Synthesis of 5-Substituted 1-Hydroxy-1,2,3-triazoles through Directed Lithiation of 1-(Benzyloxy)-1,2,3-triazole

Peter Uhlmann, Jakob Felding, Per Vedsø, and Mikael Begtrup*

Department of Medicinal Chemistry, Royal Danish School of Pharmacy, Universitetsparken 2, DK-2100 Copenhagen, Denmark

Received July 18, 1997[⊗]

1-(Benzyloxy)-1,2,3-triazole, prepared by selective benzylation of 1-hydroxy-1,2,3-triazole or by oxidative cyclization of 2-hydrazonoglyoxal *O*-benzyloxime, was metalated exclusively at the 5-position upon treatment with *n*-butyllithium. The anion formed reacted with a series of electrophiles. In this way carbon, halogen, sulfur, silicon, and tin substituents could be introduced at the 5-position. Subsequent removal of the benzyl group by palladium-catalyzed hydrogenolysis or by treatment with hydrochloric acid afforded the corresponding 5-substituted 1-hydroxy-1,2,3-triazoles.

Introduction

1-Hydroxybenzotriazole (HOBt) is an important catalyst for acylations and phosporylations.[1,2] It is widely used in peptide [3−7] and nucleotide synthesis.[8] In peptide synthesis the requirements of the catalyst are maximum reactivity combined with minimum racemization of chiral amino acids during the coupling. To improve the catalytic properties substituted 1-hydroxybenzotriazoles[3,9] and aza-substituted 1-hydroxybenzotriazoles have been prepared.[10] Introduction of substituents in the benzene ring gave only moderate changes in the catalytic properties since these substituents are remote to the N−OH functionality. A higher sensitivity to the nature of substitution is possible in the uncondensed, parent 1-hydroxy-1,2,3-triazole[11] (**3**).

Only a few uncondensed 1-hydroxytriazoles have been reported. The 4,5-dicarboxylic acid derivative was prepared by oxidation of 1-hydroxybenzotriazole.[12] The 5-methyl 4-carboxylic acid, the 4-benzoyl-5-methyl, and the 4-benzoyl 5-carboxylic acid were obtained through reaction between diazoketone and hydroxylamine.[13] The 5-*tert*-butylcarbonyl derivative was formed in a ring transformation of 4-amino-5-*tert*-butylisoxazole effected by diazotization.[14] The parent 1-hydroxytriazole (**3**) has been synthesized recently by direct oxidation of 1,2,3-triazole.[15] Finally, 1-hydroxytriazoles were prepared by debenzylation of 2-benzyltriazole 1-oxides effected with concentrated hydrobromic acid or iodotrimethylsilane or by de-methoxybenzylation of 2- or 3-(*p*-methoxybenzyl)-triazole 1-oxides accomplished by treatment with concentrated sulfuric acid.[16] The limitation of this method is the availability of the triazole 1-oxides used as the starting material.

A more general approach to substituted 1-hydroxytriazoles would be introduction of substituents in the parent 1-hydroxytriazole (**3**). Recently substituents were introduced in 1-hydroxypyrazole which was first alkylated or carbamoylated at the oxygen atom. The *N*-alkoxy or carbamoyloxy groups formed displayed strong *ortho*-directing power in lithiation reactions. Lithiation was followed by addition of electrophiles to give a series of 5-substituted derivatives.[17] If this strategy is applied to 1-hydroxytriazoles, different 5-substituents can be introduced. The proximity of the substituent makes possible effective control of the acidity of the *N*-hydroxy group which is crucial for the catalytic properties in acylation reactions.[3] In addition substituents can be introduced which can effect hydrogen bonding to the activated complex during the peptide coupling. It has been suggested that hydrogen bonding to N-7 is responsible for the increased catalytic effect of 7-aza 1-hydroxybenzotriazoles as compared to the parent 1-hydroxybenzotriazoles.[10]

Results and Discussion

Preparation of Triazole, 1-Hydroxytriazole, and *O*-Protected 1-Hydroxytriazoles. 1-Hydroxytriazole was prepared by oxidation of triazole or by palladium-catalyzed hydrogenolysis of 1-(benzyloxy)triazole obtained by oxidative cyclization of 2-hydrazonoglyoxal *O*-benzyloxime (**8**). In the first approach a new method for the preparation of 1,2,3-triazole useful for larger scale preparations was developed. In addition, the previously described procedure for oxidation of the triazole was optimized and modified to be suitable for medium scale batches.

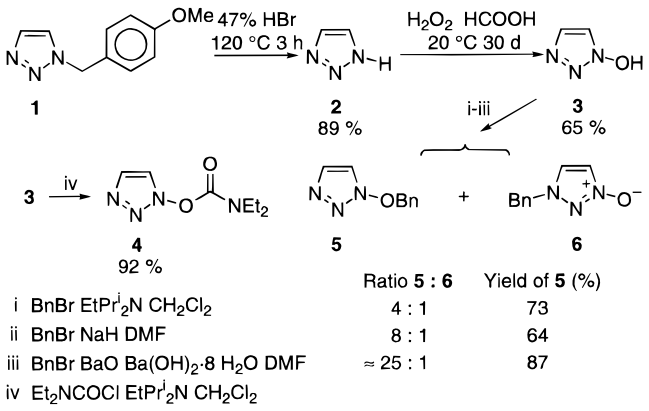
1,2,3-Triazole has been prepared by 1,3-dipolar cycloaddition of azides, like azo imide or trimethylsilyl azide, to acetylenes, like acetylene, propiolic acid, or acetylenedicarboxylic acid (or the corresponding esters).[18] With propiolic acid or acetylenedicarboxylic acid, car-

[⊗] Abstract published in *Advance ACS Abstracts,* November 15, 1997.

(1) Wreesmann, C. T. J.; Fidder, A.; Veeneman, G. H.; van der Marel, G. A.; van Boom, J. H. *Tetrahedron Lett.* **1985**, *26*, 933.
(2) van Boeckel, C. A. A.; van der Marel, G. A.; Westerduin, P.; van Boom, J. H. *Synthesis* **1982**, 399.
(3) König, W.; Geiger, R. *Chem. Ber.* **1970**, *103*, 788.
(4) König, W.; Geiger, R. *Chem. Ber.* **1970**, *103*, 2024.
(5) Castro, B.; Dormoy, J. R.; Evin, G.; Selve, C. *J. Chem. Res. (S)* **1977**, 182.
(6) Kim, S.; Chang, H.; Ko, Y. K. *Tetrahedron Lett.* **1985**, *26*, 1341.
(7) Nguyen, D. L.; Seyer, R.; Heitz, A.; Castro, B. *J. Chem. Soc., Perkin Trans. 1* **1985**, 1025.
(8) Marugg, J. E.; Tromp, M.; Jhurani, P.; Hoyng, C. F.; van der Marel, G. A.; van Boom, J. H. *Tetrahedron* **1984**, *40*, 73.
(9) Kehler, J.; Püschl, A.; Dahl, O. *Acta Chem. Scand.* **1996**, *50*, 1171.
(10) Carpino, L. A. *J. Am. Chem. Soc.* **1993**, *115*, 4397.
(11) In the following triazole refers to 1,2,3-triazole.
(12) Zincke, T.; Schwartz, P. *Liebigs Ann. Chem.* **1900**, *311*, 329.
(13) Wolff, L. *Liebigs Ann. Chem.* **1902**, *325*, 129.
(14) L'abbé, G.; Godts, F.; Toppet, S. *Tetrahedron Lett.* **1983**, *24*, 3149.
(15) Begtrup, M.; Vedsø, P. *J. Chem. Soc., Perkin Trans. 1* **1995**, 243.
(16) Begtrup, M.; Vedsø, P. *Acta Chem. Scand.* **1996**, *50*, 549.
(17) Vedsø, P.; Begtrup, M. *J. Org. Chem.* **1995**, *60*, 4995.

S0022-3263(97)01313-3 CCC: $14.00

Scheme 1



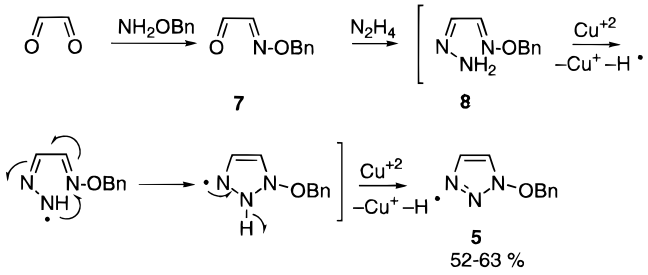
boxytriazoles were formed and then decarboxylated. To develop a safer procedure, benzyl azide has been reacted with acetylenedicarboxylic acid. Subsequent decarboxylation produced 1-benzyltriazole which was then debenzylated by hydrogenolysis at high pressure or by treatment with sodium in liquid ammonia.[19]

To avoid the inconvenient debenzylation of 1-benzyltriazole instead, 1-(4-methoxybenzyl)triazole (**1**) was demethoxybenzylated (Scheme 1) by treatment with 47% aqueous HBr to give 1,2,3-triazole (**2**) in 89% yield. The 1-(4-methoxybenzyl)triazole (**1**) was readily prepared by decarboxylation of 4,5-dicarboxy-1-(4-methoxybenzyl)triazole obtained by cycloaddition of 4-methoxybenzyl azide with acetylenedicarboxylic acid as previously described.[16]

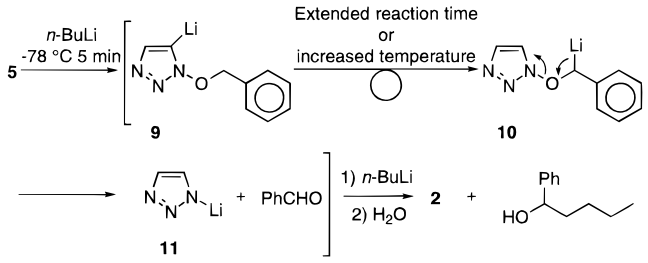
The yield by oxidation (Scheme 1) of triazole to 1-hydroxytriazole (**3**) was increased from 39% reported in ref 15 to 65% by adding the oxidant portionwise over 30 days. The pure 1-hydroxytriazole (**3**) was isolated by continuous extraction with Et_2O over 3 weeks.

O-Benzyl- and *O*-carbamoyl-protected *N*-hydroxypyrazoles have been prepared earlier in good yields and were used successfully in metalation reactions.[17] Therefore these groups were selected to protect the *N*-hydroxy group of 1-hydroxy-1,2,3-triazole (**3**) before deprotonation at the ring carbon atoms. The protection of **3** with *N*,*N*-diethylcarbamoyl chloride in dichloromethane using *N*-ethyldiisopropylamine as the base gave exclusively the *O*-protected product **4** in 92% yield. In contrast, the benzylation under similar conditions with benzyl bromide gave a 4:1 mixture of the *O*-benzylated product **5** and the known 3-benzyl-1,2,3-triazole-1-oxide (**6**)[20] resulting from the attack of N-3 (Scheme 1). The ratio **5**/**6** was improved when the reaction was carried out in DMF using NaH as the base. Finally, the best result was obtained under mild conditions using BaO/Ba(OH)$_2$·8 H_2O in DMF. Only traces of **6** (<5%) were detected in the ^{1}H NMR spectrum of the crude product, and 1-(benzyloxy)triazole (**5**) could be isolated in 87% yield. The structure of the *O*- and the *N*-benzylated products **5** and **6** was evidenced in the ^{13}C NMR spectra by the characteristic shift of the CH_2 carbon signals (82.1 ppm for **5** and 55.0 ppm for **6**). The chemical shifts of C-4 and C-5 and the C−H coupling constants of **5** are in good agreement with the values reported for 1-methoxy-1,2,3-triazole.[16]

Scheme 2



Scheme 3



The preparation of 1-(benzyloxy)triazole (**5**) by *N*-oxidation of triazole (**2**) followed by *O*-benzylation required ca. 2 months effort. More conveniently, **5** could be obtained via a one-pot process by addition of glyoxal *O*-benzyloxime (**7**)[21] to a 10-fold excess of hydrazine[22] followed by oxidative cyclization of the 2-hydrazonoglyoxal *O*-benzyloxime (**8**) formed in situ (Scheme 2). Several oxidants were tried. Copper(II) sulfate proved to be the best, but also manganese dioxide and nickel peroxide served well. The effectiveness of these oxidants indicates that the cyclization takes place by a one-electron mechanism as shown in Scheme 2.[23,24] This route to 1-(benzyloxy)triazole (**5**) is superior since (i) the total process can be carried out in 2−3 days starting from readily available starting materials; (ii) the protected species (**5**), which is easily isolated by flash chromatography,[25] is obtained directly; and (iii) the reaction can be performed in a 20 g scale. If desired, 1-(benzyloxy)-triazole (**5**) could be converted to 1-hydroxytriazole (**3**) in 96% yield by palladium-catalyzed hydrogenolysis.

Lithiation and Reaction with Electrophiles. The lithiation of 1-(benzyloxy)-1,2,3-triazole (**5**) with *n*-BuLi in THF at −78 °C for 5 min followed by quenching with D_2O resulted in quantitative incorporation of deuterium at C-5 to give 1-(benzyloxy)-5-deuterio-triazole (**12**) in 90% isolated yield (Scheme 4). The position of the deuteration was proven by the ^{1}H and ^{13}C NMR spectra of **12**. In the carbon spectra, the C-5 signal at 118.4 ppm was converted to a triplet ($J_{C-5,D}$ = 30.7 Hz), while in the proton spectra, the H-5 signal at 7.14 ppm of **5** was absent. If the lithiation time of **5** was extended, or the

(18) Wamhoff, H. in *Comprehensive Heterocyclic Chemistry*, 1st ed.; Potts, K. T., Ed.; Pergamon: Oxford, 1984; Vol. 5, p 669.

(19) Wiley: R. H.; Hussung, K. F.; Moffat, J. *J. Org. Chem.* **1956**, *21*, 190.

(20) Begtrup, M.; Vedsø, P. *J. Chem. Soc., Perkin Trans. 1* **1993**, 625.

(21) Zimmerman, B.; Lerche, H.; Severin, T. *Chem. Ber.* **1986**, *119*, 2848.

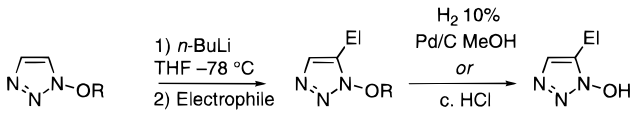
(22) If addition was reversed and 1 equiv of hydrazine was used, bis(glyoxal (benzyloxy)oxime) hydrazone was obtained in quantitative yield: mp 140−141 °C; ^{1}H NMR ($CDCl_3$) δ 8.10 (d, J = 9.1 Hz, 1H), 7.95 (d, J = 9.1 Hz, 1H), 7.50−7.20 (m, 5H), 5.20 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 157.93 (d), 147.70 (d), 136.38 (s), 128.42 (d), 128.31 (d), 128.22 (d), 77.39 (t). Anal. Calcd for $C_{18}H_{18}N_4O_2$: C, 67.07; H, 5.63; N, 17.38. Found: C, 67.10; H, 5.69; N, 17.49.

(23) Konaka, R.; Terabe, S.; Kuruma, K. *J. Org. Chem.* **1969**, *34*, 1334.

(24) Mineo, S.; Kawamura, S.; Nakagawa, K. *Synth. Commun.* **1976**, *6*, 69.

(25) Distillation of 1-alkoxytriazoles has been avoided since violent explosions of alkoxyimidazoles and alkoxypyrazoles have been reported (Flynn, A. P. *Chem. Br.* **1984**, *20*, 30).

Scheme 4



4 (R=CONEt$_2$)
5 (R=Bn)

10 – 23

24 – 28

El	R	Electrophile	Product	Yield (%)	Product	Yield (%)
D	Bn	D_2O	**12**	90		
Me	"	MeI	**13**	93	**24**	99
CHO	"	DMF	**14**	87	**25**	100
COOMe	"	ClCOOMe	**15**	76	**26**	99
$CONMe_2$	"	$ClCONMe_2$	**16**	97	**27**	98
Cl	"	C_2Cl_6	**17**	88	**28**	100
Br	"	Br_2	**18**	86		
I	"	I_2	**19**	96		
SMe	"	Me_2S_2	**20**	67		
$SiMe_3$	"	Me_3SiCl	**21**	93		
$SnBu_3$	"	Bu_3SnCl	**22**	91		
I	$CONEt_2$	I_2	**23**	87		

temperature increased, significant amounts of 1,2,3-triazole (**2**) and 1-phenyl-1-pentanol could be detected in the ^{1}H NMR spectra of the crude product. The formation of these products can be explained by an inter- or intramolecular rearrangement of **9** into **10** followed by cleavage of the N−O bond which produces 1-lithiotriazole (**11**) and benzaldehyde (Scheme 3). The latter compound upon addition of *n*-BuLi gives 1-phenyl-1-pentanol. Hence, the lithiation should be conducted at low temperature and the electrophile added shortly after.

The lithiation of **5**, followed by quenching with carbon, halogen, sulfur, silicon, and tin electrophiles, led to the expected 5-substituted 1-(benzyloxy)triazoles **12**−**22** in good to excellent yields (Scheme 4). The electrophiles were added in an excess of 1.5−5 equiv; only Bu_3SnCl was used in an equimolar amount since the separation of **22** from Bu_3SnCl was difficult. The products **12**−**22** were characterized by NMR spectroscopy and elemental analysis. In the ^{13}C NMR spectra of **12**−**22**, C-4 resonates at 130−139 ppm. The signals of C-5 can be observed at 121−129 ppm, except for the 5-bromo and the 5-iodo compounds (**18** and **19**, respectively), where the strong shielding effect of the halogens leads to a shift of the signals to a higher field (106.4 ppm for **18**, 72.6 ppm for **19**). Similar to **5**, lithiation of 1-((*N*,*N*-diethylcarbamoyl)oxy)-1,2,3-triazole (**4**) followed by quenching with iodine gave 1-((*N*,*N*-diethylcarbamoyl)oxy)-5-iodo-1,2,3-triazole (**23**) in 87% yield.

Deprotection. The benzyl group of 1-(benzyloxy)triazole (**5**) and of its 5-methyl, 5-formyl, 5-methoxycarbonyl, and 5-(dimethylamino)carbonyl substituted derivatives (**13**−**16**) could be removed readily by mild hydrogenolysis (10% Pd/C at 0 °C) to give **3** and **24**−**27**, respectively, in 96−100% yields. 1-(Benzyloxy)-5-chlorotriazole (**17**) was debenzylated at −5 °C in order to avoid dechlorination. Alternatively, 1-(benzyloxy)-5-chlorotriazole (**17**) could be debenzylated by treatment with concentrated hydrochloric acid.

Some 1-hydroxytriazoles have been prepared earlier by the debenzylation of 2-benzyltriazole 1-oxides.[16] However the synthesis via 1-(benzyloxy)triazoles offers an efficient and more general alternative. The resulting 5-substituted 1-hydroxytriazoles are of particular interest, and their properties as catalysts in peptide coupling reactions are currently being investigated.

Conclusion

A new route to 5-substituted 1-hydroxy-1,2,3-triazoles using *ortho* lithiation of 1-(benzyloxy)triazoles as the key step has been developed. 1-(Benzyloxy)-1,2,3-triazole (**5**) was obtained by oxidative cyclization of 2-hydrazonoglyoxal *O*-benzyloxime (**8**), prepared in situ. The 1-benzyloxy or 1-carbamoyloxy group in 1,2,3-triazoles served as an effective *ortho* director in metalation reactions by treatment with *n*-butyllithium. The 5-lithiotriazole thus formed reacted with a series of electrophiles. In this way carbon, halogen, sulfur, silicon, and tin substituents could be introduced at the 5-position. It was demonstrated that the benzyl group could be selectively removed by palladium-catalyzed hydrogenolysis affording the corresponding 5-substituted 1-hydroxy-1,2,3-triazoles in excellent yields even in the presence of sensitive chlorine or formyl substituents at the 5-position.

Experimental Section

General Methods and Materials. See ref 17.

1,2,3-Triazole (2). A solution of 1-(4-methoxybenzyl)-1,2,3-triazole (**1**) (24 g, 0.13 mol) in HBr (47%, 100 mL) was stirred for 3 h at 120 °C. The aqueous phase was washed with CH_2Cl_2 (2 × 100 mL), treated with trisodium phosphate dodecahydrate (20 g), and adjusted to pH 9 with NaOH. Continuous extraction with Et_2O for 16 h gave 7.8 g (89%) of 1,2,3-triazole (**2**).

1-Hydroxy-1,2,3-triazole (3). A mixture of 1,2,3-triazole (**2**) (15.9 g, 0.23 mol), formic acid (22 mL), and hydrogen peroxide (60%, 30 mL) was stirred at 0 °C for 1 h and then at 20 °C for 3 d. Within the next 30 d, seven portions of formic acid (11 mL) and hydrogen peroxide (60%, 15 mL) were added, and 71% of **2** was converted to 1-hydroxy-1,2,3-triazole (**3**) according to ^{1}H NMR spectroscopy. Purification using the procedure described in ref 15 extending the time for the continuous extraction to 3 weeks afforded 12.7 g (65%) of pure **3**.

Protection. 1-(Benzyloxy)-1,2,3-triazole (5). Method a. A suspension of 1-hydroxy-1,2,3-triazole (**3**) (7.4 g, 87 mmol), barium hydroxide octahydrate (6.4 g, 20 mmol), and barium oxide (26.8 g, 175 mmol) in DMF (400 mL) was treated with three portions of benzyl bromide (12.5 mL, 105 mmol; additional 5 mL, 42 mmol, after 8 and 16 h, respectively) and stirred vigorously for 24 h. The mixture was diluted with $CHCl_3$ (1 L), filtered over Celite, and concentrated. Flash chromatography (AcOEt−heptane 1:1) gave 13.3 g (87%) of **5** as an oil: R_f (AcOEt−heptane 1:1) 0.35; ^{1}H NMR ($CDCl_3$) δ 7.51 (d, J = 1.0 Hz, H-4), 7.42−7.26 (m, 5H), 7.24 (d, J = 1.0 Hz, H-5), 5.39 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 132.4 (s), 131.7 (dd, $J_{C-4,H-4}$ = 197.0, $J_{C-4,H-5}$ = 9.9 Hz, C-4), 129.4 (d), 129.4 (d), 128.4 (d), 118.5 (dd, $J_{C-5,H-5}$ = 201.0, $J_{C-5,H-4}$ = 15.4 Hz, C-5), 82.2 (t). Anal. Calcd for $C_9H_9N_3O$: C, 61.70; H, 5.18; N, 23.99. Found: C, 62.00; H, 5.33; N, 23.81.

(Benzyloxy)ammonium Chloride. The reported procedure[26] was improved as follows. *N*-Hydroxyphthalimide (98.0 g, 0.60 mol) and Na_2CO_3 (171 g, 0.598 mol) were dissolved in a mixture of DMF (800 mL), acetonitrile (150 mL), and water (800 mL). Benzyl chloride (80.5 g 0.636 mol) was added, and the mixture was stirred for 4 h. Filtration and washing with water (3 × 200 mL) and with 0 °C methanol (2 × 150 mL) yielded 149.4 g (94%) of *N*-(benzyloxy)phthalimide, mp 143−144 °C (reported[26] mp 143−144 °C). The *N*-(benzyloxy)phthalimide was treated with hydrazine as described previously[26] to give crude (benzyloxy)ammonium chloride which was recrystallized from 1-propanol to give 93% of (benzyloxy)ammonium chloride.

1-(Benzyloxy)-1,2,3-triazole (5). Method b. Hydrazine hydrate (86.5 g, 1.71 mol) was dissolved in MeOH (500 mL) and cooled to 0 °C. A solution of **7** (28.7 g, 0.176 mol), prepared from (benzyloxy)amine and glyoxal as described previously,[21]

(26) Rougny, A.; Daudon, M. *Bull. Soc. Chim. Fr.* **1976**, 833.

in MeOH (1000 mL) was then added dropwise during 15 min. The reaction mixture was stirred for 30 min and then evaporated in vacuo to yield a colorless oil. The oil was redissolved in pyridine (1000 mL), and the mixture was heated to 100 °C. $CuSO_4 \cdot 5H_2O$ (87.7 g, 0.351 mol) was added, and after 30 min the black reaction mixture was evaporated in vacuo. Water (1000 mL) was added and the aqueous phase extracted with diethyl ether (5 × 200 mL). The organic extracts were combined and washed with water (3 × 300 mL), dried over $MgSO_4$, and filtered, and the solvent was then removed in vacuo to afford a brown oil. Purification by flash chromatography (EtOAc−heptane 1:1) yielded 16.0−19.4 g (52−63%) of 1-(benzyloxy)-1,2,3-triazole (**5**) identical with the material above.

1-((*N*,*N*-Diethylcarbamoyl)oxy)-1,2,3-triazole (4). A solution of 1-hydroxy-1,2,3-triazole (**3**) (260 mg, 3.06 mmol) and *N*-ethyldiisopropylamine (0.55 mL, 3.21 mmol) in dry CH_2Cl_2 (3 mL) was cooled to 0 °C. *N*,*N*-Diethylcarbamoyl chloride (4.3 mL, 3.39 mmol) was added and the mixture stirred for 18 h. The mixture was concentrated and flash chromatographed (AcOEt−heptane 1:1) to give 520 mg (92%) of **4** as an oil. Recrystallization (AcOEt−heptane) gave mp 26 °C: R_f (AcOEt−heptane 1:1) 0.21; ^{1}H NMR ($CDCl_3$) δ 7.73 (d, J = 1.1 Hz, 1H), 7.72 (d, J = 1.1 Hz, 1H), 3.49 (q, J = 7.1 Hz, 2H), 3.39 (q, J = 7.1 Hz, 2H), 1.31 (t, J = 7.1 Hz, 3H), 1.22 (t, J = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 151.1 (s), 132.2 (d, C-4), 120.4 (d, C-5), 43.5 (t), 41.9 (t), 13.8 (q), 12.7 (q). Anal. Calcd for $C_7H_{12}N_4O_2$: C, 45.65; H, 6.57; N, 30.42. Found: C, 45.55; H, 6.51; N, 30.61.

Lithiation of 1-((*N*,*N*-Diethylcarbamoyl)oxy)-1,2,3-triazole (4) and 1-(Benzyloxy)-1,2,3-triazole (5) followed by Reaction with an Electrophile. General Procedure. Under N_2 at −78 °C, a 0.1 M solution of 1-(benzyloxy)-1,2,3-triazole (**5**) in dry THF was treated dropwise with 1.2 equiv of *n*-BuLi (1.6 M in hexane). After 5 min the electrophile was added (neat or dissolved in THF) and, stirring was continued for 1 h at −78 °C and 1 h at rt. The mixture was then quenched with saturated NH_4Cl, and the product was extracted with CH_2Cl_2. The organic phase was washed with H_2O, dried ($MgSO_4$), and concentrated.

1-(Benzyloxy)-5-deuterio-1,2,3-triazole (12). Using the general procedure, lithiation of **5** was followed by quenching with deuterium oxide (15 equiv). Flash chromatography (AcOEt−heptane 1:1) gave 90% of **12** as an oil. The ^{1}H NMR spectrum was identical with that of the starting material **5** except that the signal at 7.24 ppm was absent, indicating quantitative deuteration at the 5-position.

1-(Benzyloxy)-5-methyl-1,2,3-triazole (13). Using the general procedure, the reaction of **5** (84 mg, 0.48 mmol) with methyl iodide (0.09 mL, 1.44 mmol) as the electrophile gave after flash chromatography (Et_2O−pentane 2:1) 84 mg (93%) of **13** as an oil. Recrystallization (AcOEt−heptane) gave mp 34 °C: R_f (AcOEt−heptane 1:1) 0.23; ^{1}H NMR ($CDCl_3$) δ 7.41−7.24 (m, 6H), 5.41 (s, 2H), 1.84 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 132.7 (s), 130.8 (d), 130.0 (d), 129.7 (d), 128.7 (d), 128.0 (s), 81.9 (t), 6.7 (q). Anal. Calcd for $C_{10}H_{11}N_3O$: C, 63.48; H, 5.86; N, 22.21. Found: C, 63.46; H, 5.97; N, 22.20.

1-(Benzyloxy)-5-formyl-1,2,3-triazole (14). The general procedure was used for the reaction of **5** (1.75 g, 10 mmol) with DMF (3.7 mL, 50 mmol) as the electrophile. The crude mixture was stirred for 15 min with 2 M HCl (50 mL) before workup. Flash chromatography (AcOEt−heptane 1:2) gave 1.77 g (87%) of **14** as a solid. Recrystallization (CH_2Cl_2−pentane) gave mp 56 °C: R_f (AcOEt−heptane 1:1) 0.31; ^{1}H NMR ($CDCl_3$) δ 9.50 (s, 1H), 8.04 (s, 1H), 7.43−7.27 (m, 5H), 5.58 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 176.5 (d), 134.9 (d), 131.4 (s), 130.2 (d), 130.0 (d), 129.4 (s), 128.8 (d), 83.4 (t). Anal. Calcd for $C_{10}H_9N_3O$: C, 59.11; H, 4.46; N, 20.68. Found: C, 59.18; H, 4.63; N, 20.54.

1-(Benzyloxy)-5-(methoxycarbonyl)-1,2,3-triazole (15). Using the general procedure, the reaction of **5** (260 mg, 1.48 mmol) with methyl chloroformate (885 mg, 9.37 mmol) as the electrophile gave after flash chromatography (AcOEt−heptane 1:1) 263 mg (76%) of **15** as a solid. Recrystallization (AcOEt−heptane) gave mp 62.5−63.5 °C: R_f (AcOEt−heptane 1:1) 0.44; ^{1}H NMR ($CDCl_3$) δ 8.03 (s, 1H), 7.54−7.32 (m, 5H), 5.50 (s, 2H), 3.89 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 156.6 (s), 136.1 (d), 131.8 (s), 130.0 (d), 129.7 (d), 128.5 (d), 122.9 (s), 83.3 (t), 52.4 (q). Anal. Calcd for $C_{11}H_{11}N_3O_3$: C, 56.65; H, 4.75; N, 18.02. Found: C, 56.94; H, 4.75; N, 18.00.

1-(Benzyloxy)-5-((dimethylamino)carbonyl)-1,2,3-triazole (16). Using the general procedure, the reaction of **5** (362 mg, 2.07 mmol) with dimethylcarbamoyl chloride (1.27 g, 11.82 mmol) as the electrophile gave after flash chromatography (AcOEt−heptane 2:1) 494 mg (97%) of **16** as an oil: R_f (AcOEt−heptane 1:1) 0.11; ^{1}H NMR ($CDCl_3$) δ 7.75−7.60 (s br, 1H), 7.53−7.25 (m, 5H), 5.50 (s, 2H), 3.00 (s, 3H), 2.74 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 157.1 (s), 131.8 (s), 131.0 (br d), 129.5 (d), 129.1 (d), 128.1 (d), 125.8 (br s), 82.8 (t), 37.6 (q), 34.4 (q). Anal. Calcd for $C_{12}H_{14}N_4O_2$: C, 58.53; H, 5.73; N, 22.75. Found: C, 58.56; H, 5.88; N, 22.51.

1-(Benzyloxy)-5-chloro-1,2,3-triazole (17). Using the general procedure, the reaction of **5** (245 mg, 1.40 mmol) with hexachloroethane (662 mg, 2.80 mmol) dissolved in THF (2 mL) as the electrophile gave after flash chromatography (AcOEt−heptane 1:2) 257 mg (88%) of **17** as a solid. Recrystallization (AcOEt−heptane) gave mp 39 °C: R_f (AcOEt−heptane 1:1) 0.44; ^{1}H NMR ($CDCl_3$) δ 7.48 (s, 1H), 7.73−7.33 (m, 5H), 5.41 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 131.7 (s), 130.0 (d), 129.8 (d), 129.7 (d), 128.6 (d), 121.0 (s), 82.8 (t). Anal. Calcd for $C_9H_8ClN_3O$: C, 51.56; H, 3.85; N, 20.04. Found: C, 51.36; H, 3.80; N, 20.11.

1-(Benzyloxy)-5-bromo-1,2,3-triazole (18). Using the general procedure, the reaction of **5** (124 mg, 0.71 mmol) with bromine (55 mL, 1.07 mmol) as the electrophile gave after flash chromatography (AcOEt−heptane 1:2) 155 mg (86%) of **18** as a solid. Recrystallization (AcOEt−heptane) gave mp 67 °C: R_f (AcOEt−heptane 1:1) 0.44; ^{1}H NMR ($CDCl_3$) δ 7.55 (s, 1H), 7.41−7.38 (m, 5H), 5.42 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 133.1 (d), 131.7 (s), 130.1 (d), 129.9 (d), 128.7 (d), 106.1 (s), 82.9 (t). Anal. Calcd for $C_9H_8BrN_3O$: C, 42.54; H, 3.17; N, 16.54. Found: C, 42.56; H, 3.19; N, 16.54.

1-(Benzyloxy)-5-iodo-1,2,3-triazole (19). Using the general procedure, the reaction of **5** (100 mg, 0.57 mmol) with iodine (224 mg, 0.88 mmol) dissolved in THF (1 mL) as the electrophile gave after flash chromatography (AcOEt−heptane 1:2) 165 mg (96%) of **19** as a solid. Recrystallization (AcOEt−heptane) gave mp 105 °C: R_f (AcOEt−heptane 1:1) 0.43; ^{1}H NMR ($CDCl_3$) δ 7.50 (s, 1H), 7.33−7.27 (m, 5H), 5.33 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 138.9 (d), 131.8 (s), 130.2 (d), 129.9 (d), 128.7 (d), 82.9 (t), 72.7 (s). Anal. Calcd for $C_9H_8IN_3O$: C, 35.90; H, 2.68; N, 13.96. Found: C, 35.99; H, 2.71; N, 13.94.

1-(Benzyloxy)-5-(methylthio)-1,2,3-triazole (20). Using the general procedure, the reaction of **5** (237 mg, 1.35 mmol) with dimethyl disulfide (0.24 mL, 2.71 mmol) as the electrophile gave after flash chromatography (AcOEt−heptane 1:2) 201 mg (67%) of **20** as a solid. Recrystallization (AcOEt−heptane) gave mp 45 °C: R_f (AcOEt−heptane 1:1) 0.31; ^{1}H NMR ($CDCl_3$) δ 7.48 (s, 1H), 7.43−7.34 (m, 5H), 5.41 (s, 2H), 2.32 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 132.6 (d), 132.0 (s), 129.8 (d), 129.5 (d), 128.4 (d), 128.0 (s), 82.1 (t), 16.7 (q). Anal. Calcd for $C_{10}H_{11}N_3OS$: C, 54.28; H, 5.01; N, 18.99. Found: C, 54.29; H, 5.07; N, 19.17.

1-(Benzyloxy)-5-(trimethylsilyl)-1,2,3-triazole (21). Using the general procedure, the reaction of **5** (120 mg, 0.68 mmol) with trimethylsilyl chloride (0.52 mL, 0.81 mmol) as the electrophile gave after flash chromatography (AcOEt−heptane 1:2) 158 mg (93%) of **21** as a solid. Recrystallization (AcOEt−heptane) gave mp 51 °C: R_f (AcOEt−heptane 1:1) 0.42; ^{1}H NMR ($CDCl_3$) δ 7.55 (s, 1H), 7.39 (br s, 5H), 5.50 (s, 2H), 0.25 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 138.6 (d), 132.7 (s), 129.6 (d), 129.4 (d), 129.0 (s), 128.7 (d), 81.5 (t), −2.0 (q). Anal. Calcd for $C_{12}H_{17}N_3OSi$: C, 58.26; H, 6.93; N, 16.99. Found: C, 58.44; H, 6.94; N, 17.10.

1-(Benzyloxy)-5-(tributylstannyl)-1,2,3-triazole (22). Using the general procedure, the reaction of **5** (119 mg, 0.68 mmol) with tributylstannyl chloride (0.18 mL, 0.69 mmol) as the electrophile gave after flash chromatography (AcOEt−heptane 1:2) 287 mg (91%) of **22** as a colorless oil: R_f (AcOEt−heptane 1:1) 0.51; ^{1}H NMR ($CDCl_3$) δ 7.50 (s, 1H), 7.37 (br s, 5H), 5.49 (s, 2H), 1.51−0.98 (m, 18H), 9.86 (t, J = 7.1 Hz, 9H); ^{13}C NMR ($CDCl_3$) δ 139.1 (d, $J_{Sn,C}$ = 31 Hz), 132.9 (s), 129.4 (d), 129.2 (d), 128.5 (d), 127.5 (s), 81.1 (t), 28.5 (t, $J_{Sn,C}$ = 21

Hz), 26.9 (t, $J_{Sn,C}$ = 63 Hz), 13.4 (q), 10.2 (t, $J_{Sn,C}$ = 356 Hz). Anal. Calcd for $C_{21}H_{35}N_3OSn$: C, 54.33; H, 7.60; N, 9.05. Found: C, 54.32; H, 7.60; N, 9.37.

1-((*N*,*N*-Diethylcarbamoyl)oxy)-5-iodo-1,2,3-triazole (23). Using the general procedure, the reaction of **4** (88 mg, 0.48 mmol) with iodine (181 mg, 0.72 mmol) dissolved in THF (2 mL) as the electrophile gave after flash chromatography (AcOEt−heptane 1:2) 129 mg (87%) of **23**, mp 67−68 °C: R_f (AcOEt−heptane 1:1) 0.42; ^{1}H NMR ($CDCl_3$) δ 7.68 (s, 1H), 3.44 (q, J = 7.1 Hz, 2H), 3.34 (q, J = 7.0 Hz, 2H), 1.29 (t, J = 7.1 Hz, 3H), 1.17 (t, J = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 150.4 (s), 139.3 (d), 74.9 (s), 43.9 (t), 42.2 (t), 14.1 (q), 12.9 (q). Anal. Calcd for $C_7H_{11}IN_4O_2$: C, 27.11; H, 3.58. Found: C, 27.06; H, 3.49.

Debenzylation of 1-(Benzyloxy)-1,2,3-triazoles. 1-Hydroxy-1,2,3-triazole (3). 1-(Benzyloxy)-1,2,3-triazole (**5**) (200 mg, 1.14 mmol) was dissolved in MeOH (10 mL), the solution was cooled to 0 °C and then 10% Pd on activated carbon (40 mg) was added, and the reaction mixture was stirred in an atmosphere of hydrogen (1 atm) at 0 °C for 15 min. Filtration through Celite and removal of the methanol gave 93 mg (96%) of 1-hydroxy-1,2,3-triazole (**3**), identical with the material described previously.[15]

1-Hydroxy-5-methyl-1,2,3-triazole (24). Similarly, 1-(benzyloxy)-5-methyl-1,2,3-triazole (**13**) (200 mg, 1.06 mmol) gave 104 mg (99%) of **24**. Recrystallization (acetone) gave mp 143 °C (dec): ^{1}H NMR (acetone-d_6) δ 8.87 (br s, OH), 7.51 (s, 1H), 2.23 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 130.5 (d), 127.1 (s), 7.2 (q). Anal. Calcd for $C_3H_5N_3O$: C, 36.35; H, 5.09; N, 42.42. Found: C, 36.28; H, 5.07; N, 42.72.

5-Formyl-1-hydroxy-1,2,3-triazole (25). Similarly, 1-(benzyloxy)-5-formyl-1,2,3-triazole (**14**) (200 mg, 0.99 mmol) was debenzylated to give 111 mg (100%) of **25**. Recrystallization (acetone) gave mp 179 °C (dec). ^{1}H NMR (acetone-d_6) δ 10.43 (s, 1H), 8.69 (s, 1H), 6.02 (br s, OH); ^{13}C NMR (DMSO-d_6) δ 180.1 (s), 133.4 (d), 128.9 (s). Anal. Calcd for $C_3H_3N_3O_2$: C, 31.85; H, 2.68; N, 37.17. Found: C, 31.72; H, 2.77; N, 37.06.

1-Hydroxy-5-(methoxycarbonyl)-1,2,3-triazole (26). Similarly, 1-(benzyloxy)-5-(methoxycarbonyl)-1,2,3-triazole (**15**) (205 mg, 0.88 mmol) was debenzylated in EtOH at 0 °C for 30 min to give 124 mg (99%) of 1-hydroxy-5-(methoxycarbonyl)-1,2,3-triazole (**26**). Recrystallization (acetone) gave mp 126−127 °C: ^{1}H NMR (CD_3OD) δ 8.27 (1H, s), 3.96 (3H, s); ^{13}C NMR (CD_3OD) δ 159.7 (s), 136.8 (d), 124.9 (s), 53.9 (q). Anal. Calcd for $C_4H_5N_3O_3$: C, 33.57; H, 3.52; N, 29.36. Found: C, 33.11; H, 3.61; N, 28.21.

5-((Dimethylamino)carbonyl)-1-hydroxy-1,2,3-triazole (27). Similar to **26** 5-((dimethylamino)carbonyl)-1-hydroxy-1,2,3-triazole (**27**) was obtained in 98% yield. Recrystallization (methanol) gave mp 127−128 °C: ^{1}H NMR (CD_3OD) δ 8.03 (s, 1H), 3.15 (s, 3H), 3.10 (s, 3H); ^{13}C NMR (CD_3OD) δ 161.5 (s), 132.5 (d), 128.1 (s), 39.6 (q), 36.4 (q). Anal. Calcd for $C_4H_8N_4O_2$: C, 38.46; H, 5.16; N, 35.88. Found: C, 38.74; H, 4.98; N, 35.93.

5-Chloro-1-hydroxy-1,2,3-triazole (28). Method a. Similar to **13**, 1-(benzyloxy)-5-chloro-1,2,3-triazole (**17**) (200 mg, 0.95 mmol) was debenzylated at −5 °C for 15 min[27] to give 114 mg (100%) of **28**, mp 128 °C ($CHCl_3$-acetone), identical with the material described previously.[16] Anal. Calcd for $C_2H_2ClN_3O$: C, 20.10; H, 1.69; N, 35.16. Found: C, 20.12; H, 1.74; N, 35.34.

5-Chloro-1-hydroxy-1,2,3-triazole (28). Method b. 1-(Benzyloxy)-5-chloro-1,2,3-triazole (**17**) (200 mg, 0.95 mmol) and aqueous hydrogen chloride (37%, 3 mL) were stirred at 60 °C for 10 h. The mixture was washed with CH_2Cl_2 (5 × 5 mL) and the product isolated using the workup procedure described in ref 16 for a similar debenzylation. This afforded 97 mg (85%) of **28**, identical with the material above.

Acknowledgment. This work was supported by the Danish Council for Technical and Scientific Research and the Lundbeck Foundation. The NMR spectrometer is a gift from the Velux Foundation of 1981, The Danish Council for Technical and Scientific Research, The Ib Henriksen Foundation, and the Torkil Steenbeck Foundation.

JO971313O

(27) Increasing the temperature or the reaction time led to substantial dechlorination.