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Convenient Method for the Preparation of Carbamates, Carbonates, and Thiocarbonates

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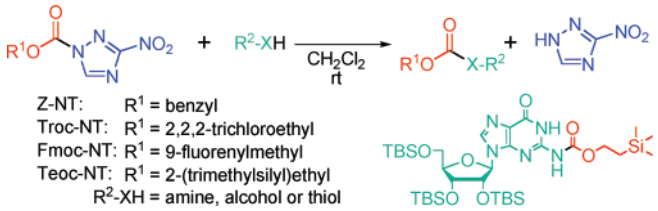
ABSTRACT



A convenient, rapid, and efficient method for the preparation of carbamates from amines with 1-alkoxycarbonyl-3-nitro-1,2,4-triazole transfer reagents is reported. Reactions of newly synthesized stable crystalline reagents with alkyl amines were completed in a few minutes without any additional base, and highly pure carbamates were obtained without chromatographic purification. These highly active reagents are also useful for the selective protection of nucleobases and preparation of carbonates and thiocarbonates.

Carbamates, carbonates, and thiocarbonates have been used as protecting groups for amines, alcohols, and thiols, respectively,[1] and these functional groups are also found in various pharmaceuticals and agrochemicals.[2] Alkyl chloroformates are the most frequently used reagents for the preparation of these functional groups. However, many commonly used alkyl chloroformates are hazardous liquids and are susceptible to thermolysis and hydrolysis, requiring careful handling and storage. Furthermore, addition of base and a long reaction time are usually necessary for completion of the reaction. Although many other active carbonate-type reagents, such as alkyl *N*-hydroxysuccinimidyl carbonates, and alkyloxycarbonylammonium-type reagents, such as imidazolium and tetrazolium salts,[3] have been used for carbamate formation, these reagents also have drawbacks in terms of reactivity and difficulty of separation of the product from the co-product. Selective protection of less reactive amines, such as the amino groups of nucleobases, is problematic in some cases. Thus, development of a more practical and convenient method for such reactions is still desirable. Herein we report novel 1-alkoxycarbonyl-3-nitro-1,2,4-triazole reagents which are useful for the preparation of carbamates, carbonates, and thiocarbonates.

To achieve rapid and clean reaction, the nature of the leaving group is important. It should have a highly electron-withdrawing nature in order to increase the electrophilicity of the carbonyl carbon, and the nucleophilicity should be low to avoid side reactions. It should also be easily separable from the product. With these requirements in mind, we focused on 3-nitro-1,2,4-triazole (NT).[4] Although NT shows nucleophilicity, we anticipated that it could be easily excluded from the reaction system because NT is almost insoluble in CH_2Cl_2 or $CHCl_3$. Sulfonyl NT[5] and phosphonium NT[6] derivatives are used as condensing reagents.

(1) Wuts, P. G. M.; Greene, T. W. *Greene's Protective Groups in Organic Synthesis*, 4th ed.; Wiley: New Jersey, 2007; pp 279−298, 416−418, 684−686, 706−771 and references therein.

(2) (a) Wu, T.; Huang, J.; Arrington, N. D.; Dill, G. M. *J. Agric. Food Chem.* **1987**, *35*, 817−823. (b) Kato, T.; Suzuki, K.; Takahashi, J.; Kamoshita, K. *J. Pesticide Sci.* **1984**, *9*, 489−495.

(3) (a) Vilkas, E. *Bull. Chem. Soc. Fr.* **1978**, 11−37. (b) Watkins, B. E.; Rapoport, H. *J. Org. Chem.* **1982**, *47*, 4471−4477.

(4) (a) Katritsky, A. R., Ed. *Physical Methods in Heterocyclic Chemistry*; Academic Press: New York, 1963; Vol. 1. (b) Brown, E. J. *Aust. J. Chem.* **1969**, *22*, 2251−2254.

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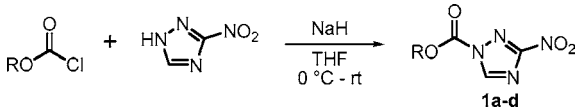
However, to our knowledge, there is no report on the use of carbonyl NT reagents for alkoxycarbonyl transfer reactions.

First, we examined the synthesis of 1-benzyloxycarbonyl-3-nitro-1,2,4-triazole (**1a**, Z-NT). Reaction of benzyl chloroformate (Z-Cl) with the sodium salt of NT in THF proceeded smoothly. Pure Z-NT was obtained as pale yellow prisms by simple filtration and subsequent recrystallization in 95% yield (Table 1, entry 1). The structure of Z-NT was confirmed by X-ray crystallographic analysis (Figure 1). Crystalline Z-NT is nonhygroscopic and thermally stable, and it was stored at 4 °C for more than 2 years without any problem.

Table 1. Synthesis of **1a**−**d**



entry	R	product	yield (%)
1	benzyl	**1a**: Z-NT	95
2	2,2,2-trichloroethyl	**1b**: Troc-NT	92
3	9-fluorenylmethyl	**1c**: Fmoc-NT	95
4	2-(trimethylsilyl)ethyl	**1d**: Teoc-NT	96

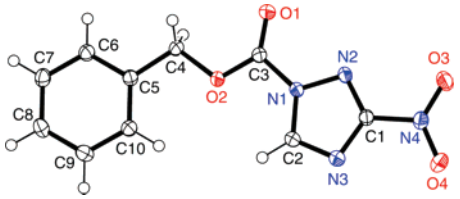
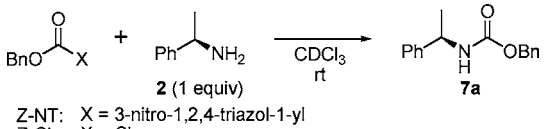


Figure 1. X-ray structure of **1a**.

Next, to compare the reactivity of **1a** with that of the known reagents, benzyl chloroformate (Z-Cl) and benzyl succinimidyl carbonate (Z-OSu), (*R*)-1-phenylethylamine (**2**) (1 equiv) was allowed to react with Z-Cl, Z-OSu, or **1a** in $CDCl_3$ at room temperature (Scheme 1), with ^{1}H NMR monitoring. The reaction with Z-Cl was rapid initially (<5 min) but stopped when the yield of **7a** reached approximately 50%, probably due to the formation of nonreactive (*R*)-1-phenylethylamine hydrochloride. Reaction of Z-OSu with **2** was also initially rapid at the beginning (5 min, 83% yield) but then slowed down (30 min, 87%; 1 h, 91%; 15.5 h, 97%), and a long reaction time was needed for completion. In contrast, reaction of **1a** reached completion in less than 5 min, and concurrent precipitation of NT was observed, suggesting that **1a** has sufficient electrophilicity, and precipitation of NT appeared to drive the reaction efficiently to completion as we had hoped. Furthermore, the insoluble NT was easily removed by simple filtration, and **7a** with >99% purity was obtained in quantitative yield without any further purification.

Scheme 1. Reaction of **2** with Z-NT, Z-Cl, and Z-OSu



Z-NT: X = 3-nitro-1,2,4-triazol-1-yl
Z-Cl: X = Cl
Z-OSu: X = succinimidyloxy

With this promising result in hand, NT reagents based on other useful protecting groups, Troc-NT (**1b**), Fmoc-NT (**1c**), and Teoc-NT (**1d**), were similarly synthesized from the corresponding chloroformates (Table 1, entries 2−4).[7,8] The products **1b**−**d** were obtained in excellent yields as crystalline solids.[9]

Reactions of these NT reagents **1a**−**d** with primary and secondary amines and amino alcohols are summarized in Table 2. The reactions of the amines **2**−**6** with 1 equiv of **1a**−**d** in CH_2Cl_2 proceeded quickly to give the corresponding carbamates in >95% yield.[10] The purity of the reaction products was determined by ^{1}H and ^{13}C NMR analyses.[11] In many cases, highly pure (>99%) carbamates were isolated by simple filtration and evapor-

(5) (a) Jones, S. S.; Rayner, B.; Reese, C. B.; Ubasawa, A.; Ubasawa, M. *Tetrahedron* **1980**, *36*, 3075−3085. (b) Ivanova, E. M.; Khalimskaya, L. M.; Romanenko, V. P.; Zarytova, V. F. *Tetrahedron Lett.* **1982**, *23*, 5447−5450. (c) Chandrasegaran, S.; Murakami, A.; Kan, L. *J. Org. Chem.* **1984**, *49*, 4951−4957.

(6) (a) Shimizu, M.; Wada, T.; Oka, N.; Saigo, K. *J. Org. Chem.* **2004**, *69*, 5261−5268. (b) Oka, N.; Shimizu, M.; Saigo, K.; Wada, T. *Tetrahedron* **2006**, *62*, 3667−3673.

(7) Hamley, P. In *Encyclopedia of Reagents for Organic Synthesis*; Paquette, L. A., Ed.; Wiley: Chichester, UK, 1995; pp 4107−4110 and references therein.

(8) Sekine, M.; Tobe, M.; Nagayama, T.; Wada, T. *Lett. Org. Chem.* **2004**, *1*, 179−182.

(9) For X-ray crystallographic structures of **1b** and **1d**, see Supporting Information.

(10) Reactions in CH_3CN or THF were also investigated. Though NT did not precipitate, **2** was smoothly reacted with **1a** and obtained **7a** in 96% yield (CH_3CN, 15 min) and 94% yield (THF, 15 min) after washing with 5% $NaHCO_3$.

(11) See Supporting Information.

(12) The compounds **1a** and **1b** were almost insoluble to MeOH at rt in the absence of base, but methyl carbonate formations were observed at elevated temperature.

(13) Iyer, R. P. In *Current Protocols in Nucleic Acid Chemistry*; Beaucage, S. L., Bergstrom, D. E., Glick, G. D., Jones, R. A., Eds.; John Wiley & Sons Inc.; New York, 2000; Vol. 1, pp 2.1.1−2.1.17.

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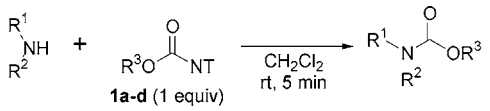
(15) (a) Hayakawa, Y.; Kato, H.; Uchiyama, M.; Kajino, H.; Noyori, R. *J. Org. Chem.* **1986**, *51*, 2400−2402. (b) Sakakura, A.; Hayakawa, Y.; Harada, H.; Hirose, M.; Noyori, R. *Tetrahedron Lett.* **1999**, *40*, 4359−4362.

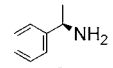
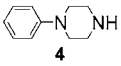
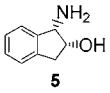
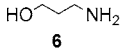
(16) Zhou, X. X.; Ugi, I.; Chattopadhyaya, J. *Acta Chem. Scand.* **1985**, *B39*, 761−765.

(17) Schneiderwind, R. G. K.; Ugi, I. *Z. Naturforsch., B: Chem. Sci.* **1981**, *36B*, 1173−1175.

(18) (a) Dreef-Tromp, C. M.; Hoogerhout, P.; van der Marel, G. A.; van Boom, J. H. *Tetrahedron Lett.* **1990**, *31*, 427−430. (b) Dreef-Tromp, C. M.; van Dam, E. M. A.; van den Elst, H.; van der Marel, G. A.; van Boom, J. H. *Nucleic Acids Res.* **1990**, *18*, 6491−6495.

Table 2. Synthesis of Carbamates Using Various Amines



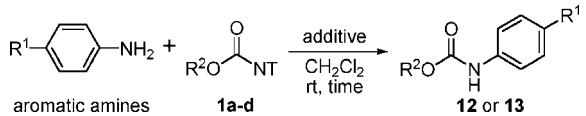
entry	amine	reagent	product	method [a]	yield (%)
1	 **2**	**1a**	**7a**	A	quant
2		**1b**	**7b**	A B	quant [b] 88
3		**1c**	**7c**	A B	quant [b] 96
4		**1d**	**7d**	C	95
5	 **3**	**1a**	**8a**	A B	quant [b] 89
6		**1b**	**8b**	A B	quant [b] 92
7		**1c**	**8c**	A B	quant [b] quant
8		**1d**	**8d**	A	quant
9	 **4**	**1a**	**9a**	A B	quant [b] 91
10		**1b**	**9b**	A	quant
11		**1c**	**9c**	A B	quant [b] 93
12		**1d**	**9d**	A	quant
13	 **5**	**1a**	**10a**	A	95
14		**1b**	**10b**	A B	95 [b] 92
15		**1c**	**10c**	A B	quant [b] 94
16		**1d**	**10d**	C	96
17 [c]	 **6**	**1a**	**11a**	A B	quant [b] 94
18 [c]		**1b**	**11b**	A B	quant [b] 95
19 [c]		**1c**	**11c**	A B	quant [b] 93
20 [c]		**1d**	**11d**	A	quant

[a] Method A: yield after filtration.[11] Method B: yield after washing with 5% $NaHCO_3$.[11] Method C: in CH_2Cl_2/5% $NaHCO_3$ (1:1), yield after separation.[11] [b] Containing a small amount of NT (<10%).[11] [c] Reaction time: 30 min.

ation of the solvent (method A). In some cases, a small amount of NT (<10%) contaminated the filtrate and decreased the purity of the carbamate. For such cases, aqueous workup with 5% $NaHCO_3$ was effective (method B), affording highly pure (>99%) carbamates without column chromatographic purification. The recovered NT was also highly pure and could be recycled. In the case of entries 4 and 16, the reaction did not go to completion and only about 80% yield of the carbamate was obtained even after a prolonged reaction time. In these cases, a biphasic system (CH_2Cl_2/5% $NaHCO_3$ (1:1)) was effective (method C), and the reaction was completed within 5 min. Simple phase separation and evaporation afforded highly pure (>99%) carbamates. It is also noteworthy that the reaction of the amino alcohols proceeded without problem, and no carbonate formation or cyclic carbamate formation was observed in any case (entries 13−20).[12] Even though an excess amount of **1** (5 equiv) was used, no carbonate was formed under these conditions. Although the reactions of the propanol amine **6** were slower than those of the other amines, the carbamates **11a**−**d** were obtained in excellent yield.

Next, the reactions of aromatic amines were also investigated (Table 3). In contrast to aliphatic amines, aromatic amines were less reactive, and the reaction did not go to completion under the conditions described above. However, the addition of Et_3N was found to be effective to promote the reactions. With 2 equiv of **1a** or **1d** in the presence of Et_3N (5 equiv), the reactions were completed within 15 min, and the carbamates **12a** and **12d** were obtained in excellent yield after chromatographic purification (entries 1 and 4). In the case of the reaction with Troc-NT, 1 equiv of **1b** and Et_3N (2 equiv) was sufficient, and highly pure **12b** was obtained by simple extraction with 5% $NaHCO_3$ (entry 2). Reaction with the Fmoc-NT (**1c**) in the presence of Et_3N was found to be problematic because the Fmoc group can be decomposed under basic conditions. The reaction of aniline with **1c** in the absence of base was slow, and the yield of **12c** was only 68% even after 24 h (entry 3).

Table 3. Reactions of **1a**−**d** with Aromatic Amines



entry	**1** (equiv)	R^1	time	additive (equiv)	product	yield (%)
1	**1a** (2)	H	15 min	Et_3N (5)	**12a**	87
2[a]	**1b** (1)	H	15 min	Et_3N (2)	**12b**	97
3	**1c** (2)	H	24 h		**12c**	68
4	**1d** (2)	H	60 min	Et_3N (5)	**12d**	94
5	**1b** (2)	PhS	20 h		**13b**	83

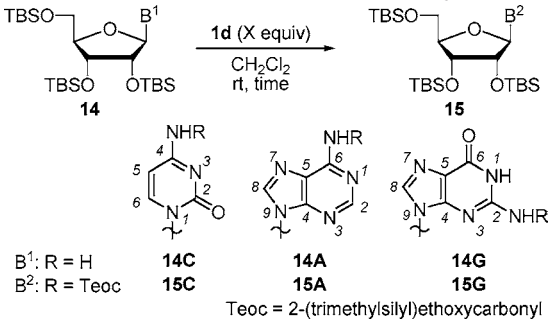
[a] Washing with 5% $NaHCO_3$ is sufficient purification.

Protection of the exocyclic amino group of nucleobases is very important for the efficient synthesis of oligonucleotides and many other biologically important nucleic acid derivatives. Carbamates are attractive protecting groups for nucleobases, but protection using chloroformates is troublesome in some cases, and many reagents for the introduction of carbamate protecting groups into nucleobases have been actively investigated to overcome this problem.[3,13] The choice of appropriate protecting groups is sometimes crucial to successful synthesis of oligonucleotides. Protecting groups which can be cleaved under neutral conditions should be useful for the synthesis of various base-sensitive oligonucleotide derivatives.[14−18] Among them, fluoride ion labile protecting groups such as 2-(trimethylsilyl)ethoxycarbonyl (Teoc)[19] are expected to be particularly useful. As far as we know, however, introduction of the Teoc group at 2-NH_2 of

(19) (a) Kozyukov, V. P.; Sheludyakov, V. D.; Mironov, V. F. *J. Gen. Chem. USSR* **1968**, *38*, 1133−1138. (b) Carpino, L. A.; Tsao, J.-H.; Ringsdorf, H.; Fell, E.; Hettrich, G. *Chem. Commun.* **1978**, 358−359. (c) Campbell, A. L.; Pilipauskas, D. R.; Khanna, I. K.; Rhodes, R. A. *Tetrahedron Lett.* **1987**, *28*, 2331−2334.

guanosine and 2′-deoxyguanosine derivatives has not been reported to date, though 6-*N*-{2-(trimethylsilyl)-ethoxycarbonyl}adenosine and 4-*N*-{2-(trimethylsilyl)-ethoxycarbonyl}cytidine derivatives and their 2′-deoxy counterparts have been obtained (in good to moderate yield).[8] One reason for this may be the instability of Teoc-Cl,[8,19] and therefore, we decided to examine the reaction of our new reagent Teoc-NT (**1d**) with nucleobases (Table 4).

Table 4. Protection of Nucleobases with Teoc by Use of **1d**



entry	substrate	X	time (h)	product	yield (%)
1	**14C**	2	1	**15C**	quant
2	**14A**	4	12	**15A**	98
3[a]	**14G**	4	4	**15G**	80

[a] Et_3N (10 equiv) was added in the reaction mixture.

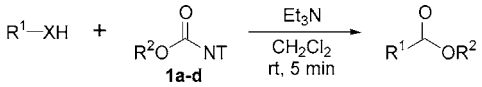
Reaction of the cytidine derivative **14C** with **1d** (2 equiv) proceeded smoothly in the absence of base, and the Teoc group was cleanly introduced onto the 4-NH_2 group to afford **15C** in quantitative yield. Selective introduction of the Teoc group at the 6-NH_2 group of the adenosine derivative **14A** was also successful. Unfortunately, reaction of the guanosine derivative **14G** with **1d** in the absence of base did not proceed. However, we were pleased to find that reaction in the presence of Et_3N (10 equiv) at room temperature proceeded smoothly to give the desired product having a Teoc group on 2-NH_2 of the guanosine derivative **15G** in good yield (Table 4, entry 3).

The mild fluoride ion assisted removal of the Teoc group from the exocyclic amino functionality of nucleobases[20] will be of great value for the synthesis of base-labile nucleotide analogues.

Finally, reactions of **1** with alcohols and thiols were investigated (Table 5). As mentioned above, **1** did not react with alcohols (Table 2, entries 13−20) in the absence of base; however, the reaction of benzyl alcohol **16** with **1a**, **1b**, and **1d** in the presence of Et_3N proceeded smoothly to afford the carbonates **20a**, **20b**, and **20d** in excellent yields (entries 1−3). Even the secondary alcohol **17** reacted with

(20) Protection of the base moiety of uridine is not necessary for the amidite method, which is generally employed for the synthesis of oligoribonucleotides.

Table 5. Synthesis of Carbonates and Thiocarbonates of Alcohols and Thiols



entry	reagent	R^1-XH	product	yield (%)
1[a]	**1a**	 **16**	**20a**	98
2[a]	**1b**		**20b**	96
3[a]	**1d**		**20d**	92
4[b,c]	**1a**	 **17**	**21a**	95
5[b]	**1b**		**21b**	96
6[b,c]	**1d**		**21d**	97
7[a]	**1b**	*p*-MeO-C_6H_4-SH **18**	**22b**	quant
8[a]	**1b**	$CH_3CH_2CH_2SH$ **19**	**23b**	94

[a] Conditions: **1** (1 equiv), Et_3N (2 equiv), yield after washing with 5% $NaHCO_3$. [b] Conditions: **1** (2 equiv), Et_3N (5 equiv), yield after column chromatography. [c] Reaction time: 1 h.

1 without problem to give the desired carbonates **21a**, **21b**, and **21d** in excellent yields (entries 4−6). Similarly, aromatic and aliphatic thiols **18** and **19** also reacted with **1b** to give the desired thiocarbonates **22b** and **23b** in the presence of Et_3N (entries 7 and 8).

In conclusion, convenient methods for the preparation of carbamates, carbonates, and thiocarbonates using the new reagents **1a**−**d** were developed. These reagents have the following advantages: (1) they are highly stable and can be stored for long periods without decomposition; (2) since they are nonhygroscopic crystalline materials, they are easy to handle and weigh accurately even on a milligram scale; (3) the reactions can be carried out even in an open flask; (4) the co-product NT can be recycled; (5) generally, carbamate formation proceeds quickly (within 5 min) under neutral conditions; (6) in most cases, highly pure carbamates were obtained without tedious column chromatographic purification.

In addition to Z-, Troc-, Fmoc-, and Teoc-NT, other alkoxycarbonyl-NT derivatives should be similarly obtainable and may be good alternatives to the existing reagents. New reagents of this type should be especially useful for the synthesis of various functionalized compounds that are difficult to access by conventional methods.

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Supporting Information Available: Experimental details and spectroscopic characterization of synthetic compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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