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N,*N*′-Di-*tert*-butoxycarbonyl-1*H*-benzotriazole-1-carboxamidine Derivatives Are Highly Reactive Guanidinylating Reagents

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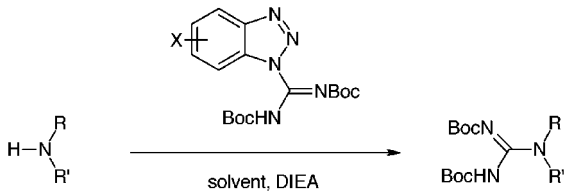
ABSTRACT



By enhancing the leaving group character of benzotriazole via electron-withdrawing substituents such as the 5-chloro or 6-nitro derivatives with the related *N*,*N*′-di-*tert*-butoxycarbonyl-1*H*-benzotriazole-1-carboxamidines, highly efficient reagents are obtained for conversion of primary and secondary amines in solution and in solid phase to diprotected guanidines.

Arginine residues in peptides and proteins are known to be crucially involved in molecular recognition processes, but guanidine groups are also essential components of the structurally most diverse primary and secondary metabolites of living organisms and of many synthetic drugs.[1] Consequently, various reagents have already been proposed and used to synthesize protected and unprotected guanidines.[2] Nonetheless, new synthetic methods for this important functional group continue to emerge, manifesting the need for alternative, more potent reagents which can be efficiently applied even for chemistry on solid support.

To facilitate purification of the reaction products and to enhance the electrophilicity of the amidino carbon toward aminolysis, recent developments were mainly based on *N*,*N*′-diprotected guanidinylating reagents.[3] Among these, one of the most commonly used reagents is *N*,*N*′-di-*tert*-butoxycarbonyl-1*H*-pyrazole-1-carboxamidine (**1**, Figure 1).[3d−f] More efficient guanidinylation of poorly nucleophilic or sterically hindered amines is obtained with the triflylguanidine derivative **2a**[3k,l] and, particularly, with the traceless resin-bound reagent **2b**.[3m]

In contrast to 1*H*-pyrazole-1-carboxamidine hydrochloride,[4] which was extensively used for the synthesis of unprotected guanidines, the 1*H*-benzotriazole-1-carboxamidinium tosylate proposed by Katritzky and co-workers[5a]

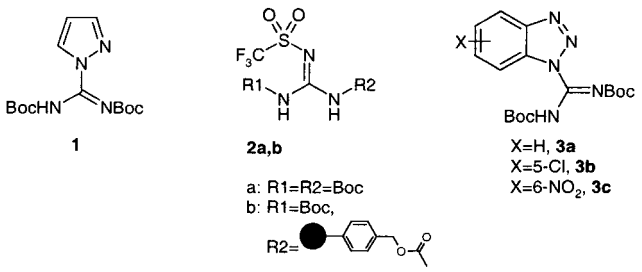


Figure 1. Reagents for the synthesis of *N*,*N*′-diprotected guanidines.

(1) (a) Berlinck, R. G. S. *Fortschr. Chem. Org. Nat.* **1995**, *66*, 119−295. (b) Berlinck, R. G. D. *Nat. Prod. Rep.* **1999**, *16*, 339−365. (c) Greenhill, J. L.; Lue, P. In *Amidines and Guanidines in Medicinal Chemistry*; Ellis, G. P., Luscombe, D. K., Eds.; Progress in Medicinal Chemistry; Elsevier Science: Amsterdam, 1993; Vol. 30, pp 203−326.

(2) Yamamoto, Y.; Kojima, S. In *The Chemistry of Amidines and Imidates*; Patai, S., Rappoport, Z., Eds.; Wiley: New York, 1991; Vol. 2, pp 486−526.

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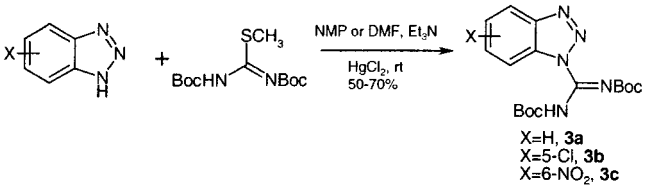
has not received due attention despite the good leaving group properties of benzotriazole. This leaving group has further been applied for the preparation of di(benzotriazol-1-yl)-methanimine, an efficient reagent for the synthesis of tri- and tetraalkylguanidines[5b] which, however, differ structurally from the target compounds addressed in this Letter. Taking advantage of the enhanced electrophilicity of the amidine carbon in *N*,*N*′-diurethane-protected carboxamidine derivatives,[3f] in the present study we have synthesized *N*,*N*′-di-*tert*-butoxycarbonyl-1*H*-benzotriazole-1-carboxamidine (**3a**) by reacting benzotriazole with *N*,*N*′-di-*tert*-butoxycarbonylthiourea[3a,c] or the commercially available *N*,*N*′-protected *S*-methylisothiourea[3b,h] in the presence of mercuric chloride (Scheme 1).[6] Moreover, to possibly improve the reactivity

Scheme 1. General Procedure for the Synthesis of the Guanidinylating Reagents **3a**−**c**



of the benzotriazole derivatives the 5-chloro- (commercially available) and 6-nitrobenzotriazole[7] were converted under identical conditions to the related carboxamidine derivatives **3b** and **3c**.

As expected from the electron-withdrawing substituents, guanidinylation of aniline as a model amine of poor nucleophilicity by the benzotriazole-based reagents occurs at rates in the rank order of **3a** < **3b** < **3c** (Figure 2); however, all three reagents are more efficient amidine donors than compounds **1** and **2a**.

A comparison of the rates of guanidinylation of the sterically hindered diisopropylamine with compounds **3a**−**c** with those previously reported for **1**,[3f] **2a**,[3k] and the resin-bound reagent **2b**[3m] is shown in Figure 3. While **2b** is more reactive than the unsubstituted benzotriazole derivative **3a**

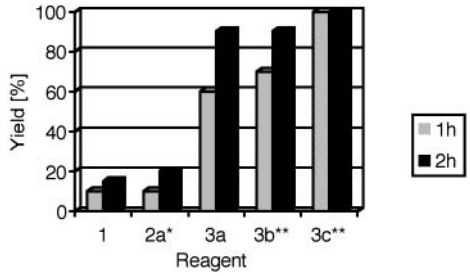


Figure 2. Yields of isolated *N*,*N*′-di-*tert*-butoxycarbonyl-*N*″-phenylguanidine upon reaction of aniline with **1**, **2a**, and **3a**−**c**.[8]

because of its stronger activation via the benzyl-type urethane group,[3m] reagent **3b** is of similar reactivity and nitro derivative **3c** shows the most reactivity. With nearly 90% conversion of diisopropylamine into *N*,*N*′-di-*tert*-butoxycarbonyl-*N*″-diisopropylguanidine, reagent **3c** is also more efficient than *N*,*N*′-di-*tert*-butoxycarbonyl-4-nitro-1*H*-pyrazole-1-carboxamidine[10] (64% conversion[10b]), where in a similar mode the nitro substituent was used to enhance the leaving group character of the pyrazole. Compared to *N*,*N*′-di-*tert*-butoxycarbonylthiourea/$HgCl_2$ (90% yield of the diisopropylamine derivative[3c]) and the related *S*-methylisothiourea/$HgCl_2$ (77% yield[3n]), which are the starting materials for the preparation of the benzotriazole-based reagents, **3c** is of similar and higher reactivity, respectively. However, it offers the decisive advantage of not requiring mercuric chloride which makes product isolation much less demanding and allows for its use even in solid-phase chemistry. In this context it is worth noting that by replacing mercuric chloride with Mukaiyama's reagent guanidinylation of resin-bound amines was reported to fail in some cases.[10b]

As shown in Figure 4, for guanidinylation of Boc-Phe(4-NH_2)-Gly-trityl-resin, the benzotriazole-based reagents are superior to the reagents comparatively analyzed and again the 6-nitro compound **3c** proved to be the most reactive one in both CH_2Cl_2 and DMF as it leads to quantitative conversion of the amine into the guanidine group within 2 h at room temperature.

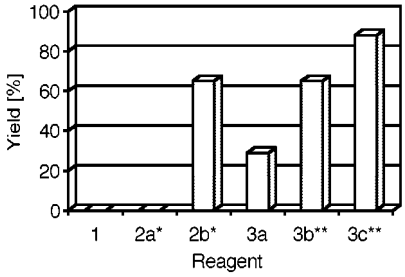


Figure 3. Yields of isolated *N*,*N*′-di-*tert*-butoxycarbonyl-*N*″-diisopropylguanidine upon reaction of diisopropylamine with **3a**−**c**.[9] With reagents **1** and **2a** in CH_2Cl_2 or $CHCl_3$ no reaction was reported,[3f,k] while with **2b** in CH_2Cl_2 after 24 h the product was isolated in 65% yield.[3m]

(3) (a) Poss, M. A.; Iwanowicz, E.; Reid, J. A.; Lin, J.; Gu, Z. *Tetrahedron Lett.* **1992**, *33*, 5933−36. (b) Verdini, A. S.; Lucietto, P.; Fossati, G.; Giordani, C. *Tetrahedron Lett.* **1992**, *33*, 6541−6542. (c) Kim, K. S.; Qian, L. *Tetrahedron Lett.* **1993**, *34*, 7677−7680. (d) Bernatowicz, M. S.; Wu, Y.; Matsueda, G. R. *Tetrahedron Lett.* **1993**, *34*, 3389−3392. (e) Wu, Y.; Matsueda, G. R.; Bernatowicz, M. S. *Synth. Commun.* **1993**, *23*, 3055−3060. (f) Drake, B.; Patek, M.; Lebl, M. *Synthesis* **1994**, 579−582. (g) Su, W. *Synth. Commun.* **1996**, *26*, 407−413. (h) Bergeron, R. J.; McManis, J. S. *J. Org. Chem.* **1987**, *52*, 1700−1703. (i) Tian, Z.; Edwards, P.; Roeske, R. W. *Int. J. Pept. Protein Res.* **1992**, *40*, 119−126. (j) Lal, B.; Gangopadhyay, A. K. *Tetrahedron Lett.* **1996**, *37*, 2483−2486. (k) Feichtinger, K.; Zapf, C.; Sings, H. L.; Goodman, M. *J. Org. Chem.* **1998**, *63*, 3804−3805. (l) Feichtinger, K.; Sings, H. L.; Baker, T. J.; Matthews, K.; Goodman, M. *J. Org. Chem.* **1998**, *63*, 8432−8439. (m) Zapf, C. W.; Creighton, C. J.; Tomioka, M.; Goodman, M. *Org. Lett.* **2001**, *3*, 1133−1136. (n) Guo, Z.-X.; Cammidge, A. N.; Horwell, D. C. *Synth. Commun.* **2000**, *30*, 2933−2943.

(4) Bernatowicz, M. S.; Wu, Y.; Matsueda, G. R. *J. Org. Chem.* **1992**, *57*, 2497−2502.

(5) (a) Katritzky, A. R.; Parris, R. L.; Allin, S. M. *Synth. Commun.* **1995**, *25*, 1173−1186. (b) Katritzky, A. R.; Rogovoy, B. V.; Chassaing, C.; Vvedensky, V. *J. Org. Chem.* **2000**, *65*, 8080−8082.

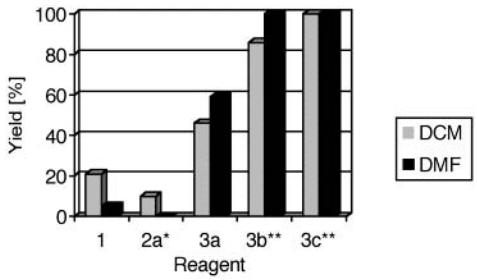


Figure 4. Conversion of Boc-Phe(NH_2)-Gly-trityl-resin into the related guanidino derivative by reaction with **1, 2a**, and **3a**−**c**.[11]

In conclusion, by incorporating electron-withdrawing substituents into benzotriazole, its leaving group property is significantly enhanced, and the resulting *N*,*N*′-diurethane-protected 1*H*-benzotriazole-1-carboxamidine derivatives are highly efficient reagents for guanidinylation of primary and secondary amines, making in particular the 6-nitro derivative a useful reagent for synthesis of guanidines in solution and on solid support.

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(6) To a stirred solution of benzotriazole, 5-chloro- or 6-nitrobenzotriazole (3 mmol), *N*,*N*′-di-*tert*-butoxycarbonylthiourea (3 mmol), and TEA (9.9 mmol) in dry DMF or NMP (6 mL) at 0 °C was added $HgCl_2$ (3.3 mmol). After 12 h at rt, the reaction was concentrated under reduced pressure, diluted with EtOAc (100 mL), and filtered through a Celite pad. The filtrate was washed with H_2O (20 mL), 5% aqueous Na_2CO_3 (20 mL), H_2O (20 mL), and brine (20 mL), and dried (Na_2SO_4). The solvent was removed, and the products were isolated as follows. *N*,*N*′-Di-*tert*-butoxycarbonyl-1*H*-benzotriazole-1-carboxamidine (**3a**): 67% upon crystallization from methyl *tert*-butyl ether/hexane; mp 143−144 °C; homogeneous on TLC (hexane/methyl *tert*-butyl ether/AcOH, 40:10:2) and HPLC (t_R = 11.70); ESI-MS *m*/*z* = 362.2 $[M + H]^+$; M_r = 361.40 calcd for $C_{17}H_{23}N_5O_4$; ^{1}H NMR ($CDCl_3$; 400 MHz) δ 9.04 (s, 1H, NH), 8.38, 8.11 (2 d, 2H, C_4H, C_7H), 7.65, 7.50 (2 t, 2H, C_5H, C_6H), 1.60, 1.57, 1.55 (18H, $6CH_3$); ^{13}C NMR ($CDCl_3$; 100 MHz) δ 115.3, 120.2, 126.0, 130.2 (4C, $C_{4,5,6,7}$) 28.1 (6C, $6CH_3$). Reaction with 5-chlorobenzotriazole leads to a mixture of the 5- and 6-chloro derivatives which were separated by flash chromatography (EtOAc/hexane, 3:1) and recrystallized from methyl *tert*-butyl ether/hexane. *N*,*N*′-di-*tert*-Butoxycarbonyl-5-chloro-1*H*-benzotriazole-1-carboxamidine (**3b**): 50%; mp 170−175 °C; homogeneous on TLC (hexane/methyl *tert*-butyl ether/AcOH, 40:10:2) and HPLC (t_R = 11.56); ESI-MS *m*/*z* = 396.0 $[M + H]^+$; M_r = 395.84 calcd for $C_{17}H_{22}N_5O_4Cl$; ^{1}H NMR ($CDCl_3$; 400 MHz) δ 8.99 (s, 1H, NH), 8.39, 8.03 (2 d, 2H, C_4H, C_7H), 7.48 (dd, 1H, C_6H), 1.53−1.61 (m, 18H, $6CH_3$); ^{13}C NMR ($CDCl_3$; 100 MHz) δ 115.8, 121.7, 128.0 (3C, $C_{4,6,7}$), 28.8 (6C, $6CH_3$). *N*,*N*'-Di-*tert*-butoxycarbonyl-6-chloro-1*H*-benzotriazole-1-carboxamidine: 9%; mp 129−132 °C; ESI-MS *m*/*z* = 396.0 $[M + H]^+$; M_r = 395.84 calcd for $C_{17}H_{22}N_5O_4Cl$; ^{1}H NMR ($CDCl_3$; 400 MHz) δ 8.99 (s, 1H, NH), 8.32, 8.09 (2 d, 2H, C_4H, C_7H), 7.60 (dd, 1H, C_5H), 1.51−1.60 (m, 18H, $6CH_3$); ^{13}C NMR ($CDCl_3$; 100 MHz) δ 116.9, 120.4, 131.7 (3C, $C_{4,5,7}$), 28.8 (6C, $6CH_3$). *N*,*N*′-Di-*tert*-butoxycarbonyl-6-nitro-1*H*-benzotriazole-1-carboxamidine (**3c**): 50% from methyl *tert*-butyl ether/hexane; mp 126−128 °C; homogeneous on TLC (hexane/methyl *tert*-butyl ether/AcOH, 40:10:2) and HPLC (t_R = 11.96); ESI-MS *m*/*z* = 407.2 $[M + H]^+$; M_r = 406.40 calcd for $C_{17}H_{22}N_6O_6$; ^{1}H NMR ($CDCl_3$; 400 MHz) δ 9.06 (s, 1H, NH) 8.53 (d, 2H, C_4H, C_5H), 8.53 (s, 1H, H_7); ^{13}C NMR ($CDCl_3$; 100 MHz) δ 116.0, 117.1, 124.9 (3C, $C_{4,5,7}$) 28.1 (6C, $6CH_3$).

(7) Zincke, Th.; Stoffel, F.; Petermann, E. *Ann. Chem.* **1900**, *311*, 277−329.

(8) A 0.2 M solution of the reagents **1**, **2a**, and **3a**−**c** (1 equiv) was reacted with aniline (1.2 equiv) in CH_2Cl_2 in the presence of 1 equiv of TEA (*) or DIEA (**) for 1 or 2 h at 20 °C, and the reaction mixtures were worked up by known procedures.[3l]

(9) A 0.2 M solution of **3a**−**c** in CH_2Cl_2 (1 equiv) was reacted with diisopropylamine (1.2 equiv) in the presence of 1 equiv of TEA (*) or DIEA (**) for 12 h at 20 °C; the resulting diurethane-protected *N*,*N*-diisopropylguanidine was isolated as reported previously.[10b]

(10) (a) Yong, Y. F.; Kowalski, J. A.; Lipton, M. A. *J. Org. Chem.* **1997**, *62*, 1540−1542. (b) Yong, Y. F.; Kowalski, J. A.; Thoen, J. C.; Lipton, M. A. *Tetrahedron Lett.* **1999**, *40*, 53−56.

(11) The resin-bound amine (1 equiv) was reacted in CH_2Cl_2 or DMF at 20 °C for 2 h with **1**, **2a**, or **3a**−**c** (2.5 equiv) in the presence of 2.5 equiv of TEA (*) or DIEA (**). Conversion yields were determined by HPLC after cleavage of the dipeptide as educt and product from resin with CH_2Cl_2/TFE/AcOH (8:1:1) at 20 °C for 1 h.