Monatsh Chem
DOI 10.1007/s00706-014-1408-1

ORIGINAL PAPER

Facile synthesis of *N*-acylbenzotriazoles from carboxylic acids mediated by 2,4,6-trichloro-1,3,5-triazine and triethylamine

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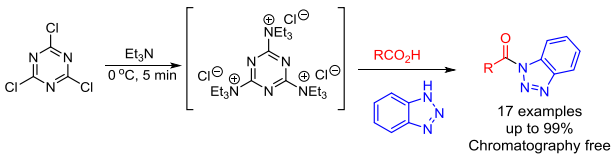
Received: 19 December 2014 / Accepted: 28 December 2014

Abstract A facile, efficient, and economic method toward *N*-acylbenzotriazoles was reported using 2,4,6-trichloro-1,3,5-triazine in combination with triethylamine as a carboxylic acid activator. Through reacting 1*H*-benzotriazole with the generated triacylated triazine intermediate, a series of *N*-acylbenzotriazoles could be rapidly prepared in high yields without column chromatography.

Graphical abstract



Keywords *N*-Acylbenzotriazole · Cyanuric chloride · Carboxylic acid · Benzotriazole · Acid activation

Introduction

N-Acylbenzotriazoles are versatile acylating agents in a number of organic transformations [1–15]. Various important classes of compounds, such as amides, peptides, esters, and diketones could be prepared through the N-, C-, S-, and O-acylations under relatively neutral and mild conditions. Surprisingly, despite being synthetically useful, only a limited number of methods have been developed for *N*-acylbenzotriazoles preparation. In the classical method involved reacting acid chlorides with 1*H*-benzotriazole (BtH) or its derivatives [9], the requisite acid chlorides need to be prepared and isolated in a separate step. Although direct conversion of carboxylic acids into their benzotriazole derivatives could be performed either by reacting a carboxylate salt with sulfonylbenzotriazole derivatives [16] or through treatment of carboxylic acids with thionyl chloride and an excessive amount of BtH [17], the reactions still suffer from some of these limitations including the use of corrosive or expensive reagents, long reaction times, high reaction temperatures, and complicated product isolation which make scaling up more difficult.

In continuation of our efforts to develop facile, economical, and efficient synthesis methods toward *N*-acylbenzotriazoles [18], 2,4,6-trichloro-1,3,5-triazine (TCT) is considered highly attractive as an alternative acid activator due to its inexpensiveness, readily availability, and high reactivity [19, 20]. Most often, TCT has been used in combination with tertiary amines, especially *N*-methylmorpholine (NMM) to provide reactive *N*-triazinylmorpholinium species before subsequent displacement with a carboxylate ion. The formed acylated triazine active ester then acts as an acylating agent in the acyl transfer process.

Generally, the acid activation step was carried out using a 1:1:1 ratio of TCT/NMM/carboxylic acid at low temperature (0–5 °C) to avoid decomposition of the reactive intermediates. Indeed, it has recently been shown that

Electronic supplementary material The online version of this article (doi:10.1007/s00706-014-1408-1) contains supplementary material, which is available to authorized users.

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Published online: 27 January 2015

N-triazinylammonium chlorides rapidly underwent dealkylation via an attack of a chloride ion on the R group which resulted in the reagent deactivation toward nucleophilic substitution [21]. Since the methyl group was more prone to dealkylation than other alkyl groups, it was thus envisioned that by replacing NMM with other tertiary amines having no methyl group, a sub-stoichiometric amount of TCT could be used while the formed quaternary *N*-triazinylammonium salt would be more stable to allow effective acid activation. Herein, we wish to report the use of TCT in combination with triethylamine in the direct conversion of carboxylic acids into *N*-acylbenzotriazoles (Scheme 1). Since the generated cyanuric acid, the remaining Et_3N, and its hydrochloride salt are all water soluble, the products could simply be isolated by simple aqueous work up without need of column chromatography.

Results and discussion

In our preliminary studies, the role of tertiary amine base in TCT activation has been investigated in the synthesis of the benzotriazole derivative of cinnamic acid as a model reaction. A 1:1:1.2 mol ratio of TCT/carboxylic acid/base was used at this stage for the ease of comparison assuming that only one chlorine atom of TCT forms a monoacyloxy-1,3,5-triazine derivative. Typically, TCT in dichloromethane was added with tertiary amine at 0 °C for 5 min prior to addition of the acid. After stirring at 0 °C for 10 min, BtH (1 equiv) was then added and the reaction was stirred at 25 °C for 30 min. According to Table 1, triethylamine gave the best yield of the product in comparison to other tested amines (entries 1–5). No Michael addition-side product or diastereomerization was observed. The low yield in the case of diisopropylethylamine was presumably due to the low reactivity of this non-nucleophilic base (entry 1). When using NMM, pyridine, and 4-dimethylaminopyridine (DMAP) (entries 3–5), the reaction gave complex mixtures with only a trace amount of the desired product suggesting these bases were incompetent under the applied reaction conditions. To our delight, it was found that the reaction could also be successfully performed using 0.4 equiv of TCT per mole of the carboxylic acid (entry 6) implying that the reaction proceeded via the proposed triacyloxy-1,3,5-triazine. It is noted that based on the reaction shown in Scheme 1, the mole ratio of TCT to carboxylic acid should be 0.33:1. However, since TCT is readily hydrolyzed under storage, a slight excess of TCT was used to compensate for the presence of cyanuric acid in TCT. In a control experiment when the reaction was carried out by adding Et_3N after cinnamic acid, the yield of the product dropped to 36 % implying the role of Et_3N in promoting formation of an active ester **II** through quaternary *N*-triazinyltriethylaminium chloride **I** (Scheme 1).

We next explored the scope and limitations of the method in the preparation of a series of *N*-acylbenzotriazoles using aromatic and aliphatic carboxylic acids. As shown in Table 2, most of the tested substrates could be efficiently converted into the corresponding *N*-acylbenzotriazoles in good to excellent yields within short reaction times. Benzoic acid and its electron-rich derivatives reacted more efficiently than the electron-deficient ones (entries 1–5 vs. entries 6–11). Only in the case of 2-methoxybenzoic acid (entry 5), a slightly lower yield of the product was

Scheme 1

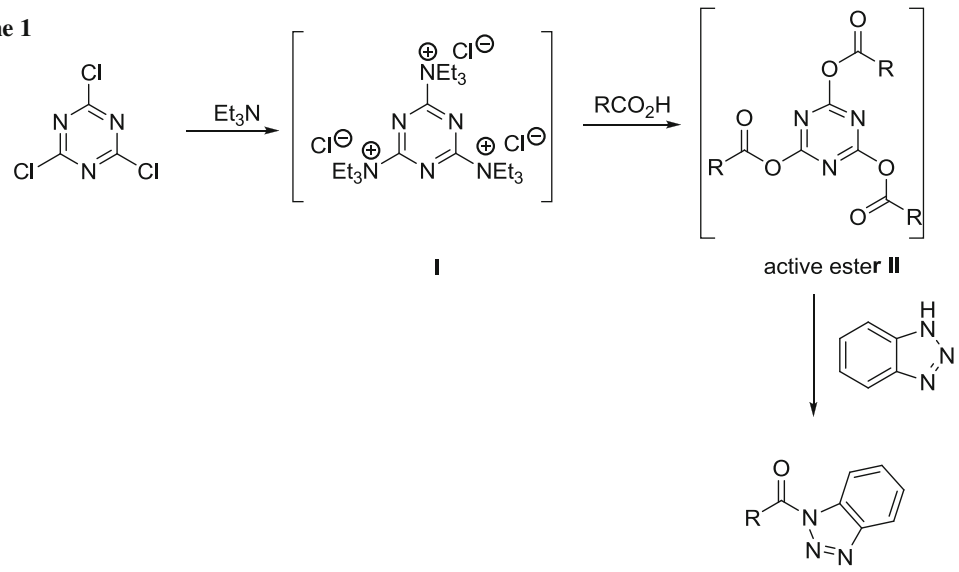
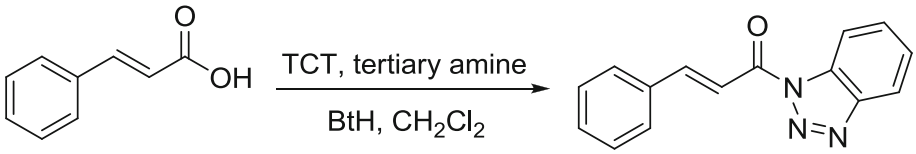


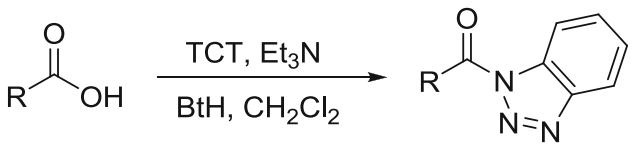
Table 1 Optimization of the reaction conditions



Entry	TCT/equiv	Amine base	Yield/%
1	1	*i*-Pr_2NEt	27
2	1	Et_3N	82
3	1	NMM	Trace
4	1	Pyridine	Trace
5	1	DMAP	Trace
6	0.4	Et_3N	84

A solution of TCT in 2 cm^3 CH_2Cl_2 was added with amine base (0.325 mmol) at 0 °C and stirred for 5 min. After adding carboxylic acid (0.271 mmol) and stirred for 10 min, BtH (0.271 mmol) was added, and the reaction mixture was stirred at 25 °C for 30 min

Table 2 Synthesis of *N*-acylbenzotriazoles promoted by TCT-Et_3N system



Entry	R	Time[a]/min	Isolated yield/%	Reference
1	C_6H_5	10	98	[22]
2	4-$CH_3C_6H_4$	10	96	[22]
3	4-$CH_3OC_6H_4$	10	94	[23]
4	3,4-$(CH_3O)_2C_6H_3$	15	98	[24]
5	2-$CH_3OC_6H_4$	30	70	[16]
6	2-IC_6H_4	30	68	[25]
7	2-ClC_6H_4	15	87	[7]
8	3-ClC_6H_4	15	89	[16]
9	4-ClC_6H_4	15	98	[16]
10	3-$NO_2C_6H_4$	60	70	[14]
11[b]	4-$NO_2C_6H_4$	120	12	[16]
12	1-Naphthyl	30	75	[26]
13	2-Naphthyl	30	70	[16]
14	Cinnamyl	30	84	[27]
15[b]	Hexanoyl	60	84	[28]
16[b]	Octanoyl	60	90	[29]
17[b]	5-Phenylvaleryl	60	74	[18]

The reaction was carried out using TCT (0.130 mmol), Et_3N (0.325 mmol), carboxylic acid (0.271 mmol), and BtH (0.271 mmol)

[a] Time after adding BtH

[b] Acid activation time was prolonged for 30 min before addition of BtH

observed, possibly due to steric hindrance of the –OMe group at the *ortho* position. Although halogen substituents on the aromatic ring did not significantly affect the reaction times and yields (entries 6–9), the strong electron-withdrawing NO_2 group dramatically reduced the product yields, especially when it was present at the *para* position (entries 10, 11).

The reaction with relatively steric hindered 1- and 2-naphthoic acids as well as α,β-unsaturated cinnamic acid (entries 12–14) proceeded smoothly without any side reactions. However, aliphatic acids including hexanoic acid, octanoic acid, and 5-phenylvaleric acid (entries 15–17) were less reactive compared with aromatic acids and both the acid activation and the reaction times needed to be prolong to give the corresponding *N*-acylbenzotriazoles in good to high yields.

To demonstrate the practical utility of the established method, the reaction of 4-chlorobenzoic acid with BtH was performed in a larger scale using 10 mmol of the acid. Upon 5 min activation of TCT with Et_3N and 15 min reaction time with BtH, the expected product was obtained in quantitative yield with high purity (based on ^{1}H NMR) after simple aqueous work up without column chromatography.

It is important to note that although there have been some reports on the formation of acid chlorides using a combination of TCT with tertiary amine bases [30–32], in our study, we did not observe formation of acid chlorides after acid activation at low temperature based on TLC which was in accordance with other studies using TCT in amide bond formation [33–36]. Nevertheless, attempts to isolate the formed intermediate led to rapid decomposition due to its high reactivity [20]. Thus, at this point, we can only assume that triacyloxy-1,3,5-triazine was being generated before reacting with BtH.

Conclusion

In conclusion, a facile, efficient, and economic protocol for the direct conversion of carboxylic acids into *N*-acylbenzotriazoles was developed using TCT-Et_3N as the promoter. The reaction was not only very rapid, but also used less than a stoichiometric amount of TCT, which minimizes the reagent utilization and waste generation. In addition, the ease of product isolation makes this method viable for the synthesis of *N*-acylbenzotriazoles.

Experimental

All reagents were purchased from Sigma-Aldrich Co., USA, and were used without further purification. Thin-layer chromatography was carried out on silica gel plates ($60F_{254}$, MERCK, Germany) and visualized under UV light (245 nm). Melting points were determined using SANYO, Gallenkamp apparatus at a heating rate of 10 °C/min. NMR measurements were conducted on a Bruker AVANCE^{TM} (400 MHz for ^{1}H) using tetramethylsilane (TMS) as an internal standard. Chemical shifts were reported in parts per million (δ/ppm) downfield from TMS. Splitting patterns are described as singlet (s), doublet (d), triplet (t), multiplet (m), doublet of doublet (dd), and triplet of doublet (td). High resolution mass spectrometry (HRMS) was performed with a MicroTOFLC (Bruker Daltonics).

General procedure for synthesis of N-acylbenzotriazoles

To a solution of 0.024 g TCT (0.130 mmol) in 2 cm^3 CH_2Cl_2 was added 0.033 g triethylamine (0.325 mmol) at 0 °C and the resulting mixture was stirred for 5 min. Carboxylic acid (0.271 mmol) was then added with continuously stirring for 10 min. Subsequently, to this mixture was added 0.032 g 1*H*-benzotriazole (0.271 mmol) and the solution was allowed to warm up to room temperature and stirred until completion of the reaction based on TLC analysis. The crude reaction mixture was extracted with saturated $NaHCO_3$, then washed with 1 M HCl and water. The combined organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure to afford the product. All known products were characterized by ^{1}H and ^{13}C NMR and their spectroscopic data were consistent with those reported in literature.

Acknowledgments The Center of Excellence for Innovation in Chemistry (PERCH-CIC), and the National Research University Project under Thailand's Office of the Higher Education Commission are gratefully acknowledged for financial support.

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