13}C-NMR ($CDCl_3$): 147.7; 146.1; 141.8; 137.5; 131.2; 129.6; 129.1; 128.6; 128.6; 126.7; 126.1; 126.0; 125.0; 124.8; 119.8; 118.6; 113.6; 112.6; 44.6; 35.6. Anal. calc. for $C_{22}H_{18}N_6$: C 71.61, H 5.35, N 23.04; found: C 71.22, H 5.07, N 23.12.

N′-*(4-Chlorophenyl)*-N-*cyclohexyl-1*H-*benzotriazole-1-carboximidamide* (**17i**). Yellow oil (40%). ^{1}H-NMR ($CDCl_3$): 8.06 (*d*, *J* = 8.2, 2 H); 7.52–7.47 (*m*, 1 H); 7.42–7.37 (*m*, 1 H); 7.22 (*d*, *J* = 8.2, 2 H); 6.90 (*d*, *J* = 8.0, 2 H); 6.09 (br. *s*, 1 H); 3.30 (br. *s*, 1 H); 1.94–1.92 (*m*, 2 H); 1.74–1.66 (*m*, 2 H); 1.52 (br. *s*, 1 H); 1.32–1.09 (*m*, 5 H) . ^{13}C-NMR ($CDCl_3$): 146.4; 145.7; 141.2; 131.6; 129.0; 128.9; 127.8; 125.0; 122.6; 119.8; 114.2; 51.3; 33.0; 25.3; 24.4. Anal. calc. for $C_{19}H_{20}ClN_5$: C 63.13, H 5.70, N 18.79; found: C 62.70, H 5.65, N 18.91.

N-*(2-Methylbutyl)*-N′-*(4-methylphenyl)-1*H-*benzotriazole-1-carboximidamide* (**17j**). Yellow oil (82%). ^{1}H-NMR ($CDCl_3$): 8.06 (*d*, *J* = 8.2, 1 H); 7.51–7.46 (*m*, 1 H); 7.42–7.37 (*m*, 1 H); 7.07 (*d*, *J* = 7.1, 2 H); 6.89 (br. *s*, 2 H); 6.22 (br. *s*, 1 H); 3.08–2.90 (*m*, 2 H); 2.30 (*s*, 3 H); 1.62–1.45 (*m*, 1 H); 1.36–1.30 (*m*, 1 H); 1.17–1.08 (*m*, 1 H); 0.88 (*d*, *J* = 6.7, 3 H); 0.81 (*t*, *J* = 7.4, 3 H). ^{13}C-NMR ($CDCl_3$): 144.2; 141.6; 132.0; 131.7; 129.4; 128.9; 126.1; 124.9; 121.3; 119.6; 117.9; 49.2; 35.1; 26.7; 20.8; 17.0; 11.0. Anal. calc. for $C_{19}H_{23}N_5$: C 71.00, H 7.21, N 21.79; found: C 71.15, H 7.45, N 21.65.

N′-*(4-Chlorophenyl)*-N-*[(furan-2-yl)methyl]-1*H-*benzotriazole-1-carboximidamide* (**17k**). Yellow oil (93%). ^{1}H-NMR ($CDCl_3$): 8.00 (*d*, *J* = 8.2, 2 H); 7.50–7.40 (*m*, 1 H); 7.35–7.30 (*m*, 1 H); 7.27 (*d*, *J* = 1.0, 1 H); 7.14 (*d*, *J* = 8.2, 2 H); 6.81 (*d*, *J* = 8.0, 2 H); 6.45 (*s*, 1 H); 6.23–6.21 (*m*, 1 H); 6.11 (*s*, 1 H); 4.26 (*s*, 2 H).

^{13}C-NMR ($CDCl_3$): 150.1; 145.0; 142.6; 141.2; 131.5; 129.2; 129.0; 128.7; 128.2; 125.1; 122.8; 120.0; 119.9; 110.4; 108.0; 40.8 Anal. calc. for $C_{18}H_{14}ClN_5O$: C 61.45, H 4.01, N 18.91; found: C 61.10, H 3.89, N 18.50.

N-*Butyl*-N′-*(4-chlorophenyl)-1*H-*benzotriazole-1-carboximidamide* (**17l**). Yellow oil (87%). ^{1}H-NMR ($CDCl_3$): 7.98 (*d*, *J* = 8.2, 1 H); 7.44–7.39 (*m*, 1 H); 7.34–7.25 (*m*, 1 H); 7.13 (*d*, *J* = 8.3, 2 H); 6.82 (*d*, *J* = 8.1, 2 H); 6.17 (*s*, 1 H); 3.03 (br. *s*, 2 H); 1.51–1.41 (*m*, 2 H); 1.28–1.18 (*m*, 2 H); 0.79 (*t*, *J* = 7.3, 3 H). ^{13}C-NMR ($CDCl_3$): 146.4; 145.6; 141.7; 131.5; 129.1; 128.8; 128.8; 127.7; 125.0; 122.8; 119.8; 43.5; 31.7; 19.7; 13.6. Anal. calc. for $C_{17}H_{18}ClN_5$: C 62.29, H 5.53, N 21.36; found: C 62.69, H 5.59, N 20.98.

General Procedure for the Preparation of Compounds **12a**–**12f**. To a stirred soln. of appropriate **17** (see *Table 3* for R and R^1; 1.6 mmol) in toluene (10 ml) was added the secondary amine (see *Table 3* for R^2 and R^3) of choice (1.6 mmol) at r.t. The reaction mixture was heated under reflux overnight. Completion of the reaction was monitored by TLC. Upon completion, the solvent was evaporated, and the residue was dissolved in CH_2Cl_2. The soln. was washed twice with sat. aq. Na_2CO_3 and dried ($MgSO_4$), and the solvent was evaporated under reduced pressure. The desired guanidines **12a**–**12f** were purified by flash CC on basic alumina (first AcOEt to remove impurities and the MeOH to elute the guanidine).

3-Benzyl-1,1-diisopropyl-2-phenylguanidine (**12a**). Yellow oil (67%). ^{1}H-NMR ($CDCl_3$): 7.22–7.08 (*m*, 8 H); 6.89–6.85 (*m*, 2 H); 4.07 (*s*, 2 H); 3.77 (*sept.*, *J* = 6.8, 2 H); 1.89 (*s*, 2 H); 1.12 (*d*, *J* = 6.9, 12 H). ^{13}C-NMR ($CDCl_3$): 151.3; 150.0; 139.1; 129.3; 128.7; 127.4; 127.3; 123.5; 121.6; 46.0; 41.6; 31.8; 19.9. Anal. calc. for $C_{20}H_{27}N_3$: N 13.58; found: N 13.73.

N-*Benzyl*-N′-*(4-methylphenyl)-4-morpholinecarboximidamide* (**12b**). Yellow oil (93%). ^{1}H-NMR ($CDCl_3$): 7.26–7.16 (*m*, 3 H); 7.13–7.10 (*m*, 2 H); 6.91 (*d*, *J* = 8.1, 2 H); 6.76 (br. *s*, 1 H); 6.52 (*d*, *J* = 8.1, 2 H); 4.11 (*s*, 2 H); 3.67–3.64 (*m*, 4 H); 3.19–3.16 (*m*, 4 H); 2.17 (*s*, 3 H). ^{13}C-NMR ($CDCl_3$): 156.0; 151.2; 146.5; 138.8; 131.2; 129.8; 129.7; 128.6; 127.4; 127.3; 122.0; 66.7; 66.4; 49.3; 48.3; 46.9; 20.6; 0.9. Anal. calc. for $C_{19}H_{23}N_3O$: C 73.76, H 7.49, N 13.58; found: C 73.36, H 7.76, N 13.26.

Ethyl 4-{[(Butylamino)(dipropylamino)methylidene]amino}benzoate (**12c**). Yellow oil (96%). ^{1}H-NMR ($CDCl_3$): 7.83 (*d*, *J* = 8.5, 2 H); 6.76 (*d*, *J* = 8.5, 2 H); 4.26 (*q*, *J* = 7.1, 2 H); 3.08 (*t*, *J* = 7.4, 4 H); 2.89 (*t*, *J* = 7.0, 2 H); 1.55–1.48 (*m*, 4 H); 1.40–1.28 (*m*, 5 H); 1.22–1.17 (*m*, 2 H); 0.82 (*t*, *J* = 7.3, 6 H); 0.79 (*t*, *J* = 7.2, 3 H). ^{13}C-NMR ($CDCl_3$): 166.9; 156.1; 130.9; 130.8; 129.7; 121.0; 60.4; 50.8; 44.5; 32.1; 21.4; 19.9; 14.4; 13.7; 11.4; 1.0. Anal. calc. for $C_{20}H_{33}N_3O_2 \cdot HCl$: C 62.96, H 9.33, N 10.14; found: C 63.24, H 9.75, N 9.91.

N′-*(4-Chlorophenyl)*-N-*cyclohexyl-3,4,5,6-tetrahydro-2,6-dimethyl-2*H-*pyridine-2-carboximidamide* (**12d**). Yellow oil (93%). ^{1}H-NMR ((D$_6$)DMSO) 7.41 (*d*, *J* = 8.9, 2 H); 7.24 (*d*, *J* = 8.9, 2 H); 6.30 (*d*, *J* = 7.8, 1 H); 3.51–3.45 (*m*, 1 H); 3.02–2.97 (*m*, 2 H); 1.80–1.64 (*m*, 7 H); 1.55–1.42 (*m*, 2 H); 1.33–1.10 (*m*, 3 H). ^{13}C-NMR ((D$_6$)DMSO) 154.3; 139.7; 128.4; 124.1; 118.8; 52.2; 47.49; 32.9; 30.1; 25.2; 24.3; 22.4; 19.4. Anal. calc. for $C_{20}H_{30}ClN_3 \cdot HCl$: N 10.93; found: N 11.13.

N′-*(3-Cyanophenyl)*-N-*(2-phenylethyl)pyrrolidine-1-carboximidamide* (**12e**). Yellow oil (91%). ^{1}H-NMR ($CDCl_3$): 7.32–7.21 (*m*, 4 H); 7.2 (*d*, *J* = 6.9, 2 H); 7.1 (*d*, *J* = 7.6, 1 H); 7.03–7.00 (*m*, 2 H); 4.95 (br. *s*, 1 H); 3.39–3.31 (*m*, 2 H); 3.16–3.11 (*m*, 4 H); 2.82–2.78 (*m*, 2 H); 1.83–1.79 (*m*, 4 H). ^{13}C-NMR ($CDCl_3$): 153.0; 138.5; 132.0; 129.5; 128.7; 128.6; 126.6; 126.5; 124.6; 123.2; 119.5; 112.3; 48.0; 44.7; 36.0; 25.3. Anal. calc. for $C_{20}H_{22}N_4$: C 75.44, H 6.96, N 17.59; found: C 75.62, H 7.19, N 17.28.

3-Butyl-1,1-diethyl-2-(2,4,6-trimethylphenyl)guanidine (**12f**). Yellow oil (93%). ^{1}H-NMR ($CDCl_3$): 6.73 (*s*, 2 H); 3.19 (*q*, *J* = 7.0, 4 H); 2.83 (*t*, *J* = 7.0, 2 H); 2.15–2.12 (*m*, 5 H); 1.97 (*s*, 6 H); 1.09 (*t*, *J* = 7.0, 6 H); 1.26–1.17 (*m*, 2 H); 0.75 (*t*, *J* = 7.0, 3 H). ^{13}C-NMR ($CDCl_3$): 154.9; 130.6; 129.6; 129.0; 128.6; 44.5; 42.6; 32.9; 20.7; 19.8; 18.3; 13.7; 12.8. Anal. calc. for $C_{18}H_{31}N_3$: C 74.69, H 10.79, N, 14.32; found: C 74.68, H 10.91, N 13.88.

General Procedure for the Preparation of Compounds **20a**–**20f**. To a soln. of the appropriate **17** (see *Table 3* for R and R^1; 2.2 mmol) in toluene (10 ml), the amine (see *Table 3* for R^2; 2.2 mmol) was added with stirring. The reaction mixture was heated under reflux until full conversion of starting materials (TLC control). Upon completion, the solvent was evaporated under reduced pressure; the crude product was dissolved in CH_2Cl_2, washed twice with sat. aq. Na_2CO_3, dried ($MgSO_4$), and filtered. The solvent was removed under reduced pressure. The desired guanidines were isolated by flash CC on basic alumina (first AcOEt to remove impurities and MeOH to elute guanidine) to give **20a**–**20f**.

1-Benzyl-3-butyl-2-phenylguanidine (**20a**). Yellow oil (99%). ^{1}H-NMR ($CDCl_3$): 7.27–7.26 (*m*, 4 H); 7.21–7.16 (*m*, 3 H); 6.89–6.83 (*m*, 3 H); 4.30 (*s*, 2 H); 3.86 (br. *s*, 1 H); 3.03 (*t*, *J* = 7.0, 2 H); 1.34 (*quint.*, *J* = 7.2, 2 H); 1.16 (*sext.*, *J* = 7.2, 2 H); 0.79 (*t*, *J* = 7.3, 3 H). ^{13}C-NMR ($CDCl_3$): 151.3; 150.0; 139.1; 129.3; 128.7; 127.4; 127.3; 123.6; 121.6; 46.03; 41.6; 31.8; 19.9; 13.7. Anal. calc. for $C_{18}H_{23}N_3$: C 76.43, H 8.95, N 14.93; found: C 75.84, H 8.50, N 14.76.

1-Benzyl-3-pentyl-2-(4-methylphenyl)guanidine (two tautomers; **20b**). Yellow oil (93%). ^{1}H-NMR ($CDCl_3$): 7.26–7.17 (*m*, 5 H); 7.00 (*d*, *J* = 8.0, 2 H); 6.81 (*d*, *J* = 8.2, 2 H); 4.29 (*s*, 2 H); 2.90 (*t*, *J* = 6.9, 2 H);

2.29 (*s*, 3 H); 1.96 (*s*, 3 H) 1.44 – 1.34 (*m*, 2 H); 1.26 – 1.10 (*m*, 3 H); 1.05 – 0.87 (*m*, 1 H); 0.84 – 0.74 (*m*, 4 H). ^{13}C-NMR ($CDCl_3$): 179.3; 155.6; 155.4; 137.5; 133.7; 133.7; 129.7; 128.5; 128.5; 127.4; 127.0; 127.0; 122.1; 48.8; 46.1; 43.1; 34.6; 28.8; 28.5; 26.5; 24.4; 22.0; 20.6; 16.7; 13.7; 10.8. Anal. calc. for $C_{20}H_{27}N_3$: C 77.63, H 8.79, N 13.58; found: C 77.58, H 8.43, N 13.61.

1-Isopropyl-2-(4-methylphenyl)-3-(1-phenylethyl)guanidine (**20c**). Yellow oil (71%). ^{1}H-NMR ($CDCl_3$): 7.38 – 7.21 (*m*, 5 H); 7.09 – 7.06 (*m*, 2 H); 6.79 (*d*, *J* = 7.8, 2 H); 4.62 – 4.60 (*m*, 1 H); 3.76 (br. *s*, 1 H); 2.30 (*s*, 3 H); 1.39 – 1.37 (*m*, 3 H); 1.08 (*d*, *J* = 6.3, 3 H); 0.90 (*d*, *J* = 6.3, 3 H). ^{13}C-NMR ($CDCl_3$): 151.3; 144.5; 129.9; 128.8; 128.6; 127.4; 125.7; 125.6; 123.2;51.8; 43.0; 23.8; 23.3; 22.8; 20.8. Anal. calc. for $C_{19}H_{25}N_3$: C 77.85, H 8.61, N 13.54; found: C 77.63, H 8.44, N 13.10.

1-Isopropyl-2-mesityl-3-phenylguanidine (**20d**). Yellow oil (96%). ^{1}H-NMR ($CDCl_3$): 7.27 – 7.19 (*m*, 3 H); 7.06 – 6.99 (*m*, 3 H); 6.81 (*s*, 1 H); 3.74 (br. *s*, 1 H); 2.19 (*s*, 3 H); 2.16 (*s*, 6 H); 1.93 (*s*, 1 H); 1.00 (*d*, *J* = 6.6, 6 H). ^{13}C-NMR ($CDCl_3$): 151.1; 138.9; 129.5; 129.3; 128.8; 124;7; 123.9; 123.4; 114.9; 43.7; 23.0; 20.8; 18.1. Anal. calc. for $C_{19}H_{25}N_3$: C 77.85, H 8.61, N 13.54; found: C 77.70, H 8.46, N 13.09.

1-Benzyl-3-(2-methylbutyl)-2-(4-methylphenyl)guanidine (**20e**). Yellow oil (85%). ^{1}H-NMR ($CDCl_3$): 7.36 – 7.25 (*m*, 5 H); 7.06 (*d*, *J* = 8.1, 2 H); 6.91 (*d*, *J* = 8.1, 2 H); 4.30 (*s*, 2 H); 2.85 (*dd*, *J* = 3.0, 6.0, 1 H); 2.71 (*dd*, *J* = 13.0, 7.1, 1 H); 2.28 (*s*, 3 H); 1.99 (*s*, 2 H); 1.52 – 1.40 (*m*, 1 H); 1.23 – 1.18 (*m*, 1 H); 1.03 – 0.96 (*m*, 1 H); 0.74 (*d*, *J* = 7.4, 3 H); 0.73 (*d*, *J* = 7.4, 3 H). ^{13}C-NMR ($CDCl_3$): 156.3; 137.0; 134.8; 130.0; 129.0; 128.0; 127.1; 124.9; 122.5; 49.4; 46.7; 34.8; 26.6; 20.8; 16.9; 11.0. Anal. calc. for $C_{20}H_{27}N_3 \cdot HCl$: N 12.15; found: N 11.78.

1-Butyl-2-(4-chlorophenyl)-3-(2-furylmethyl)guanidine (**20f**). Yellow oil (91%). ^{1}H-NMR ($CDCl_3$): 7.38 – 7.37 (*m*, 1 H); 7.23 (*d*, *J* = 8.5, 2 H); 6.89 (*d*, *J* = 8.5, 2 H); 6.34 – 6.33 (*m*, 1 H); 6.28 – 6.27 (*m*, 1 H); 4.42 (*s*, 2 H); 3.15 (*t*, *J* = 7.1, 2 H); 1.52 – 1.44 (*m*, 2 H); 1.34 – 1.26 (*m*, 2 H); 0.85 (*t*, *J* = 7.3, 3 H). ^{13}C-NMR ($CDCl_3$): 152.5; 151.2; 142.4; 129.5; 129.4; 124.7; 124.0; 110.5; 107.8; 42.3; 39.4; 31.5; 19.9; 13.7. Anal. calc. for $C_{16}H_{20}ClN_3O \cdot HCl$: C 56.15, H 6.18, N 12.28; found: C 56.28, H 6.20, N 12.36.

REFERENCES

[1] R. G. S. Berlinck, *Nat. Prod. Rep*. **1999**, *16*, 339; L. Heys, C. G. Moore, P. J. Murphy, *J. Chem. Soc. Rev.* **2000**, *29*, 57.

[2] O. E. Levy, J. E. Semple, M. L. Lim, J. Reiner, W. E. Rote, E. Dempsey, B. M. Richard, E. Zhang, A. Tulinsky, W. C. Ripka, R. F. Nutt, *J. Med. Chem.* **1996**, *39*, 4527; M. J. Rynkiewicz, B. A. Seaton, *Biochem. J.* **1996**, *35*, 16174.

[3] I. J. McAlpine, R. W. Armstrong, *Tetrahedron Lett.* **2000**, *41*, 1849.

[4] V. D. Le, C. H. Wong, *J. Org. Chem.* **2000**, *65*, 2399.

[5] C. G. Silva, E. Parolo, E. L. Streck, M. Wajner, C. M. D. Wannmacher, A. T Wyse, *Brain Res.* **1999**, *838*, 78.

[6] N. L. Reddy, W. Fan, S. S. Magar, M. E. Perlman, E. Yost, L. Zhung, D. Berlove, J. B. Fischer, K. B. Howie, T. Wolcott, G. J. Durant, *J. Med. Chem.* **1998**, *41*, 3298.

[7] P. W. Smith, S. L. Sollis, P. D. Howes, P. C. Cherry, I. D. Starkey, K. N. Cobley, H. Weston, J. Scicinski, A. Merritt, A. Whittington, P. Wyatt, N. Taylor, D. Green, R. Bethell, S. Madar, R. J. Fenton, P. J. Morley, T. Pateman, A. Beresford, *J. Med. Chem.* **1998**, *41*, 787.

[8] A. R. Katritzky, B. Rogovoy, *Arkivoc* **2005**, *Part iv*, 49.

[9] K. Wermann, M. Walther, E. Anders, *Arkivoc* **2002**, 24; T. Genski, G. Macdonald, X. Wei, N. Lewis, R. J. K. Taylor, *Arkivoc* **2000**, 266.

[10] D. H. R. Barton, J. D. Elliott, S. D. Gero, *J. Chem. Soc., Perkin Trans. 1*. **1982**, 2085.

[11] K. Feichtinger, C. Zapf, H. L. Sings, M. Goodman, *J. Org. Chem.* **1998**, *63*, 3804.

[12] M. S. Bernatowicz, Y. Wu, G. R. Matsueda, *Tetrahedron Lett.* **1993**, *34*, 3389.

[13] C. A. Maryanoff, R. C. Stanzione, J. N. Plampin, J. E. Mills, *J. Org. Chem.* **1986**, *51*, 1882.

[14] D. R. Kent, W. L. Cody, A. M. Doherty, *Tetrahedron Lett.* **1996**, *37*, 8711.

[15] Z. X. Guo, A. N. Cammidge, D. C. Horwell, *Synth. Commun.* **2000**, *30*, 2933.

[16] K. S. Kim, L. Qian, *Tetrahedron Lett.* **1993**, *34*, 7677.

[17] C. Levallet, J. Lerpiniere, S. Y. Ko, *Tetrahedron Lett.* **1997**, *53*, 5251.

[18] E. J. Iwanowicz, M. A. Poss, J. Lin, *Synth. Commun.* **1993**, *23*, 1443.

[19] Y. F. Yong, J. A. Kowalski, M. A. Lipton, *J. Org. Chem.* **1997**, *62*, 1540.

[20] M. A. Poss, E. Iwanowicz, J. A. Reid. J. Lin, Z. Gu, *Tetrahedron Lett.* **1992**, *33*, 5933.

[21] C. R. Rasmussen, F. J. Villani, L. E. Weaner, B. E. Reynolds, A. R. Hood, L. R. Hecker, S. O. Nortey, A. Hanslin, M. J. Costanzo, E. T. Powell, A. J. Molinari, *Synthesis* **1988**, *23*, 456.

[22] C. R. Rasmussen, F. J. Villani, B. E. Reynolds, J. N. Plampin, A. R. Hood, L. R. Hecker, S. O. Nortey, A. Hanslin, M. J. Costanzo, R. M. Howse, A. J. Molinari, *Synthesis* **1988**, *23*, 460.
[23] Y. Q. Wu, S. K. Hamilton, D. E. Wilkinson, G. S. Hamilton, *J Org. Chem.* **2002**, *67*, 7553.
[24] P. Molina, M. Alajarin, J. Saez, *Synth. Commun.* **1983**, *13*, 67.
[25] A. R. Katritzky, R. L. Parris, S. M. Allin, *Synth. Commun.* **1995**, *25*, 1173.
[26] A. R. Katritzky, B. Rogovoy, C. Klein, H. Insuasty, V. Vvedensky, B. Insuasty, *J. Org. Chem.* **2001**, *66*, 2854.
[27] A. R. Katritzky, B. V. Rogovoy, V. Vvedensky, *J Org. Chem.* **2000**, *65*, 8080.
[28] A. R. Katritzky, B. V. Rogovoy, X. Cai, N. Kirichenko, K. V. Kovalenko, *J. Org. Chem.* **2004**, *69*, 309.
[29] A. W. Johnson, S. C. K. Wong, *Can. J. Chem*. **1966**, *44*, 2793.
[30] D. F. Gavin, W. J. Schnabel, E. Kober, M. Roninson, *J. Org. Chem.* **1967**, *32*, 2511.
[31] M. Mikolajczyk, P. Kielbasinski, *Tetrahedron* **2000**, *37*, 233.
[32] A. Trani, E. Bellasio, *J. Heterocycl. Chem.* **1974**, *11*, 257.
[33] J. Burkhardt, K. Hamann, *Chem. Ber*. **1967**, *100*, 2569.
[34] A. R. Katritzky, S. Ledoux, R. M. Witek, S. K. Nair, *J. Org. Chem.* **2004**, *69*, 2976.
[35] C. Larsen, K. Steliou, D. N. Harpp, *J. Org. Chem.* **1978**, *43*, 337.
[36] E. M. Briggs, *Synthesis* **1980**, 295.
[37] P. Laszlo, *Tetrahedron Lett.* **1984**, *25*, 4651.
[38] V. N. Fetyukhin, *Zh. Obshch. Khim*. **1983**, *53*, 1763.

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