Synthesis of *N*,*N*-Disubstituted 3-Amino-1,2,4-triazoles

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Abstract: A general method for the synthesis of *N*,*N*-disubstituted 3-amino-1,2,4-triazoles **5** from di(benzotriazolyl)methanimines **1** and **1′**, hydrazine and substituted hydrazines is developed. The desired compounds were prepared regioselectively under mild conditions by simple procedures in yields of up to 95%.

Key words: acylation, cyclization, regioselectivity, triazoles, benzotriazole, hydrazines

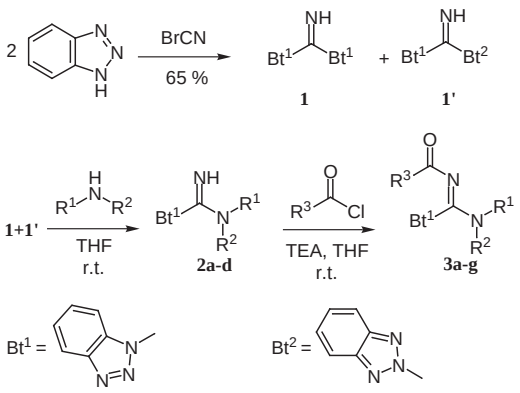
Aminotriazole derivatives are well known to be biologically active: 3-amino-1,2,4-triazole inhibits the synthesis of catalase,[1] a major detoxification enzyme against active oxygen species, such as hydrogen peroxides. 3-Amino-1,2,4-triazole was also used as an inhibitor of histidine biosynthesis in the cloning of arg1 gene.[2] Several 3-aminotriazole derivatives are effective in eosinophilia models for the treatment of chronic bronchial asthma.[3] Benzopyrans with triazolylamino substituents were patented[4] as potassium channel activators for the treatment of disorders associated with smooth muscle contraction. Sufotidine bismuth citrate, an aminotriazole,[5] is a histamine H_2-receptor antagonist which is used in the treatment of duodenal and gastric ulceration and other conditions where histamine is a known mediator. 3-Amino-1,2,4-triazoles were also evaluated for herbicide activity.[6]

Most previously described syntheses of the 1,5-disubstituted-3-amino-1,2,4-triazoles **5** are based on reactions of aminoguanidines with carboxylic acids.[7a,b] An enhanced synthetic route utilizing reactions of aminoguanidine with methyl benzoates was developed by Mullican et al.[7c] to synthesize 3-amino-5-aryl-1,2,4-triazoles under relatively mild conditions (reflux in MeOH, 18 h) in high yields. Arylcarbohydrazides are transformed into 2-aroyl-1-hydrazinecarboximidamides and cyclized in a sealed tube at 220 °C.[7d] Aminoguanidine smoothly reacts with ketones to form hydrazones: cyclization of these derivatives allows variation of the substituents at 1-nitrogen of the 1,2,4-triazole ring.[7e] Less general synthetic routes to triazoles **5** are reactions of amidrazones with carbodiimides[8] and of *N*-cyanoazomethines with hydrazines.[9a,b] Most of the previously known methods do not allow the direct synthesis of triazoles **5** bearing a substituted 3-amino group; however, reaction of 1-benzoyl-*S*-methylisothiosemicarbazide with dimethylamine in a sealed tube at 100 °C leads to 3-dimethylamino-5-phenyl-1,2,4-triazole (53%) accompanied by 2-amino-5-phenyl-1,3,4-oxadiazole and 3-methylthio-5-phenyl-1,2,4-triazole.[9c] 3-Monosubstituted-amino-1,2,4-triazoles can be prepared by reductive amination of unsubstituted analogs.[9d,e] 3(5)-Dimethylamino-1,2,4-triazole was prepared from dimethylcyanamide and formyl hydrazine at 140 °C.[9f]

Now we report a regiospecific, mild and convenient synthesis of 3-(*N*,*N*-disubstituted)amino-5-substituted-1*H*-1,2,4-triazoles and 3-(*N*,*N*-disubstituted)amino-1,5-disubstituted-1*H*-1,2,4-triazoles.

Recently we reported a convenient method for the preparation of benzotriazole-1-carboximidamides **2** from di(benzotriazolyl)methanimine **1** and various primary and secondary amines.[10a] Two examples suggested that compounds **2** could easily be transformed into acyl derivatives **3**, promising precursors for the synthesis of triazoles **5**.[10a] We have now prepared further acyl derivatives **3a–g** (Scheme 1, Table 1) and reacted them with hydrazines (Scheme 2).

Cyclization of acyl derivatives **3a–g** with unsubstituted, methyl, phenyl and benzyl hydrazines lead to the desired 3-amino-1,2,4-triazoles **5a–k** (Scheme 2, Table 2). Although reaction of **3** with substituted hydrazines could



Scheme 1

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Table 1 Preparation of Acyl Derivatives of Benzotriazole-1-carboximidamides **3a–g**

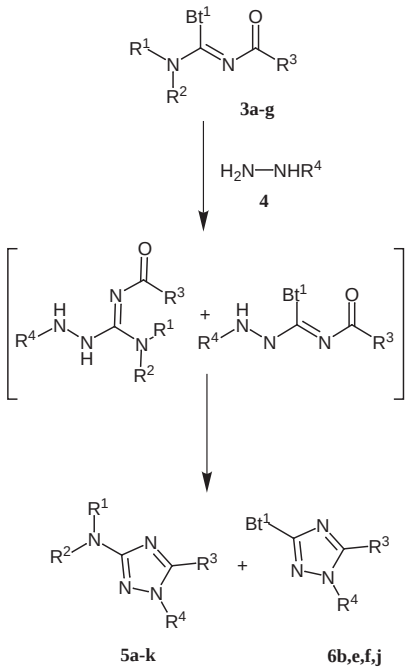
Entry	Compound **2**	Compound **3**	R^1	R^2	R^3	Yield of Compound **3** (%)
1	**2a**	**3a**	C_2H_5	C_2H_5	$(CH_3)_3C$	62
2	**2b**	**3b**	Allyl	Allyl	C_6H_5	74
3	**2c**	**3c**	$-(CH_2)_2O(CH_2)_2-$		Naphthalen-1-yl	94
4	**2c**	**3d**	$-(CH_2)_2O(CH_2)_2-$		C_6H_5	93
5	**2c**	**3e**	$-(CH_2)_2O(CH_2)_2-$		Thiophen-2-yl	64
6	**2d**	**3f**	$CH(CH_3)_2$	$CH(CH_3)_2$	C_6H_5	83
7	**2c**	**3g**	$-(CH_2)_2O(CH_2)_2-$		C_2H_5	91

lead to mixtures of 3-amino-5-substituted and 3-substituted-5-amino isomers, the final products were obtained as single isomers **5a–k** (Scheme 2).

The position of the substituents was confirmed by X-ray crystallography for compound **5g** (Figure, Tables 3, 4) and other structures were assigned by analogy and by spectral comparison.

The analysis of structure **5g** suggests the following mechanism of the cyclization reaction: first, the unsubstituted nitrogen atom in the hydrazine displaces the benzotriazolyl moiety, and then cyclization at the carbonyl group in the acyl fragment takes place (Scheme 2).

Phenyl and benzyl hydrazine, in contrast to unsubstituted hydrazine and methylhydrazine, react with acyl derivatives **3a**,**c**,**e**,**f** with the competitive formation of 3-aminotriazoles **5b**,**e**,**f**,**j** and 3-Bt-substituted triazoles **6b**,**e**,**f**,**j** (Bt = benzotriazole). The lower the electron-donating character of the substituent R^4 of the hydrazine, the more of the side product **6b**,**e**,**f**,**j** is formed (Scheme 2, Table 2). However, more experiments are needed to completely rationalize the influence of the R^4 group. The nature of the substituents R^1-R^3 in the amino and acyl groups seems not to affect the yield and selectivity of the cyclization. In analogy to similar known reactions, competitive displacement of the dialkylamino group rather then benzotriazole moiety in the reaction of **3a**,**c**,**e**,**f** with phenyl and benzylhydrazine is unexpected. Indeed, selective substitution of the benzotriazole moiety rather than the dialkylamino group in the reaction of compounds of the type $R_2NC{=}(O,NH)Bt$ with amines $R^1{}_2NH$ proceeds with the formation of the derivatives $R_2NC{=}(O,NH)NR^1{}_2$ and no symmetrical product is formed.[10]



Scheme 2

An attempt to synthesize compound **6k** by reacting **1**, **1'** with benzoic hydrazide gave only oxadiazole **7** in quantitative yield (Scheme 3).

In summary, we have developed a general procedure for the preparation of 3-(*N*,*N*-disubstituted)amino-5-substituted-1,2,4-triazoles **5a–k** utilizing di(benzotriazolyl)-methanimines **1** and **1′** as intermediates. The reaction sequence was performed under mild conditions with simple purification of the intermediates and final products.

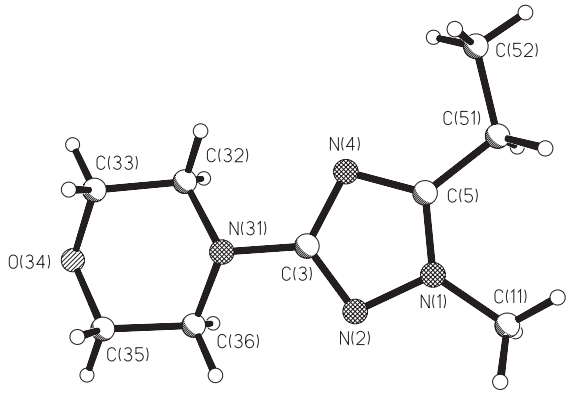


Figure Perspective view and atom labeling of one of the two independent molecules in the X-ray crystal structure of **5g**

able 2 Preparation of 3-(*N*,*N*-Dialkyl)amino-1,2,4-triazoles **5a–k**

+6	3	R^1	R^2	R^3	R^4	Yield of Compound **5** (%)	Yield of Compound **6** (%)
	3a	C_2H_5	C_2H_5	$(CH_3)_3C$	CH_3	75	0
	3a	C_2H_5	C_2H_5	$(CH_3)_3C$	$C_6H_5CH_2$	36	30
	3b	Allyl	Allyl	C_6H_5	H	72	0
	3b	Allyl	Allyl	C_6H_5	CH_3	84	0
	3c	$-(CH_2)_2O(CH_2)_2-$		Naphthalen-1-yl	CH_3	90	0
	3c	$-(CH_2)_2O(CH_2)_2-$		Naphthalen-1-yl	$C_6H_5CH_2$	45	17
	3c	$-(CH_2)_2O(CH_2)_2-$		C_2H_5	CH_3	82	0
	3e	$-(CH_2)_2O(CH_2)_2-$		Thiophen-2-yl	$C_6H_5CH_2$	42	29
	3f	$CH(CH_3)_2$	$CH(CH_3)_2$	C_6H_5	CH_3	95	0
	3f	$CH(CH_3)_2$	$CH(CH_3)_2$	C_6H_5	C_6H_5	25	13
	3c	$-(CH_2)_2O(CH_2)_2-$		C_6H_5	H	84	0

Table 3 Bond Lengths [Å] for **5g**

Atom	Atom	Distance	Atom	Atom	Distance
N(1)	C(5)	1.329(2)	N(1')	C(5')	1.328(3)
N(1)	N(2)	1.387(2)	N(1')	N(2')	1.381(2)
N(1)	C(11)	1.441(3)	N(1')	C(11')	1.443(3)
N(2)	C(3)	1.317(3)	N(2')	C(3')	1.318(2)
C(3)	N(4)	1.365(2)	C(3')	N(4')	1.370(2)
C(3)	N(31)	1.394(2)	C(3')	N(31')	1.387(2)
N(4)	C(5)	1.327(2)	N(4')	C(5')	1.326(2)
C(5)	C(51)	1.503(3)	C(5')	C(51')	1.497(3)
N(31)	C(32)	1.456(3)	N(31')	C(32')	1.460(2)
N(31)	C(36)	1.472(2)	N(31')	C(36')	1.469(2)
C(32)	C(33)	1.509(3)	C(32')	C(33')	1.511(3)
C(33)	O(34)	1.427(2)	C(33')	O(34')	1.431(2)
O(34)	C(35)	1.416(2)	O(34')	C(35')	1.419(2)
C(35)	C(36)	1.509(3)	C(35')	C(36')	1.519(3)
C(51)	C(52)	1.496(3)	C(51')	C(52')	1.502(3)

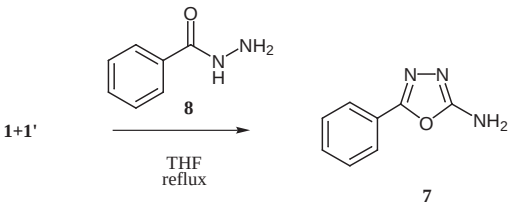
Melting points were determined using a capillary melting point apparatus equipped with a digital thermometer and were uncorrected. ^1H and ^{13}C NMR spectra were recorded on a Varian GEMINI-300 MHz spectrometer (300 MHz and 75 MHz respectively) using $CDCl_3$ or DMSO-d_6 (compound **7**) as solvents with tetramethylsilane as internal standard. THF was distilled under nitrogen immediately before use from sodium/benzophenone. All other reagents were of reagent grade and were used without purification. Column chromatography was conducted with silica gel 230–400 mesh. Di(1*H*-benzotriazol-1-yl)methanimine (**1**) and 1*H*-benzotriazol-1-yl(2*H*-benzotriazol-2-yl)methanimine (**1'**), (utilized as a 2:1 mixture of isomers) were prepared and characterized according to the previously published procedure.[10a]

Preparation of Benzotriazole-1-carboximidamides 2; General Procedure

Di(benzotriazolyl)methanimines **1** and **1'** (500 mg, 2 mmol) was suspended in dry THF (20 mL) under inert atmosphere. The appropriate amine (2 mmol, 1 equiv) was added dropwise, and the resulting mixture was allowed to react for 8–12 h until complete

able 4 Bond Angles [°] for **5g**

tom	Atom	Atom	Angle	Atom	Atom	Atom	Angle
(5)	N(1)	N(2)	110.19(17)	C(5')	N(1')	N(2')	110.78(17)
(5)	N(1)	C(11)	129.38(19)	C(5')	N(1')	C(11')	128.27(19)
(2)	N(1)	C(11)	120.21(17)	N(2')	N(1')	C(11')	120.70(17)
(3)	N(2)	N(1)	101.06(14)	C(3')	N(2')	N(1')	101.21(15)
(2)	C(3)	N(4)	115.85(17)	N(2')	C(3')	N(4')	115.18(16)
(2)	C(3)	N(31)	122.41(16)	N(2')	C(3')	N(31')	122.77(16)
(4)	C(3)	N(31)	121.71(18)	N(4')	C(3')	N(31')	122.02(17)
(5)	N(4)	C(3)	102.43(17)	C(5')	N(4')	C(3')	102.95(16)
(4)	C(5)	N(1)	110.46(18)	N(4')	C(5')	N(1')	109.85(18)
(4)	C(5)	C(51)	126.52(18)	N(4')	C(5')	C(51')	126.42(18)
(1)	C(5)	C(51)	122.90(18)	N(1')	C(5')	C(51')	123.64(19)
(3)	N(31)	C(32)	114.43(15)	C(3')	N(31')	C(32')	114.81(15)
(3)	N(31)	C(36)	115.18(15)	C(3')	N(31')	C(36')	115.79(16)
(32)	N(31)	C(36)	111.55(15)	C(32')	N(31')	C(36')	112.43(15)
(31)	C(32)	C(33)	109.65(16)	N(31')	C(32')	C(33')	109.00(17)
(34)	C(33)	C(32)	111.67(17)	O(34')	C(33')	C(32')	111.80(17)
(35)	O(34)	C(33)	109.71(16)	C(35')	O(34')	C(33')	109.74(16)
(34)	C(35)	C(36)	111.87(16)	O(34')	C(35')	C(36')	111.40(16)
(31)	C(36)	C(35)	109.73(16)	N(31')	C(36')	C(35')	109.19(16)
(52)	C(51)	C(5)	113.24(17)	C(5')	C(51')	C(52')	113.42(18)



Scheme 3

conversion of **1**, as monitored by TLC. The mixture was then concentrated in vacuo and dissolved in CH_2Cl_2 (20 mL). The organic layer was washed twice with aqueous Na_2CO_3(10%), dried over $MgSO_4$, and the solvent removed under reduced pressure to afford compounds **2a–d** with analytical purity. The preparation and characterization of compounds **2c**,**d** were described previously in our earlier work.[10a]

N,*N*-Diethyl-1*H*-benzotriazole-1-carboximidamide (**2a**)
Yellow oil, yield 95%.

^{1}H NMR: δ = 1.24 (t, 6H, *J* = 7.1 Hz), 3.36 (q, 4H, *J* = 7.1 Hz), 6.64 (br s, 1H), 7.45 (t, 1H, *J* = 7.5 Hz), 7.59 (t, 1H, *J* = 8.1 Hz), 7.72 (br s, 1H), 8.11 (d, 1H, *J* = 8.3 Hz).

^{13}C NMR: δ = 12.9, 43.0, 110.8, 120.0, 124.7, 128.8, 132.0, 145.3, 150.7.

This compound was used as crude product without isolation and purification for further transformation. See compound **3a**.

N,*N*-Diallyl-1*H*-benzotriazole-1-carboximidamide (**2b**)
Colorless oil, yield 86%.

^{1}H NMR: δ = 3.95–3.93 (d, 4H, *J* = 5.9 Hz), 5.23–5.17 (m, 4H), 5.97–5.84 (m, 2H), 7.44 (t, 1H, *J* = 7.7 Hz), 7.58 (t, 1H, *J* = 7.2 Hz), 7.75 (d, 1H, *J* = 8.2 Hz), 8.10 (d, 1H, *J* = 8.1 Hz).

^{13}C NMR: δ = 50.8, 111.3, 118.3, 120.0, 124.7, 128.9, 132.1, 132.5, 145.4, 151.2.

Anal. Calcd for $C_{13}H_{15}N_5$: C, 64.71; H, 6.27; N, 29.02. Found: C, 64.33; H, 6.40; N, 29.22.

Preparation of Acyl Derivatives of 1*H*-Benzotriazol-1-carboximidamides 3a–g; General Procedure

Compound **2** (1 equiv) was dissolved in chloroform and acyl chloride (1 equiv) was added followed by addition of triethylamine (1 equiv). The mixture was allowed to react for 2–4 h at ambient temperature. The completion of the reaction was monitored by

TLC. Then the chloroform solution was washed with water to remove triethylamine hydrochloride. The chloroform layer was separated, dried and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel with ethyl acetate–hexanes (1:1) as eluent for compounds **3b**,**e** or by recrystallization for compounds **3a**,**c**,**d**,**g**. The preparation and characterization of compound **3f** was described previously in our earlier work.[10a]

N-[1*H*-Benzotriazol-1-yl(diethylamino)methylidene]-2,2-dimethylpropanamide (**3a**)
White prisms, mp 106–108 °C, yield 62%.

^{1}H NMR: δ = 1.15 (s, 9H), 1.27 (t, 6H, *J* = 7.1 Hz), 3.49 (q, 4H, *J* = 6.8 Hz), 7.38–7.44 (m, 1H), 7.54 (s, 2H), 8.08 (d, 1H, *J* = 8.3 Hz).

^{13}C NMR: δ = 13.1, 27.4, 41.2, 43.6, 110.2, 120.4, 124.6, 128.8, 133.3, 144.9, 145.2, 189.3.

Anal. Calcd for $C_{16}H_{23}N_5O$: C, 63.76; H, 7.69; N, 23.24. Found: C, 64.06; H, 8.07; N, 23.35.

N-[1*H*-Benzotriazol-1-yl(diallylamino)methylidene]benzamide (**3b**)
White prisms, mp 87–88 °C, yield 74%.

^{1}H NMR: δ = 4.13 (d, 4H, *J* = 6.0 Hz), 5.31–5.26 (m, 4H), 6.06–5.93 (m, 2H), 7.40–7.26 (m, 5H), 7.51–7.46 (m, 1H), 8.08–7.99 (m, 3H).

^{13}C NMR: δ = 51.5, 110.4, 119.6, 120.4, 124.8, 128.0, 129.1, 129.5, 131.5, 132.2, 132.6, 135.3, 145.1, 147.3, 174.5.

Anal. Calcd for $C_{20}H_{19}N_5O$: C, 69.55; H, 5.54; N, 20.28. Found: C, 69.56; H, 5.85; N, 20.25.

N-[1*H*-Benzotriazol-1-yl(morpholino)methylidene]-1-naphthamide (**3c**)
White prisms, mp 153–154 °C, yield 94%.

^{1}H NMR: δ = 3.67–3.70 (m, 4H), 3.88–3.92 (m, 4H), 7.36–7.55 (m, 6H), 7.80 (dd, 1H, *J* = 7.6 Hz, *J* = 1.7 Hz), 7.93 (d, 1H, *J* = 8.2 Hz), 8.05–8.08 (m, 1H), 8.25 (dd, 1H, *J* = 7.3 Hz, *J* = 1.3 Hz), 8.47 (dd, 1H, *J* = 8.2 Hz, *J* = 1.3 Hz).

^{13}C NMR: δ = 47.9, 66.3, 110.8, 120.4, 124.3, 125.1, 125.9, 126.0, 127.3, 128.2, 129.5, 130.4, 131.0, 132.4, 132.5, 132.8, 133.7, 145.4, 146.0, 177.0.

Anal. Calcd for $C_{22}H_{19}N_5O_2$: C, 68.56; H, 4.97; N, 18.17. Found: C, 68.78; H, 5.00; N, 18.38.

N-[1*H*-Benzotriazol-1-yl(morpholino)methylidene]benzamide (**3d**)
White prisms, mp 183–184 °C, yield 93%.

^{1}H NMR: δ = 3.65−3.68 (m, 4H), 3.89−3.92 (m, 4H), 7.37−7.53 (m, 6H), 8.01−8.10 (m, 3H).

^{13}C NMR: δ = 48.0, 66.3, 110.9, 120.5, 125.1, 128.1, 129.4, 129.6, 132.4, 132.5, 135.2, 145.5, 147.0, 174.9.

Anal. Calcd for $C_{18}H_{17}N_5O_2$: C, 64.47; H, 5.11; N, 20.88. Found: C, 64.63; H, 5.51; N, 21.05.

N-[1*H*-Benzotriazol-1-yl(morpholino)methylidene]-2-thiophenecarboxamide (**3e**)
White prisms, mp 148–150 °C, yield 64%.

^{1}H NMR: δ = 3.68–3.71 (m, 4H), 3.91–3.94 (m, 4H), 7.08 (t, 1H, *J* = 4.3 Hz), 7.40–7.55 (m, 4H), 7.71 (d, 1H, *J* = 3.4 Hz), 8.11 (d, 1H, *J* = 8.1 Hz).

^{13}C NMR: δ = 48.2, 66.3, 111.0, 120.5, 125.2, 128.0, 129.6, 132.4, 132.5, 141.2, 145.5, 147.4, 169.1.

Anal. Calcd for $C_{16}H_{15}N_5O_2S$: C, 56.29; H, 4.43; N, 20.51. Found: C, 56.30; H, 4.39; N, 20.49.

N-[1*H*-Benzotriazol-1-yl(morpholino)methylidene]propanamide (**3g**)
White prisms, mp 56–57 °C, yield 91%.

^{1}H NMR: δ = 1.01 (t, 3H, *J* = 7.2 Hz), 2.44 (q, 2H, *J* = 7.2 Hz), 3.46–3.51 (m, 4H), 3.82–3.85 (m, 4H), 7.42–7.48 (m, 1H), 7.60–7.62 (m, 2H), 8.10 (d, 1H, *J* = 7.6 Hz).

^{13}C NMR: δ = 8.9, 32.6, 47.4, 66.1, 110.5, 120.6, 125.2, 129.5, 132.4, 143.9, 145.4, 185.0

Anal. Calcd for $C_{14}H_{17}N_5O_2$: C, 58.52; H, 5.96. Found: C, 58.37; H, 5.88.

Preparation of 3-(*N*,*N*-Dialkyl)amino-1,5-disubstituted Triazoles 5 and 6; General Procedure

Compound **3** (1 equiv) was dissolved in chloroform and hydrazine **4** (1 equiv) was added. The completion of the reaction was monitored by TLC. The mixture was concentrated under reduced pressure. Separation and purification of compounds **5** and **6** were performed by column chromatography using a mixture of ethyl acetate/hexanes (1:1) as eluent for compounds **5a–d**,**j**,**k** and **6b**,**g**; $CHCl_3$–MeOH (19:1) for compounds **5e**,**i**,**g**,**h**, **6h**; CH_2Cl_2–Et_2O (9:1) for compounds **5f**, **6f**.

5-(*tert*-Butyl)-*N*,*N*-diethyl-1-methyl-1*H*-1,2,4-triazol-3-amine (**5a**)
Colorless oil, yield 75%.

^{1}H NMR: δ = 1.13 (t, 6H, *J* = 7.1 Hz), 1.39 (s, 9H), 3.39 (q, 4H, *J* = 7.0 Hz), 3.78 (s, 3H).

^{13}C NMR: δ = 12.8, 28.9, 32.2, 37.1, 41.7, 160.6, 162.7.

Anal. Calcd for $C_{11}H_{22}N_4$: C, 62.82; H, 10.54; N, 26.64. Found: C, 62.75; H, 10.83; N, 26.89.

1-Benzyl-5-(*tert*-butyl)-*N*,*N*-diethyl-1*H*-1,2,4-triazol-3-amine (**5b**)
Colorless oil, yield 36%.

^{1}H NMR: δ = 1.15 (t, 6H, *J* = 7.1 Hz), 1.32 (s, 9H), 3.43 (q, 4H, *J* = 7.1 Hz), 5.33 (s, 2H), 7.07 (d, 2H, *J* = 7.1 Hz), 7.22–7.29 (m, 3H).

^{13}C NMR: δ = 12.7, 29.5, 32.6, 41.8, 52.6, 126.1, 127.1, 128.4, 137.5, 161.4, 163.0.

Anal. Calcd for $C_{11}H_{22}N_4$: N, 19.56. Found: N, 19.39.

N,*N*-Diallyl-*N*-(5-phenyl-1*H*-1,2,4-triazol-3-yl)amine (**5c**)
White microcrystals, mp 116–117 °C, yield 72%.

^{1}H NMR: δ = 4.04 (d, 4H, *J* = 5.5 Hz), 5.16−5.25 (m, 4H), 5.78−5.87 (m, 2H), 7.26−7.36 (m, 3H), 7.80 (br s, 1H), 7.94−7.98 (m, 2H).

^{13}C NMR: δ = 51.1, 117.7, 126.4, 128.5, 129.4, 129.8, 133.1, 158.2, 159.5.

Anal. Calcd for $C_{14}H_{16}N_4$: C, 69.97; H, 6.71; N, 23.31. Found: C, 70.27; H, 7.00; N, 23.55.

N,*N*-Diallyl-*N*-(3-methyl-5-phenyl-1*H*-1,2,4-triazol-3-yl)amine (**5d**)
Colorless oil, yield 84%.

^{1}H NMR: δ = 3.78 (s, 3H), 4.06 (d, 4H, *J* = 5.8 Hz), 5.14−5.24 (m, 4H), 5.83−5.96 (m, 2H), 7.43−7.48 (m, 3H), 7.60−7.63 (m, 2H).

^{13}C NMR: δ = 36.2, 49.7, 116.6, 128.4, 128.5, 128.6, 129.6, 134.3, 153.8, 164.2.

Anal. Calcd for $C_{15}H_{18}N_4$: C, 70.84; H, 7.13; N, 22.03. Found: C, 70.53; H, 7.17; N, 22.45.

4-[1-Methyl-5-(1-naphthyl)-1*H*-1,2,4-triazol-3-yl]morpholine (**5e**)
White prisms, mp 115–117 °C, yield 90%.

^{1}H NMR: δ = 3.49–3.51 (m, 4H), 3.60 (s, 3H), 3.84–3.88 (m, 4H), 7.52–7.58 (m, 4H), 7.76–7.78 (m, 1H), 7.90–7.93 (m, 1H), 7.96–8.00 (m, 1H).

^{13}C NMR: δ = 35.7, 46.9, 66.5, 124.9, 125.0, 125.6, 126.5, 127.3, 128.3, 128.4, 130.5, 131.5, 133.5, 153.2, 165.4.

Anal. Calcd for $C_{17}H_{18}N_4O$: N, 19.03. Found: N, 19.04.

4-[1-Benzyl-5-(1-naphthyl)-1*H*-1,2,4-triazol-3-yl]morpholine (**5f**)
Off-white microcrystals, mp 125–127 °C, yield 45%.

^{1}H NMR: δ = 3.50–3.53 (m, 4H), 3.83–3.86 (m, 4H), 5.02 (s, 2H), 7.00–7.03 (m, 2H), 7.19–7.24 (m, 3H), 7.44–7.55 (m, 4H), 7.75 (dd, 1H, *J* = 6.5 Hz, *J* = 1.5 Hz), 7.89 (dd, 1H, *J* = 5.3 Hz, *J* = 1.8 Hz), 7.96 (dd, 1H, *J* = 5.0 Hz, *J* = 2.2 Hz).

^{13}C NMR: δ = 46.9, 52.2, 66.5, 124.8, 125.1, 125.6, 126.5, 127.2, 127.3, 127.7, 128.2, 128.3, 128.4, 130.6, 131.6, 133.5, 135.9, 153.3, 165.5.

Anal. Calcd for $C_{23}H_{22}N_4O$: N, 15.12. Found: N, 14.92.

4-(5-Ethyl-1-methyl-1*H*-1,2,4-triazol-3-yl)morpholine (**5g**)
White prisms, mp 87–89 °C, yield 82%.

^{1}H NMR: δ = 1.29 (t, 3H, *J* = 7.6 Hz), 2.66 (q, 2H, *J* = 7.5 Hz), 3.34–3.37 (m, 4H), 3.67 (s, 3H), 3.78–3.81 (m, 4H).

^{13}C NMR: δ = 11.9, 19.3, 34.4, 46.9, 66.4, 156.1, 164.6

Anal. Calcd for $C_9H_{16}N_4O$: C, 55.08; H, 8.82; N, 28.55. Found: C, 55.24; H, 8.82; N, 28.27.

Crystal data for **5g**: $C_9H_{16}N_4O$, MW 196.26, monoclinic, $P2_1$, a = 6.862(2) Å, b = 15.206(5) Å, c = 10.245(4) Å, β = 109.482(4)°, V = 1007.7(6) Å^3, Z = 4, T = –110 °C, μ (MoKα) = 0.089 mm^{-1}, D_{calcd} = 1.294 g·cm^{-3}, $2\theta_{max}$ 53° (SMART CCD area detector), w$R(F^2)$ = 0.0903 (all 3839 data), R = 0.0375 (3193 data with I > 2σI).

4-[1-Benzyl-5-(2-thienyl)-1*H*-1,2,4-triazol-3-yl]morpholine (**5h**)
Greenish microcrystals, mp 114–116 °C, yield 42%.

^{1}H NMR: δ = 3.45–3.48 (m, 4H), 3.80–3.83 (m, 4H), 5.40 (s, 2H), 7.04 (t, 1H, *J* = 3.8 Hz), 7.17–7.37 (m, 6H), 7.42 (d, 1H, *J* = 4.9 Hz).

^{13}C NMR: δ = 46.8, 52.4, 66.5, 126.4, 127.7, 127.8, 128.0, 128.4, 128.8, 129.1, 135.9, 148.6, 165.1.

Anal. Calcd for $C_{17}H_{18}N_4OS$: C, 62.55; H, 5.56. Found: C, 62.48; H, 5.59.

N,*N*-Diisopropyl-1-methyl-5-phenyl-1*H*-1,2,4-triazol-3-amine (**5i**)
Off-white prisms, mp 41–43 °C, yield 95%.

^{1}H NMR: δ = 1.33 (d, 12H, *J* = 6.7 Hz), 3.78 (s, 3H), 4.02–4.15 (m, 2H), 7.39–7.48 (m, 3H), 7.60–7.65 (m, 2H).

^{13}C NMR: δ = 20.7, 36.2, 46.3, 128.5, 128.6, 128.9, 129.3, 152.7, 162.9.

Anal. Calcd for $C_{15}H_{22}N_4$: C, 69.73; H, 8.58; N, 21.68. Found: C, 69.59; H, 8.67, N, 22.02.

N,*N*-Diisopropyl-1,5-diphenyl-1*H*-1,2,4-triazol-3-amine (**5j**)
White prisms, mp 188–189 °C, yield 25%.

^{1}H NMR: δ = 1.37 (d, 12H, *J* = 6.8 Hz), 4.11–4.19 (m, 2H), 7.26–7.33 (m, 8H), 7.44–7.48 (m, 2H).

^{13}C NMR: δ = 20.7, 46.4, 124.9, 127.4, 128.3, 128.8, 128.9, 129.1, 129.2, 138.7, 151.5, 163.3.

Anal. Calcd for $C_{20}H_{24}N_4$: C, 74.97; H, 7.55; N, 17.48. Found: C, 74.96; H, 7.97, N, 17.52.

4-(5-Phenyl-1*H*-1,2,4-triazol-3-yl)morpholine (**5k**)
White microcrystals, mp 128−129 °C, yield 84%.

^{1}H NMR: δ = 3.32−3.35 (m, 4H), 3.63−3.66 (m, 4H), 7.34−7.36 (m, 3H), 7.85−7.88 (m, 2H), 9.22 (br s, 1H).

^{13}C NMR: δ = 46.6, 66.0, 126.2, 128.7, 129.0, 129.8, 157.7, 162.4.

Anal. Calcd for $C_{12}H_{14}N_4O$: C, 62.59; H, 6.13; N, 24.33. Found: C, 62.26; H, 6.49, N, 23.94.

1-[1-Benzyl-5-(*tert*-butyl)-1*H*-1,2,4-triazol-3-yl]-1*H*-benzotriazole (**6b**)
White prisms, mp 134–135 °C, yield 30%.

^{1}H NMR: δ = 1.51 (s, 9H), 5.63 (s, 2H), 7.22 (d, 2H, *J* = 6.6 Hz), 7.31–7.36 (m, 3H), 7.44 (t, 1H, *J* = 7.1 Hz), 7.59 (t, 1H, *J* = 7.1 Hz), 8.13 (d, 1H, *J* = 8.3 Hz), 8.28 (d, 1H, *J* = 8.3 Hz).

^{13}C NMR: δ = 29.4, 33.3, 54.1, 112.9, 119.9, 124.7, 126.5, 128.0, 128.7, 128.8, 131.6, 135.5, 145.9, 153.9, 163.8.

Anal. Calcd for $C_{19}H_{20}N_6$: C, 68.29; H, 6.06; N, 25.28. Found: C, 68.29; H, 6.46, N, 24.98.

1-[1-Benzyl-5-(1-naphthyl)-1*H*-1,2,4-triazol-3-yl]-1*H*-benzotriazole (**6f**)
Yellow oil, yield 17%.

^{1}H NMR: δ = 5.31 (s, 2H), 7.10–7.13 (m, 2H), 7.24–7.26 (m, 3H), 7.47–7.64 (m, 6H), 7.77 (d, 1H, *J* = 7.6 Hz), 7.98 (d, 1H, *J* = 8.1 Hz), 8.05–8.10 (m, 1H), 8.17 (dt, 1H, *J* = 8.3 Hz, *J* = 1.0 Hz), 8.36 (dt, 1H, *J* = 8.3 Hz, *J* = 1.0 Hz).

^{13}C NMR: δ = 53.4, 98.1, 113.0, 120.0, 124.3, 124.8, 124.9, 124.9, 126.8, 127.7, 127.8, 128.4, 128.6, 128.7, 128.8, 129.0, 131.4, 131.5, 131.7, 133.5, 134.7, 146.0, 154.9.

Anal. HRMS (FAB) Calcd for $C_{25}H_{19}N_6$ (M + 1): 403.1671. Found: 403.1666.

1-[1-Benzyl-5-(2-thienyl)-1*H*-1,2,4-triazol-3-yl]-1*H*-benzotriazole (**6h**)
Off-white solid, mp 148–150 °C, yield 29%.

^{1}H NMR: δ = 5.63 (s, 2H), 7.07 (t, 1H, *J* = 3.7 Hz), 7.22–7.58 (m, 9H), 8.08 (d, 1H, *J* = 8.4 Hz), 8.28 (d, 1H, *J* = 8.5 Hz).

^{13}C NMR: δ = 53.5, 112.9, 120.0, 124.9, 126.7, 127.7, 128.1, 128.4, 129.0, 129.1, 129.6, 129.8, 131.6, 134.7, 146.0, 150.4, 155.3.

Anal. Calcd for $C_{19}H_{14}N_6$: C, 63.67; H, 3.94. Found: C, 63.58; H, 4.19.

1-(1,5-Diphenyl-1*H*-1,2,4-triazol-3-yl)-1*H*-benzotriazole (**6j**)
White prisms, mp 170–180 °C, yield 13%.

^{1}H NMR: δ = 7.38–7.51 (m, 9H), 7.62–7.67 (m, 3H), 8.18 (dd, 1H, *J* = 0.8 Hz, *J* = 7.6 Hz), 8.42 (dd, 1H, *J* = 0.8 Hz, *J* = 7.6 Hz).

^{13}C NMR: δ = 112.9, 120.1, 124.9, 125.6, 126.7, 128.7, 129.0, 129.1, 129.5, 129.6, 130.7, 131.6, 137.6, 146.0, 154.7, 156.0.

Anal. Calcd for $C_{20}H_{14}N_6$: C, 70.99; H, 4.17; N, 24.84. Found: C, 70.98; H, 4.45, N, 24.78.

Preparation of 5-Phenyl-1,3,4-oxadiazol-2-ylamine 7

Compound **1** (0.5 g, 1.9 mmol) and benzoic hydrazide (0.29 g, 1.9 mmol) were dissolved in THF (25 mL) and heated under reflux for 3 h. Compound **7** precipitated after cooling of the reaction mixture. The precipitate was filtered off and washed with cold THF to give compound **7** as white needles 0.575 g (94%); mp 240–241 °C.

^{1}H NMR: δ = 7.30 (s, 2H), 7.53−7.58 (m, 3H), 7.81−7.84 (m, 2H).

^{13}C NMR: δ = 124.4, 125.0, 129.2, 130.4, 157.4, 163.9.

Anal. Calcd for $C_8H_7N_3O$: C, 59.62; H, 4.38; N, 26.07. Found: C, 59.61, H, 4.26, N, 26.26.

References

(1) (a) Khadir, A.; Verreault, J.; Averill, D. A. *Archives of Biochemistry and Biophysics* **1999**, *370*, 163. (b) Pedraza-Chaverri, J.; de los Granados-Silvestre, M. A.; Medina-Campos, O. N.; Hernandez-Pando, R. *Free Radical Biology & Medicine* **1999**, *27*, 245. (c) Streb, P.; Feierabend, J. *Botanica Acta* **1996**, *109*, 125. (d) Matsuda, Y.; Okuda, T.; Sagisaka, S. *Biosci. Biotech. Biochem.* **1994**, *58*, 906.

(2) Ventura, L.; PerezGonzales, J. A.; Ramon, D. *Fems Microbiology Lett.* **1997**, *149*, 207.

(3) Naito, Y.; Akahoshi, F.; Takeda, S.; Okada, T.; Kajii, M.; Nishimura, H.; Sigiura, M.; Fukaya, C.; Kagitani, Y. *J. Med. Chem.* **1996**, *39*, 3019.

(4) Stemp, G.; Burrell, G. Eur. Patent Appl. EP 399834, **1990**.

(5) Clitherow, J. W. Eur. Patent Appl. EP 367484, **1989**.

(6) (a) Wermann, K.; Hartmann, M.; Bauer, H.-J. *Z. Chem.* **1984**, *24*, 120. (b) Hartmann, M.; Bauer, H.-J.; Wermann, K. *Biocide Polymers* **1985**, 195.

(7) (a) Temple, C. Jr. In *Triazoles 1,2,4;* Mongomery, J. A., Ed.; John Wiley and Sons: New York, **1981**, 130. (b) Polya, J. B. In *Comprehensive Heterocyclic Chemistry*, Vol. 5; Potts, K. T., Ed.; Pergamon Press: Oxford, **1984**, 733. (c) Mullican, M. D.; Wilson, M. W.; Connor, D. T.; Kostlan, C. R.; Schrier, D. J.; Dyer, R. D. *J. Med. Chem.* **1993**, *36*, 1090. (d) Lipinski, C. A.; LaMattina, J. L.; Hohnke, L. A. *J. Med. Chem.* **1985**, *28*, 1628. (e) Gyorgydeak, Z.; Holzer, W. *Heterocycles* **1998**, *48*, 1395.

(8) (a) Reimlinger, H.; Billiau, F.; Lingier, W. R. F. *Synthesis* **1970**, 260. (b) Reimlinger, H.; Lingier, W. R. F.; Vandewalle, J. J. M.; Goes, E. *Synthesis* **1970**, 433.

(9) (a) von Kristinsson, H.; Winkler, T. *Helv. Chim. Acta* **1983**, *66*, 1129. (b) Heitke, B. T.; McCarty, C. G. *J. Org. Chem.* **1974**, *39*, 1522. (c) Hoggarth, E. *J. Chem. Soc.* **1950**, 1579. (d) Akahoshi, F.; Okada, T.; Takeda, S.; Naito, Y.; Fukaya, C.; Kuwahara, S.; Kajii, M.; Nishimura, H.; Sugiura, M. WO 95/03286, **1995**. (e) Okide, G. B. *Indian J. Chem., Sect. B* **1993**, *32*, 422. (f) *Chem. Abstr.* **1966**, *64*, 8196.

(10) (a) Katritzky, A. R.; Rogovoy, B. V.; Chassaing, C.; Vvedensky, V. *J. Org. Chem.* **2000**, *65*, 8080. (b) Katritzky, A. R.; Pleynet, D. P. M.; Yang, B. *J. Org. Chem.* **1997**, *62*, 4155.