Trapping of Isocyanates with Benzotriazole in situ – Preparation of Carbamoyl Benzotriazoles as an Isocyanate Alternative via Curtius Rearrangement

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Abstract: *N*-Aryl and *N*-alkenyl carbamoyl benzotriazoles were prepared in good to excellent yields from acyl azides and benzotriazole via Curtius rearrangement, while *N*-alkylcarbamoyl benzotriazoles were formed from *N*-alkanoyl benzotriazoles and sodium azide in one pot. The carbamoyl benzotriazoles can be used as a stable isocyanate alternative, as has been demonstrated by its reaction with amines to synthesize ureas in excellent yields.

Key words: carbamoyl benzotriazoles, isocyanate alternative, acyl azides, Curtius rearrangement, ureas

Curtius rearrangement, where acyl azides undergo thermal rearrangement to form isocyanates, has proven itself to be a versatile and important transformation in organic synthesis. However, since isocyanates are reactive compounds that cannot always be subjected to chromatography, the trapping of isocyanate with various reagents in order to prepare an intermediate has drawn attention in recent years. The intermediate should function as an isocyanate alternative and could be used conveniently for further transformation into amines, ureas, heterocyclic compounds or other target molecules. Sunami reported the trapping of isocyanates with resin-bound alcohols after the Curtius rearrangement.[1] Migawa found a more general procedure whereby the isocyanates could be generated and subsequently trapped using amine-bound resins.[2] Trapping of isocyanates with azide could also be performed to form carbamoyl azides.[3] Although carbamoyl azides can be used to produce amines, carbamates or ureas smoothly, they are potentially explosive compounds[4] and should be handled with care. In addition, carbamoyl azides are sensitive to heat and to both acidic and basic conditions. Therefore, it is still desirable to trap isocyanate in its more stable form but at the same time keeping good reactivity. Herein, we wish to report the preparation of a broad spectrum of carbamoyl benzotriazoles via trapping of isocyanate with benzotriazole in situ.

Benzotriazole is a useful auxiliary in organic synthesis and a great number of its derivatives have proven to be stable and crystalline and showed moderate to good reactivity.[5] Among the benzotriazole derivatives, acyl benzotriazoles, which are readily available either from carboxylic acids, benzotriazole and thionyl chloride[6a] or from carboxylic acids and *N*-(1-methanesulfonyl)benzotriazole,[6b] have gained much attention[6c] in recent years as stable alternatives to acyl chlorides. However, carbamoyl benzotriazole has received much less attention. Carbamoyl benzotriazoles have been prepared by di(benzotriazol-1-yl)methanone and an amine,[7] but the disadvantages are obvious: 1) the preparation of di(benzotriazol-1-yl)methanone uses phosgene, which is highly toxic and requires care in handling; 2) carbamoyl benzotriazoles with *N*-alkenyl substitution could not be prepared due to the instability of ketenamines. It was also reported that isocyanate could react with benzotriazole to afford carbamoyl benzotriazoles,[8] however, only very limited examples were given and their potential use was not explored. Very recently,[9] several carbamoyl benzotriazoles were synthesized from 1,2-diaminobenzene in two steps by diazotization of the key intermediate *o*-aminophenylurea. The overall yields were not high due to the need to isolate the intermediates and the relatively low efficiency of the diazotization.

Herein, we wish to disclose a new process involving a one-pot reaction of aroyl azides or α,β-unsaturated acyl azides with benzotriazole to form the *N*-aryl and *N*-alkenyl carbamoyl benzotriazoles in good to excellent yields. Furthermore, the synthesis of the *N*-alkyl carbamoyl benzotriazoles was successfully achieved via the one-pot reaction of *N*-alkanoyl benzotriazoles and sodium azide.

We first chose benzoyl azide **1a** as a model substrate, and its reaction with benzotriazole was carried out in toluene at 70–80 °C. After completion of the reaction, carbamoyl benzotriazole **2a** precipitated out from the cold toluene. Its structure was ascertained by ^{1}H NMR, ^{13}C NMR, IR, MS and elemental analysis.

To explore the generality of the reaction, a variety of aroyl azides and cinnamoyl azides, which were prepared according to literature procedures,[10] were subjected to the same reaction conditions (Scheme 1). Except for *p*-nitrobenzoyl azide (Table 1, entry 5), all the aroyl and cinnamoyl azides examined afforded the expected carbamoyl benzotriazoles in good to excellent yields (Table 1). Crotonoyl azide also gave moderate yield of the desired product (Table 1, entry 11).

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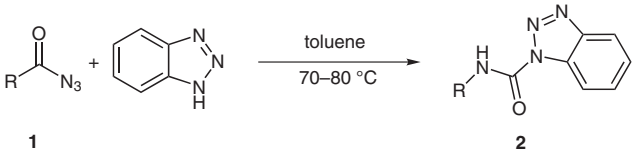
Table 1 Synthesis of *N*-Aryl and *N*-Alkenyl Carbamoyl Benzotriazoles[11] from Aroyl Azides and α,β-Unsaturated Acyl Azides

Entry	Benzotriazole **1** (R)		Time (h)	Product	Mp (Lit °C)	Yield (%)[a]
1	**1a**	Ph	1	**2a**	141–143 (138–140)[9]	74.5
2	**1b**	4-MeC_6H_4	1	**2b**	169–172	88.4
3	**1c**	4-$MeOC_6H_4$	0.75	**2c**	152–154	94.5
4	**1d**	4-ClC_6H_4	0.75	**2d**	188–191	94.5
5	**1e**	4-$O_2NC_6H_4$	2	**2e**	–	n.r.[b]
6	**1f**	4-IC_6H_4	1	**2f**	202–204	92.2
7	**1g**	PhCH=CH	1	**2g**	192–194	67.8
8	**1h**	4-MeC_6H_4CH=CH	1	**2h**	181–183	84.5
9	**1i**	4-$MeOC_6H_4CH$=CH	1	**2i**	179–181	89.5
10	**1j**	4-ClC_6H_4CH=CH	1	**2j**	209–211	87.2
11	**1k**	MeCH=CH	1	**2k**	135–138	61.8

[a] Isolated yield based on *N*-acyl azides.
[b] No reaction.

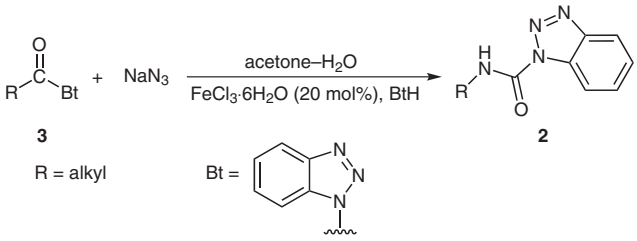


Scheme 1

Since pure alkanoyl azides are not readily available due to their low stability, we therefore turned our attention to the synthesis of *N*-alkyl carbamoyl benzotriazoles through an alternative approach.

In our previous studies on the synthesis of acyl azides by acylation of sodium azide with acyl benzotriazoles, we observed that, in a mixed solvent of acetone and water, the reaction did occur, but did not proceed rapidly at room temperature. Raising the temperature to 32–40 °C resulted in decomposition of the alkanoyl azides. Unexpectedly, during the decomposition of the acyl azides, *N*-alkylcarbamoyl benzotriazoles were isolated in 30–46% yields. In light of this finding, we attempted to improve the yields of the *N*-alkylcarbamoyl benzotriazoles by addition of $FeCl_3{\cdot}6H_2O$ as a catalyst, together with a two-fold increase in the amount of benzotriazole. To our delight, the *N*-alkylcarbamoyl benzotriazoles were thus prepared in good yields (Scheme 2 and Table 2). The method was compatible with the presence of a methoxy functionality (Table 2, entry 4); however, when a chloro group was present in the alkyl R, the reaction failed to afford the expected product, with only a complex mixture being obtained.

The formation of *N*-alkylcarbamoyl benzotriazoles **2l–o** could be explained as follows: 1) *N*-alkanoyl benzotriazoles acylated sodium azide to form alkanoyl azides whilst the benzotriazole anion was liberated; 2) alkanoyl azides



Scheme 2

Table 2 Synthesis of *N*-Alkylcarbamoyl Benzotriazoles[12] from Alkanoyl Benzotriazoles and Sodium Azide[a]

Entry	Benzotriazole **3** (R)		Temp (°C)	Product	Mp (°C)	Yield (%)[b]
1	**3a**	Et	32	**2l**	88–90	72.3
2	**3b**	*n*-Pr	40	**2m**	58–59	70.1
3	**3c**	*n*-Hex	40	**2n**	44–45	71.7
4	**3d**	$MeOCH_2$	40	**2o**	90–92	68.2
5	**3e**	$ClCH_2$	45	**2p**	–	–[c]

[a] Reaction time: 3 h.
[b] Isolated yield based on *N*-acylbenzotriazoles.
[c] Not isolated.

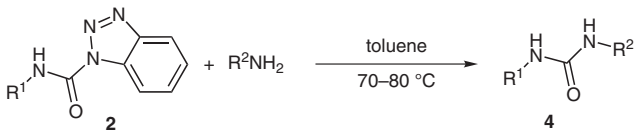
underwent the Curtius rearrangement at 32–40 °C to form the isocyanate; 3) the benzotriazole anion present in the system then attacks the isocyanates, thus affording the carbamoyl benzotriazoles. Isocyanates have been reported to be very reactive and the presence of water may result in unwanted side reactions. It is noteworthy that, under the present conditions, the benzotriazole anion competes with H_2O, which could trap the formed isocyanate in situ.

Table 3 Synthesis of Ureas[14] from Carbamoyl Benzotriazoles and Amines

Entry	Benzotriazole (R^1)		Amine (R^2)	Time (h)	Product	Mp (Lit. °C)	Yields (%)[a]
1	**2a**	Ph	4-MeC_6H_4	0.5	**4a**	217–219 (219–220)[15]	93.5
2	**2a**	Ph	*n*-Bu	0.5	**4b**	133–135 (135)[16]	94.3
3	**2h**	4-MeC_6H_4CH=CH	4-MeC_6H_4	0.5	**4c**	220–222 (219)[17]	81.2
4	**3a**	$MeCH_2$	*n*-Bu	1	**4d**	58–59 (57–58)[18]	91.6
5	**3a**	$MeCH_2$	Bn	2	**4e**	101–102 (103–104)[19]	89.4
6	**3a**	$MeCH_2$	4-MeC_6H_4	12	**4f**	–	n.r.[b]

[a] Isolated yield based on carbamoyl benzotriazoles.
[b] No reaction.

All the carbamoyl benzotriazoles synthesized here were crystalline solids and could be kept in open air at room temperature for several months without any noticeable changes, showing their good stability. Since *N*-acyl benzotriazoles are good acylating agents, the carbamoyl benzotriazoles, which contain the *N*-acyl benzotriazole moiety, are thus promising stable isocyanate alternatives. To demonstrate this point, a variety of amines were reacted with carbamoyl benzotriazoles (Scheme 3). It was interesting to find that both *N*-phenylcarbamoyl benzotriazole and *N*-alkenylcarbamoyl benzotriazole could react with aromatic amines with high efficiency to afford good to excellent yields of the anticipated ureas (Table 3, entries 1 and 3), however, *N*-alkylcarbamoyl benzotriazole **3a** was unreactive to aromatic amine (Table 3, entry 6), thus displaying less reactivity than its *N*-aryl counterparts and *N*-alkylcarbamoyl azides.[13] Nevertheless, **3a** reacted with aliphatic amines smoothly and the corresponding ureas were prepared in excellent yields (Table 2, entries 4 and 5). The ability of *N*-alkylcarbamoyl benzotriazole to distinguish between aliphatic and aromatic amines may be useful in selective formation of a specific urea moiety when a substrate with multiple amino groups is used.



Scheme 3

In conclusion, a variety of N-substituted carbamoyl benzotriazoles were prepared by Curtius rearrangement via trapping of isocyanates with benzotriazole in situ. The potential of the carbamoyl benzotriazoles to act as stable isocyanate alternatives has been demonstrated in part in the synthesis of ureas.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(11) **General Procedure for the Preparation of *N*-Aryl and *N*-Alkenyl Carbamoyl Benzotriazoles 2a–k**: To the aroyl azide **1** (1 mmol) in toluene (3 mL), was added benzotriazole (1.1 mmol, 0.31 g). The mixture was stirred at 70–80 °C for the time indicated in Table 1 (reaction monitored by TLC). After cooling, the crude product precipitated out and was washed with cold EtOH to give pure *N*-aryl or *N*-alkenyl carbamoyl benzotriazoles **2a–k**.
(12) **General Procedure for the Preparation of *N*-Alkyl-carbamoyl Benzotriazoles 2l–o**: To *N*-alkanoyl benzotriazole **3** (1 mmol) in acetone (3 mL), was added a fresh solution of NaN_3 (3 mmol) dissolved in H_2O (2 mL), and $FeCl_3 \cdot 6H_2O$ (0.2 mmol, 54.1 mg). The mixture was

stirred at room temperature for 5 min, until the complete conversion of *N*-alkanoyl benzotriazole was observed (monitored by TLC). Additional benzotriazole (2 mmol, 0.238 g) was added and the reaction mixture was heated gently at 32–40 °C for the time indicated in Table 2. After being extracted with Et_2O (3 × 10 mL), the organic layer was washed successively with sat. Na_2CO_3 and brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Purification by flash column chromatography [petroleum ether (60–90)–EtOAc, 8:1] gave pure *N*-alkylcarbamoyl benzotriazoles **2l–o**.

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(14) **General Procedure for the Preparation of Ureas 4a–e**: The amine (1.1 mmol) was stirred with N-substituted carbamoyl benzotriazole **2** (1 mmol) in toluene (5 mL) at 70–80 °C for 0.5 h (reaction monitored by TLC). After cooling, the solid precipitated out and was washed with cold EtOH to give pure ureas **4a–e**.

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