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Direct Preparation of Guanidine from Trichloroacetamide. A Potentially Important Method to (-)-Tetrodotoxin

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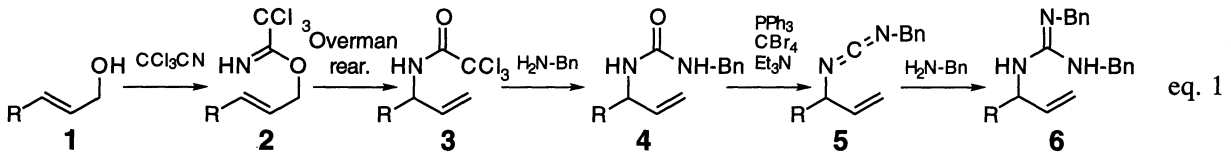
Trichloroacetamides obtained *via* Overman [3,3] sigmatropic rearrangement were converted into dibenzyl guanidines. The key step was conversion of carbodiimide intermediate into guanidine by scandium or ytterbium trifluoromethane-sulfonates. This method was applied to a synthesis of guanidinium ring of (-)-tetrodotoxin.

Among many naturally occurring compounds guanidinium group plays important roles in expressing biological activity due to its cationic nature. This ionic nature has long time obliged its synthesis at the very last stage of multi-step synthesis.[1] Various synthetic methods have been developed to access to the guanidinium group through intermediates such as thioureas, aminoiminomethanesulfonic acids, chloroformamidines, dichloroisocyanides, carbodiimides or cyanamides, and through Mitsunobu protocol.[2] During our synthetic studies toward tetrodotoxin which contains a cyclic guanidinium moiety,[3] the above method should be modified since the guanidinium had to be protected because of the low solubility of the free guanidinium derivative. In our previous study, non-protected guanidinium moiety was derived from well-known cyanamides at the last step of a model compound synthesis. That study included Overman-imidate rearrangement from the allylic alcohol **1**, *via* its trichloroacetimidate (**2**) and trichloroacetamide (**3**), that amide was hydrolyzed to the corresponding free amine.[4] In this communication we now report a synthesis of protected guanidinium as summarized in eq. 1. The same Overman rearrangement product **3** was used for the following 3-step conversion initiated by haloform-type C-C bond cleavage reaction to the allyl benzyl urea **4**.[5] The carbodiimide (**5**) obtained by dehydration was designed as a candidate of reactive intermediate leading he dibenzylguanidine (**6**).

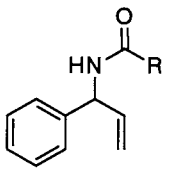
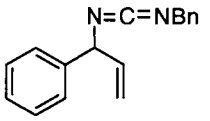
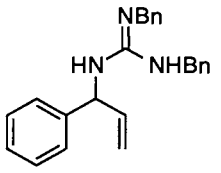
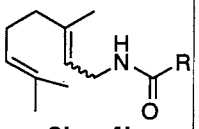
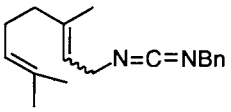
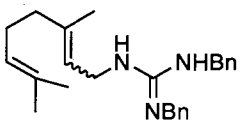
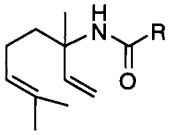
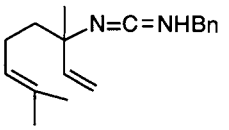
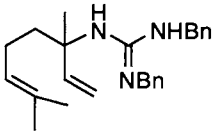
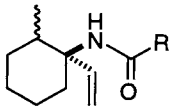
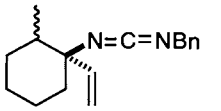
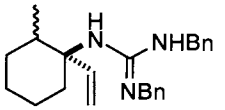


eq. 1

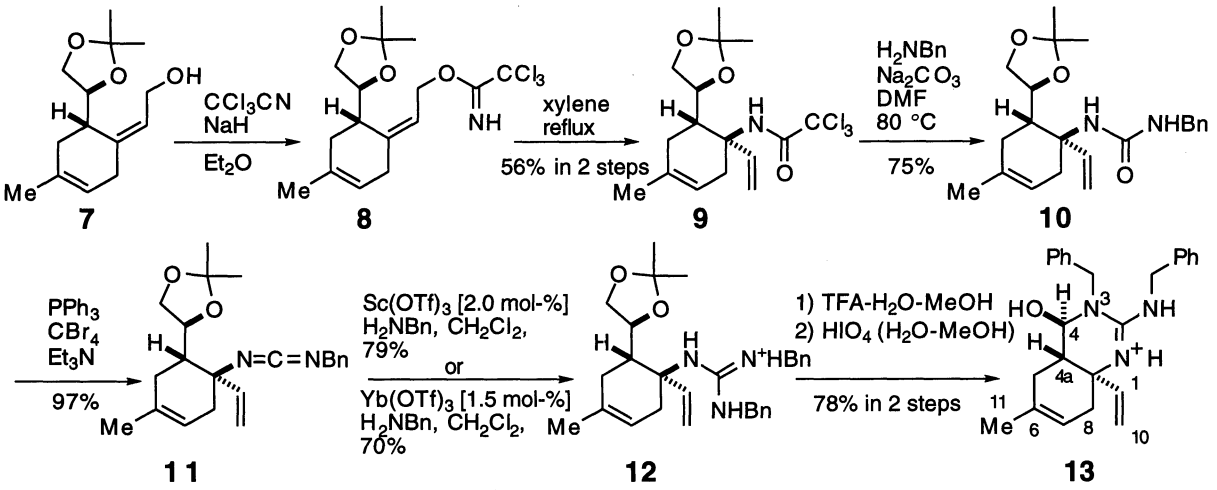
For the establishment of this transformation 4 substrates containing primary, secondary and tertiary trichloroacetamides (**3a-d**) were selected and shown in Table 1. These amides were prepared by Overman rearrangement[4] from the corresponding allylic alcohols (**1**), respectively, by treatment with sodium hydride and trichloroacetonitrile in Et_2O solvent.[3,4] Heating each of the amides **3a-d** at 80 °C with benzylamine (1.2 equiv.) and Na_2CO_3 (5 equiv.) in N,N-dimethylformamide (DMF) solvent afforded the corresponding ureas **4a-d** in those yields listed in Table 1.[6] Dehydration of these ureas **4** with carbon tetrabromide (1.2 equiv.),

triphenylphosphine (1.2 equiv.) and triethylamine (1.2 equiv.) in dichloromethane solvent at -20 °C (or at rt) afforded the corresponding benzyl carbodiimides **5a-d**.[7] Crucial condition from the carbodiimide **5** to the corresponding guanidine **6** was examined with **5a** under various temperatures. These preliminary experiments suggested that this transformation should be carried out at low temperatures to avoid a side reaction.[8] Acid catalysts such as Lewis acid or Brϕnsted acid did not give the guanidinium product since it deactivated the benzylamine nucleophile. Predominant activation of the C=N bonds in the carbodiimide was necessary under a condition with preserving the nucleophilicity of benzylamine. In entry 1 with the carbodiimide **5a**, the first candidate was $LiClO_4$ (3M) in diethyl ether, which gave, in fact, the guanidine **6a** in moderate yield (49%). Secondly, two rare earth triflates, $Sc(OTf)_3$ and $Yb(OTf)_3$, were examined in a mixture of tetrahydrofuran (THF) and water (9:1) solvent, since both triflates were known as stable acids in aqueous media.[9] When the reaction with **5a** was operated in the aqueous THF solvent using only 10 mol-% of $Sc(OTf)_3$ or $Yb(OTf)_3$, the guanidine **6a** was obtained in 70 or 89% yields, respectively. This aqueous system converted **5b** into **6b** in 60% yield (entry 2). With both the *tert*-carbodiimides **5c** and **5d**, on the other hand, the aqueous solvent system did not afford the guanidinium product even stirring for 4 days at rt. In these cases, dichloromethane solvent and either one of the above two triflates in 120 mol-% were necessary to accomplish the reaction. The amount of the triflates was no more catalytic in non-aqueous solvent in entry 3 and 4.[9] Lithium perchlorate with **5c** gave **6c** in very low yield (17%, entry 3). These facts validated the role of the rare earth triflates in the addition of benzylamine to the carbodiimides.

Table 1. Preparation of the Guanidine from the Trichloroacetamide (Substrate concentration **5**→**6**: 0.1 *M*)

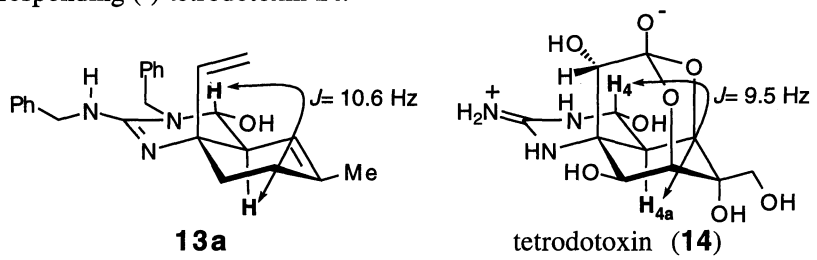
entry	urea **4** (R = NHBn) from **3** (R = CCl_3)	yield % **3**→**4**	carbodiimide **5**	yield % **4**→**5**	condition: acid	condition: solvent	guanidine **6**	yield % **5**→**6**
1	 **3a** **4a**	92	 **5a**	99	$LiClO_4$ (300%)	Et_2O	 **6a**	49
					$Sc(OTf)_3$ (10%)	THF:H_2O (9:1)		70
					$Yb(OTf)_3$ (10%)	THF:H_2O (9:1)		89
2	 **3b** **4b**	77	 **5b**	34	$Sc(OTf)_3$ (10%)	THF:H_2O (9:1)	 **6b**	60
3	 **3c** **4c**	64	 **5c**	96	$LiClO_4$ (300%)	Et_2O	 **6c**	17
					$Sc(OTf)_3$ (120%)	CH_2Cl_2		69
					$Yb(OTf)_3$ (120%)	CH_2Cl_2		85
4	 **3d** **4d**	70	 **5d**	70	$Sc(OTf)_3$ (120%)	CH_2Cl_2	 **6d**	70
					$Yb(OTf)_3$ (120%)	CH_2Cl_2		75

These model studies providing dibenzyl guanidinium compounds were directly applied to the synthesis of a (-)-tetrodotoxin model compound **13**. Scheme 1 illustrates a practical route corresponding to equation 1. The optically active allylic alcohol (**7**)[10] was synthesized from levoglucosenone in 5 steps (synthetic data not shown) and it was converted in 2 steps into the trichloroacetamide **9** [IR (KBr) ν_{max} 1727 cm^{-1}; ^{1}H-NMR δ 5.28 (dd, *J*= 11, 1 Hz), 5.32 (dd, *J*= 17, 1 Hz), 5.82 (dd, *J*= 17, 11 Hz)] which already possessed the carbon skeleton of tetrodotoxin. Conversion of the amide **9** to the guanidinium compound **12** was straight forward; thus, through the urea **10** [IR (KBr) ν_{max} 1647 cm^{-1}] and the carbodiimide **11** [IR (KBr) ν_{max} 1734 cm^{-1}]. Its guanidinium formation was effected by benzylamine in the presence of either $Sc(OTf)_3$ or $Yb(OTf)_3$ to give **12** [FAB-MS m/z 460 (M+H)] in 79% or 70% yield, respectively. Dibenzyl guanidine **12** was further converted into cyclic guanidine by heating at 50 °C with a mixture of TFA-H_2O-MeOH and then stirring at rt with HIO_4 to give the dibenzyl cyclic guanidine **13** [FAB-MS m/z 388 (M+H)]. In our previous report the non-protected cyclic guanidine (similar to **13** with 2 H's instead of 2 CH_2Ph's) showed no solubility in any solvent, while the dibenzyl guanidine **12** and **13** showed high solubility even in dichloromethane and in methanol. This nature made the purification by silica gel chromatography possible.



Scheme 1.

Configuration of the C-4 of **13** was determined from its ^{1}H-NMR in $CDCl_3$, since the coupling constant between H-4 and H-4a was 10.6 Hz as shown in **13a**.[11] This *J* value was comparable with that (*J*= 9.5 Hz) of the corresponding (-)-tetrodotoxin **14**.



13a tetrodotoxin (**14**)

The current methodology as exemplified in eq. 1 for preparation of guanidinium group was demonstrated by application to synthesizing the cyclic guanidinium moiety of tetrodotoxin (Scheme 1). The method is of significance in the synthesis of such compounds having guanidinium with other complex functional groups in the target molecules, since the notorious insolubility problem of guanidinium function in organic molecule has been solved.

The authors are indebted to Ms. Atanasova for communication with a reprint of their work on urea synthesis (Ref. 5), and to Dr. Yoshiyasu Ichikawa and Mr. Toshio Nishikawa for valuable discussions. Financial supports for this study was due to Grant-in-Aid for Scientific Research from the Ministry of Education, Science and Culture of Japan.

References

1) Y. Kishi, T. Fukuyama, M. Aratani, F. Nakatsubo, T. Goto, H. Inoue, H. Tanino, S. Sugiura, and H. Kakoi, *J. Am. Chem. Soc.*, **94**, 9219 (1972).

2) Thioureas: M. A. Poss, E. Iwanowicz, J. A. Reid, and Z. Gu, *Tetrahedron Lett.*, **33**, 5933 (1992). K. S. Kim, and L. Qian, *Tetrahedron Lett.*, **34**, 7677 (1993); Aminoiminomethanesulfonic acids: K. Kim, Y-T. Lin, and H. S. Mosher, *Tetrahedron Lett.*, **29**, 3183 (1988); Chloroformamides: H. Bredereck and K. Bredereck, *Chem. Ber.*, **94**, 2278 (1961); Dichloroisocyanides: C. R. Rasmussen, U. S. Patent 4 211 867 (1983); Carbodiimides: F. Kurzer and P. M. Sanderson, *J. Chem. Soc.*, **1960**, 3240; Cyanamides: T. L. Davis, *Org. Synth.*, **7**, 46 (1927); Mitsunobu protocols: D. S. Dodd and A. P. Kozikowski, *Tetrahedron Lett.*, **35**, 977 (1994).

3) M. Isobe, Y. Fukuda, T. Nshikawa, P. Chabert, and T. Goto, *Tetrahedron Lett.*, **31**, 3327 (1990).

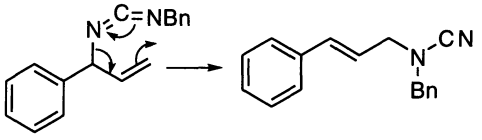
4) L. E. Overman, *J. Am. Chem. Soc.*, **98**, 2901 (1976).

5) Zh. Petrov, I. Atanasova, A. Balabanova, and N. Mollov, *Izv. Khim.*, **23**, 53 (1990).

6) Using Et_3N instead of Na_2CO_3, the deprotected amines were obtained.

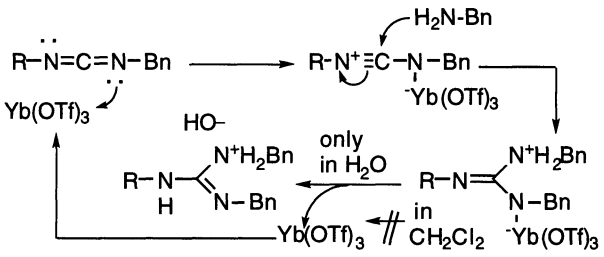
7) Unstability of **3a** gave **4b** in low yield that decomposed during silica gel chromatographic purification.

8) Simple heating of **5a** with benzylamine did not afford the guanidine **6a**, but gave the allyl cyanamides **15** *via* [3,3] sigmatropic rearrangement instead.



5a' **15**

9) For the reactivity of lanthanide triflates in aqueous media; see, S. Kobayashi, *Chem. Lett.*, **1991**, 2187. The stoichiometry of the Lewis acids in dichloromethane solvent was more than 1 equiv. probably due to low solubility of a zwitter intermediate, which may not be reused as in aqueous media. Right scheme suggests a possible mechanism.



10) Preparation of **7** from levoglucosenone was achieved by Diels-Alder reaction with isoprene in the presence of Lewis acid. The details of this synthesis will be published elsewhere.

11) ^{1}H-NMR data for the cyclic guanidinium compound **13**: δ (in $CDCl_3$) 1.68 (3H, br s, H-11), 1.71-1.79 (1H, m, H-5), 2.02-2.10 (1H, m, H-8), 2.30-2.41 (2H, m, H-4a &H-8), 2.46 (1H, br dd, J = 18, 5, H-5), 4.44 (2H, d, J = 5.1, PhCH_2NH), 4.55 (1H, d, J = 17.2, Htrans-10), 4.72 (1H, d, J = 16.3, PhCH_AH$_B$N), 4.85 (1H, d, J = 16.3, PhCH$_A$$H_B$N), 5.01 (1H, d, J = 10.7, Hcis-10), 5.24 (1H, brs, H-7), 5.37 (1H, d, J = 10.6, H-4), 6.66 (1H, br s, N*H*), 7.03-7.06 (2H, m, Ph), 7.26-7.39 (8H, m, 2Ph).

12) Our recent studies on tetrodotoxin synthesis: see N. Yamamoto and M. Isobe, *Tetrahedron*, **49**, 6581 (1993) and the references cited therein.

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