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Tetrahedron Letters 45 (2004) 9423–9426
Tetrahedron Letters

Solvent-free synthesis of azole carboximidamides

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Received 15 July 2004; revised 15 October 2004; accepted 20 October 2004

Abstract—A one-pot procedure is described for the preparation of 1*H*-pyrazole-carboximidamides **2**, 1*H*-benzotriazole-carboximidamides **3** and guanidinylation of amines with **3**. The X-ray crystal structure of *N*,*N*-dimethyl-1*H*-benzotriazole-1-carboximidamide **3b**, has been determined.

Amidino (carboximidamide) group transfer reagents are useful tools for the preparation of guanidines from amines, both in solution and on a solid support.[1–13] Derivatives of pyrazole **2** (Scheme 1) are selective inhibitors of inducible nitric oxide synthase.[14–16] The benzene ring in benzotriazole causes **3** to be more reactive than **2**.[17,18] *N*,*N*′-diBoc-acylated **3**, is significantly superior in N-amidination of poorly nucleophilic or sterically hindered secondary amines, than the corresponding pyrazol or triflyl compounds.[19] The latter generate protected guanidines, which require an additional deprotection step.

A survey of the literature reveals that compounds **2** and **3** have been prepared by (i) prolonged heating of benzotriazole/pyrazole with acids and cyanamides in organic solvents,[1,17,20] (ii) from azoles and carbodiimide,[19] (iii) from aminoguanidine and β-diketones[11] or pyrimidines[21] and (iv) by reaction of amines with di(benzotriazol-1-yl)methanimine[22] or benzotriazole-1-carboximidoyl chlorides.[23] In contrast to **2**, benzotriazole–carboximidamide **3**[17,18] is an ideal reagent for the synthesis of guanidines.[24,25] It has higher reactivity and longer shelf stability, while removal/regeneration and monitoring of **3** and benzotriazole at the end of the reaction sequence is easier. In spite of these known advantages its use in solution- and solid-phase synthesis is relatively recent.[26–31]

For the preparation of **2** and **3** (Scheme 1 and Table 1) we apply solvent-free classical heating (Method A)[‡] or

Keywords: Solvent-free; *N*-Carboximidamides; Pyrazole; Benzotriazole; Cyanamides; Guanidinylation; MW irradiation.
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† Contract/grant sponsor: EU. Contract/grant number: ENGEM QLK3-CT-2001-00448 and Contract/grant sponsor: CNR, Italy. Contract/grant number: 01.00122.PF33.

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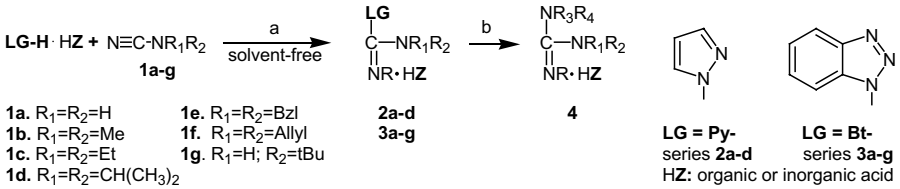
doi:10.1016/j.tetlet.2004.10.114

‡ Method A: Typical procedure for preparation of **2** or **3** (on example **3b**, Table 1, entry 16): 0.1 mol (15.56 g) dry powdered Bt–H·HCl and 0.12 mol (8.41 g) Me_2NCN were stirred at 80 °C (oil bath, under N_2). Bt–H·HCl was dissolved in 1–2 min. Some heat is evolved and external cooling with ice water is necessary to keep the temperature below 100 °C. After ~5–7 min the crystals of **3b** were formed. The reaction mixture was heated at 80 °C for 15 min, the crystals were cooled, washed with *t*BuOMe (30 mL) and petroleum benzene (30 mL) and dried. Yield 18.5–18.7 g (97.8–98.9%), purity 96–98.5% (HPLC), mp 188–191 (dec.), increased to 191–192 (dec.) when crystallized from EtOH/toluene. ^{1}H NMR (DMSO-d_6): δ 11.56, (br s, 1H); 8.16 (d, J = 7.7 Hz, 1H); 7.98, (d, J = 7.7 Hz, 1H) 7.93, (t, J = 8.2 Hz, 1H) 7.83, (t, J = 8.2, 1H), 2.76, (s, 6H); ESI-MS (OR 30): 221.2 (2%, MNa+), 190.2 (76%, MH+), 162.2 (85%, MH+–N_2), 146.1 (81%, MH+–NMe_2); 120.1 (100%, Bt–H·H+).
The hydrochlorides of 3,5-dimethyl-1*H*-pyrazole, 1*H*-Indazole, 1*H*-[1,2,3]triazole, 1*H*-[1,2,4]triazole and the trifluoromethanesulfonates of 5-nitro-1*H*-benzotriazole, 5-chloro-1*H*-benzotriazole, 1*H*-benzotriazole-5-carboxylic acid 5,6-dichloro-1*H*-benzotriazole reacts in a similar way, but the hydrochlorides, 4-methylbenzene-sulfonates or trifluoromethanesulfonates of 1*H*-imidazole and 1*H*-tetrazole do not react.



Scheme 1. Reagents and conditions: (a) Method A: Δ (−20 to +80 °C), 5–360 min; Method B: MW irradiation, 0.5–12 min; (b) **1** or **2** (5 M in MeCN)/NEt_3/HNR_3R_4 = 2/2/1, 60 °C, 2–6 h.

Table 1. Solvent-free reaction of cyanamides with salts of pyrazole/benzotriazole to **1a–d** or **2a–h** under heating or MW irradiation

Entry	Cyanamide	Azole salt	Molar ratio column **2/3**	Reaction conditions			Purity[b] (%)	Yield (%)
				min	°C	Method		
Pyrazole carboximidamides hydrochlorides (**1**)								
1	**1a**	Py–H·HCl	1.0/1.0	720	24	Δ	92	90
2	**1a**	Py–H·HCl	1.3/1.0	6	80	Δ[c]	98	98
3	**1a**	Py–H·HCl	1.3/1.0	0.4	80[d]	MW[a]	95	92
4	**1b**	Py–H·HCl	1.2/1.0	30	80	Δ	96	94
5	**1b**	Py–H·HCl	1.2/1.0	0.5	80[d]	MW[a]	94	92
6	**1b**	Py–H·HCl	1.2/1.0	0.5	80[d]	MW[a]	94	90
7	**1c**	Py–H·HCl	1.2/1.0	30	80	Δ	97	95
8	**1d**	Py–H·HCl	1.2/1.0	720	80	Δ	45	30
Salts of benzotriazole carboximidamides (**2**)								
9	**1a**	Bt–H·Tos–OH	1.0/1.0	1440	100	Δ		**77**[17]
10	**1a**	Bt–H·Tos–OH	1.2/1.0	10	80	Δ[c]	99	99
11	**1a**	Bt–H·Tos–OH	1.2/1.0	0.8	80[d]	MW[a]	97	96
12	**1a**	Bt–H·HCl	1.1/1.0	360 (720)	23	Δ	92 (97)	85(90)
13	**1a**	Bt–H·HCl	1.1/1.0	30	80	Δ[c]	98	96
14	**1a**	Bt–H·HCl	1.1/1.0	2 × 0.5	80[d]	MW[a]	97	95
15	**1a**	Bt–H·TFMSA	1.2/1.0	30	−20 to +24	Δ	87	—
16	**1b**	Bt–H·HCl	1.2/1.0	30	80	Δ	98	94
17	**1b**	Bt–H·HCl	1.2/1.0	1	80[d]	MW[a]	94	91
18	**1c**	Bt–H·HCl	1.2/1.0	30	80	Δ	96	92
19	**1d**	Bt–H·HCl	1.3/1.0	1440	80	Δ	25	—
20	**1d**	Bt–H·TFMSA	1.3/1.0	4	−20 to +40	Δ	68	—
21	**1e**	Bt–H·HCl	1.2/1.0	60	80	Δ	97	92
22	**1f**	Bt–H·HCl	1.2/1.0	60	80	Δ	95	90
23	**1g**	Bt–H·HCl	1.2/1.0	60	80	Δ	96	90

Δ—heating in oil bath; MW—heating by domestic microwave oven type LG, MS-255NB (1300 W).

[a] 260 W.

[b] Determined by RP HPLC (area): Column Zorbax 300SB 5RP18, gradient 0–100% MeCN containing 0.1% TFA in 15 min, and/or TLC (SiO_2): $CHCl_3$/MeOH/AcOH = 10/3/1; DCM/EtOAc/EtOH/AcOH (7:1:1:1).

[c] 0.1 M scale, 20 M Bt–H·HCl in MeCN.

[d] Final temperature, according to the glass thermometer immediately after stopping MW-heating.

microwave irradiation[32] (Method B)[§] of pyrazole or benzotriazole salts with organic or inorganic acids (pK_a from −2 to −13) and 5–30% excess of various cyanamides. These methods were extended to a number of azoles.[‡] All cyanamides, with an exception of those sterically hindered (Table 1, entries 8 and 20), afford the expected products **2** and **3** almost quantitatively and the reaction time is exceedingly short. The synthesis of **2** and **3** by Method B is advantageous since the reaction rate is speed-up by several orders of magnitude. The optimal temperature for azole salts with Tos–OH, H_2SO_4 and HCl was ~60–80 °C; for TFMSA salts it was <40 °C, but the conversion rate is high even at room temperature (Table 1, entries 1 and 12). In terms of yields, reaction times as well as the ease of work-up and scale-up, both methods are superior to those previously reported[1,14,17] (Table 1, entry 9). The use/cost of the solvents have been minimized. Crude **3** was found sufficiently pure to be used in a simple, one-pot guanidinylation of amines. In addition, both **3** and benzotriazole,

[§] Method B: MW assisted one-pot parallel synthesis of reagents **3a** (**3b**) and guanidinylation[11] of amines (see Table 2): 0.156 g (1 mmol) Bt–H·HCl, 1.2 mmol H_2NCN or Me_2NCN were heated for 0.5 min in domestic MW oven (260 W) in a 2 mL stopped tube. Two minutes later were added 0.5 mmol of the corresponding amine (see Table 2) in 0.5 mL MeCN and 1 mmol TEA. The tubes were stopped again, sonificated for 30 s (Branson 2200) and heated for 6 h at 60 °C in Multi-Block heater. The solvents were evaporated to dryness (SpeedVac Concentrator), the dried compound was dissolved in water (3 × 2 mL), pH was adjusted (if necessary) with 0.1 N HCl to pH ~ 7.5 and extracted with EtOAc (5 × 3 mL). The water phases were desalted/purified separately on anion-exchange resin columns (Fractogel EMD TMAE 650, Merck in HO^- form, 10 mL each one) by eluting with water. The collected fractions of **4** were freeze-dried. The NMR/HPLC purity of prepared guanidines were 93–99%.

Table 2. Guanidinylation of selected amines[§] with reagents **3a** and **3b**: series **3a**, R = H; series **3b**, R = Me

Amine	Reagent	Guanidine (**4**)	Yield (%)	MH+ (found) (ESI-MS)[e]
Z–Orn–OH[a]	**3a**	Z–Arg–OH	97	309.2
	3b	Z–aDma–OH	95	337.2
Boc–NHNH_2	**3a**	Boc–NHNHC(=NH)NR_2	97	175.2
	3b		98	203.1
$C_6H_5CH_2NH_2$	**3a**	$C_6H_5CH_2NHC(=NH)NR_2$	99	150.2
	3b		99	178.2
$C_6H_5CH_2ONH_2$	**3a**	$C_6H_5CH_2ONHC(=NH)NR_2$	99	166.1
	3b		99	194.2
$C_6H_5CH_2NHCH_3$	**3a**	$C_6H_5CH_2ON(CH_3)C(=NH)NR_2$	94	164.3
	3b		87	192.1
$C_6H_5NH_2$	**3a**	$C_6H_5NHC(=NH)NR_2$	98	136.1
	3b		95	164.1
2,4-$(MeO)_2C_6H_5NH_2$	**3a**	2,4-$(MeO)_2C_6H_5NHC(=NH)NR_2$	95	196.1
	3b		95	224.1
4-$NH_2C_6H_4NH_2$	**3a**	4-$NH_2C_6H_4NHC(=NH)NR_2$	98[b]	151.2
	3b		98[b]	179.1
$[(CH_3)_2CH]NH$	**3a**		0	—
	3b		0	—
$(NH_2CH_2CH_2)_2NH$	**3a**	$[R_2N(HN=)CNHCH_2CH_2]_2NH$	99[c]	216.4
	3b		99[d]	244.4
H–Lys–OH	**3b**	$Me_2NC(NH)$–Lys$[C(NH)NMe_2]$–OH	96	287.3[f]

[a] 0.2 M in MeCN/H_2O = 5/1, 2.5 h at 60 °C. The half time for guanidinylation of Z–Orn–OH with **3a/3b** was <1 min.
[b] Only $NH_2C_6H_4NHC(NH)NH_2$, respectively $NH_2C_6H_4NHC(=NH)N(CH_3)_2$ were detected by LCMS.
[c] Triamine/monoguandylated-/diguanidinylated-/triguanidinylated-triamine = 0.0/0.1/99.1/0.8 (ESI-MS).
[d] Triamine/monoguandylated-/diguanidinylated-/triguanidinylated-triamine = 0.00/0.15/99.60/0.25 (ESI-MS).
[e] In water/MeCN (1/1, v/v), containing 0.2% HCOOH.
[f] 0.2 M in MeCN/H_2O = 4/1 reaction with 4 equiv **3b**, 4 h at 60 °C, and this procedure was repeated one more time.

present in crude **3** or as result of N-amidination, are well soluble in organic solvents, so the isolation[11] of the corresponding guanidines (up to tetra-substituted) can be carried out without activating agents or protecting group manipulations (Table 2).[§] The crystal structure[¶] of **3b**, a reagent for the preparation of N^{ω},N^{ω}-dimethyl-arginine (aDma) in solution and on solid support,[‖] has been determined.

In conclusion, we have presented two simple eco-friendly methods for the preparation of azole carboximidamides that are valuable synthons for guanidinylation of amines both in solution and on the solid supports.

[¶] The structure of **3b** (crystals from MeCN, see Supplementary data) was unambiguously confirmed by X-ray crystallographic analysis using synchrotron radiation data collected at ELETTRA (XRD-1 beamline), Trieste, Italy. Crystallographic data have been deposited with the Cambridge Crystallographic Data Centre (CCDC) as supplementary publication number CCDC 235826. An interesting feature of the crystal structure **3b** is the twisting of the *N*,*N*-dimethyl-carboxamidinium moiety out of the plane of the benzotriazole ring system. The angle between the mean planes is of 37.9°. The corresponding angle in the crystal structure of the structurally related benzotriazole-1-carboxamidinium[17] is of 20.5° [Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1 EZ, UK (fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk)].

[‖] Guanidinylation of resin bound ornithine-containing peptides: Boc-***Orn***-Ser(But)-Ile-Asn(Trt)-Ile-Asp(OBut)-Leu-Thr(But)-Lys(Boc)-2-ClTrt Resin (0.05 mmol, loading 0.32 mmol/g) react with 4 equivs **3a**–**c**/4 equiv DIEA in THF (0.3 M) overnight at room temperature, after clevage/deprotection form quantitatively (LCMS) H-***Orn*[*C(NH)N(R)*$_2$]**-SINIDLTK-OH, where R_1 = R_2 = H, Me or Et.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2004.10.114.

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