TCT-mediated synthesis of *N*-acylbenzotriazoles in aqueous media

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TCT-mediated synthesis of *N*-acylbenzotriazoles in aqueous media

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Abstract

The synthesis of *N*-acylbenzotriazoles has been demonstrated by the 2,4,6-trichloro-1,3,5-triazine (TCT)-mediated condensation of carboxylic acids with 1*H*-benzotriazole in aqueous media. In saturated aqueous sodium bicarbonate, TCT was found to be relatively stable and functioned as an efficient acid activator in the acyl transfer process. This operationally simple and economic method allows the scalable synthesis of *N*-acylbenzotriazoles in good to excellent yields.

Keywords cyanuric chloride; aqueous; *N*-acylbenzotriazoles; carboxylic acids

Introduction

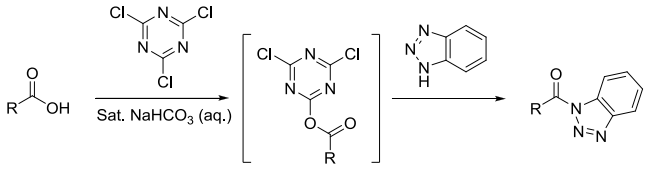
In the recent years, considerable attention has been directed toward the use of water as a media in organic synthesis due to it being inexpensive, readily available, nontoxic, and non-inflammable.[1] Additionally, the ability to a form hydrogen bonding network, high surface tension, high heat capacity, and large dielectric constant have often been shown to enhance reactions rate and selectivity.[2] Thus, the development of new aqueous-mediated processes are of great benefit in terms of safety, handling simplicity, as well as reaction outcomes that may not be readily achieved with organic solvents.

N-Acylbenzotriazoles are neutral acylating agents which have been applied as acid chloride replacements in a number of organic transformations, including the synthesis of diketones,[3] amides or peptides,[4] oxazolines,[5] and thiazoline.[5] Unlike acid chlorides which are unstable or difficult to isolate, *N*-acylbenzotriazoles are stable solids that can be kept at room temperature without decomposition.[6] Acylation reactions using these benzotriazole derivatives have also been shown to give high yields and high regiospecificity without racemization.

Despite their distinct synthetic advantages, methods aimed toward the synthesis of *N*-acylbenzotriazoles are rather limited. The classical procedure involves treatment of acid chlorides with 1*H*-benzotriazole (BtH) or its derivatives.[6c] However, an additional step is needed for the formation of the requisite acid chlorides. A more convenient and straightforward method is *via* the *in situ* generation of the activated acid-derivative for the reaction with BtH. Different systems such as $SOCl_2$ with excess BtH,[6] PPh_3/I_2,[7] and 2,4,6-trichloro-1,3,5-triazine (TCT)/Et_3N[8] have been shown to effectively convert various carboxylic acids into their benzotriazole derivatives. Nevertheless, these reactions were carried out in harmful organic solvents which require drying of solvents and/or reactants prior use.

Among the known acid activating systems for the preparation of amides,[9] TCT is considered highly attractive in terms of its low cost, stability, and availability.[10] This reagent is generally employed in organic solvents in the presence of organic tertiary amine bases.[11] To the best of our knowledge, TCT mediated acid activation in water has only been described in one study that reported the use of TCT in 4:1 acetonitrile-water.[11d] In a continuation of our interest in reactions promoted by TCT, herein, we report the TCT-mediated condensation of carboxylic

acids with BtH in aqueous media as a facile and economic procedure for the preparation of *N*-acylbenzotriazoles (Scheme 1).



Scheme 1. TCT-mediated condensation of carboxylic acids with BtH in aqueous media.

Results and discussion

To successfully perform the condensation reaction in water, there are various factors that must be considered. Firstly, the reactants need to be soluble in the reaction media, while TCT should selectively react with the carboxyl group rather than with water, to give an activated acid-derivative in the first activation step. Secondly, in the acyl transfer process, the activated acid must be preferentially react with BtH in order to give the desired *N*-acylbenzotriazole faster than its solvolysis. Finally, the formed *N*-acylbenzotriazole should be stable enough to survive the aqueous conditions.

Based on previous studies,[4h-4j] *N*-acylbenzotriazoles have occasionally been used in aqueous reactions and thus should not undergo hydrolysis under weakly basic conditions such as in saturated sodium bicarbonate. Although TCT has a tendency to react with water, at low temperature (*ca.* 0 ^{o}C), TCT is known to be stable for at least 12 h without detectable decomposition.[12] Considering the solubility of all the reactants, both BtH and carboxylic acids are soluble in aqueous basic media. However, TCT exhibits low solubility and thus requires the addition of a small amount of acetone, as well as a surfactant, to facilitate its reaction in water.

In our initial investigation, the condensation between benzoic acid and BtH was carried out by adding a solution of TCT in acetone (0.54 mmol in 1 mL) to a saturated aqueous $NaHCO_3$ solution of the acid (0.54 mmol in 5 mL). The mixture was stirred at 0 ^{o}C for 30 min before treatment with BtH (0.59 mmol), followed by stirring at 25 ^{o}C for 20 min. Without any surfactant, the reaction resulted in low product yield (44%).

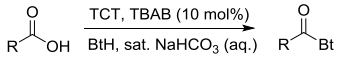
We then screened for a suitable additive using various surfactants including neutral (Triton X100), anionic (SDS), and cationic (tricaprylylmethylammonium chloride) derivatives, as well as phase transfer catalysts. Using 10 mol% of a surfactant (the concentration higher than their critical micelle concentrations in water),[13] the reaction conducted in the presence of Triton X100 gave no conversion, while SDS yielded only 34% of the product, possibly due to excessive bubble formation. Using 10 mol% of tricaprylylmethylammonium chloride gave no bubbles and the product yield was increased to 66%. However, excellent yields (93% and 91%, respectively) were obtained from reactions catalyzed by tetrabutylammonium bromide (TBAB) and tetrabutylammonium chloride (TBAC), respectively, while tetrabutylammonium iodide (TBAI) gave a slightly lower yield (87%). The TBAB-catalyzed reaction was then carried out using 0.66 equiv of TCT per mole of acid which provided the product in a comparative yield (92%). Additionally, decreasing the amount of TCT to 0.33 equiv. gave lower conversion (65%), possibly due to partial hydrolysis of the reagent.

We next investigated the applicability of the method using 0.66 equiv. of TCT and catalytic TBAB using a range of carboxylic acids including aromatic, aliphatic, and α,β-unsaturated acids.[14] As shown in Table 1, benzoic acid and its derivatives bearing electron-donating or withdrawing substituents reacted rapidly within 15-30 min to give the desired products in good to excellent yields (entries 1-10). The presence of a substituent at the *ortho* position lowered the product yields, possibly due to steric hindrance (entries 2, 5, 8). Notably, substrates containing secondary amines were well tolerated under the weakly basic conditions (entries 7,8). Even carboxylic acids with low aqueous solubility such as 1-naphthoic acid and cinnamic acid (entries 11,12), gave the corresponding BtH derivatives in good yields with no Michael addition side reaction or double bond isomerization being observed in the latter case (entry 12). Aliphatic acids containing up to a six-carbon chain were also found to react smoothly (entries 13-18).

To demonstrate the practicality of the developed method, the benzotriazole derivative of benzoic acid was prepared on a multi-gram scale. In the scale-up reaction, it was found that the amidation of 20 mmol of benzoic acid could be carried out using 0.66 equiv of TCT per mole of acid and after 30 min activation time and 30 min reaction time with BtH, *N*-benzoylbenzotriazole

was obtained in 88% yield after extraction with dichloromethane, followed by passing through a short pad of silica.

Table 1. Preparation of *N*-acylbenzotriazoles in aqueous media[a]



entry	R	time (min)	yield (%)
1	C_6H_5	15	94[15]
2	2-$CH_3C_6H_4$	30	65[7]
3	3-$CH_3C_6H_4$	30	89[7]
4	4-$CH_3C_6H_4$	15	87[15]
5	2-$CH_3OC_6H_4$	30	68[16]
6	4-$CH_3OC_6H_4$	15	85[17]
7	3-$(CH_3)_2NC_6H_4$	15	70
8	2-$PhNHC_6H_4$	15	59
9	4-ClC_6H_4	15	87[16]
10	4-$NO_2C_6H_4$	30	81[16]
11	1-naphthyl	15	85[16]
12	cinnamyl	15	90[18]
13	1-napthylacetyl	15	89[19]
14	2-(2-methoxyphenyl)acetyl	15	73[20]
15	2-(2,6-dichlorophenyl)acetyl	15	89
16	5-phenylvaleryl	30	92[7]
17	pentanoyl	15	84[16]
18	hexanoyl	15	90[21]

[a]Reaction conditions: To a sat. aqueous $NaHCO_3$ (5 mL) containing the carboxylic acid (0.54 mmol) was added TBAB (0.054 mmol) then TCT (0.54 mmol) in acetone (1 mL) and stirred for 30 min at 0 ^oC. BtH (0.59 mmol) was added and stirred at 25 ^oC for the specified time.

It is important to note that unlike the previous reports on the TCT-mediated carboxylic acid activation where TCT was used with a tertiary amine base and volatile organic solvent,[11, 12]

this work has demonstrated that TCT could also be effectively applied to reactions in aqueous media using an inexpensive inorganic base. Moreover, since the residual hydroxyl derivatives of TCT and the remaining reactants are all soluble in aqueous base, a simple solvent extraction and filtration was sufficient to provide *N*-acylbenzotriazoles in high purity based on ^{1}H-NMR spectroscopic analysis of the isolated products.

In summary, a practical TCT-mediated condensation of carboxylic acids with BtH in aqueous media was reported. The protocol enabled a range of *N*-acylbenzotriazoles to be synthesized under mild and relatively neutral conditions using inexpensive and easy to handle reagents. The operational simplicity, high product yields, and scalability of the method will be of great benefit and could potentially lead to the development of more economic synthesis of other important carboxylic acid derivatives from water soluble nucleophiles.

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References

(1) (a) Liu, L.; Wang, D. *Handb. Green Chem.* **2010,** *5*, 207-228. (b) Chanda, A.; Fokin, V. V. *Chem. Rev.* **2009,** *109*, 725-748. (c) Cravotto, G.; Borretto, E.; Oliverio, M.; Procopio, A.; Penoni, A. *Catal. Commun.* **2015,** *63*, 2-9. (d) Gawande, M. B.; Bonifacio, V. D. B.; Luque, R.; Branco, P. S.; Varma, R. S. *Chem. Soc. Rev.* **2013,** *42*, 5522-5551. (e) Datta, S.; Sood, A.; Torok, M. *Curr. Org. Synth.* **2011,** *8*, 262-280. (f) Lombardo, M.; Trombini, C. *Curr. Opin. Drug Discovery Dev.* **2010,** *13*, 717-732. (g) Kunishima, M.; Kawachi, C.; Hioki, K.; Terao, K.; Tani, S. *Tetrahedron* **2001,** *57*, 1551-1558.

(2) (a) Kavitha, B. T. V. V.; Ravi Sankar Reddy, D.; Naresh, P. *J. Chem. Pharm. Sci*. **2012,** *5*, 92-97, 96 pp. (b) Fan, X.; He, Y.; Zhang, X.; Wang, J. *Green Chem.* **2014,** *16*, 1393-1398. (c) Tongsakul, D.; Nishimura, S.; Ebitani, K. *ACS Catal.* **2013,** *3*, 2199-2207. (d) Zhu, Q.; Chu, X.; Zhang, Z.; Dai, W.-L.; Fan, K. *RSC Adv.* **2013,** *3*, 1744-1747. (e) Tanaka, A.; Hashimoto, K.; Kominami, H. *J. Am. Chem. Soc*. **2012,** *134*, 14526-14533. (f) Singh, C. B.; Kavala, V.; Samal, A. K.; Patel, B. K. *Eur. J. Org. Chem.* **2007**, 1369-1377. (g) Liang, H.-C.; Das, S. K.; Galvan, J. R.; Sato, S. M.; Zhang, Y.; Zakharov, L. N.; Rheingold, A. L. *Green Chem.* **2005,** *7*, 410-412.

(3) (a) Katritzky, A. R.; Wang, Z.; Wang, M.; Wilkerson, C. R.; Hall, C. D.; Akhmedov, N. G. *J. Org. Chem.* **2004,** *69*, 6617-6622. (b) Katritzky, A. R.; Pastor, A. *J. Org. Chem.* **2000,** *65*, 3679-3682.

(4) (a) Katritzky, A. R.; Gyanda, R.; Meher, N. K.; Song, Y. *Heterocycles* **2009,** *77*, 1249-1259. (b) Katritzky, A. R.; Cai, C.; Singh, S. K. *J. Org. Chem.* **2006,** *71*, 3375-3380. (c) Katritzky, A. R.; Wang, Z.; Wang, M.; Hall, C. D.; Suzuki, K. *J. Org. Chem.* **2005,** *70*, 4854-4856.(d) Katritzky, A. R.; Rogovoy, B. V.; Kirichenko, N.; Vvedensky, V. *Bioorg. Med. Chem. Lett.* **2002,** *12*, 1809-1811. (e) Katritzky, A. R.; Huang, T.-B.; Voronkov, M. V. *J. Org. Chem.* **2001,** *66*, 1043-1045. (f) Katritzky, A. R.; He, H.-Y.; Suzuki, K. *J. Org. Chem.* **2000,** *65*, 8210-8213. (g) Katritzky, A. R.; Suzuki, K.; Singh, S. K. *Synthesis* **2004**, 2645-2652. (h) Avan, I.; Tala, S. R.; Steel, P. J.; Katritzky, A. R. *J. Org. Chem.* **2011,** *76*, 4884-4893. (i) Katritzky, A. R.; Abo-Dya, N. E.; Tala, S. R.; Ghazvini-Zadeh, E. H.; Bajaj, K.; El-Feky, S. A. *Synlett* **2010**, 1337-1340. (j) Katritzky, A. R.; Sakhuja, R.; Khelashvili, L.; Shanab, K. *J. Org. Chem.* **2009,** *74*, 3062-3065.

(5) Katritzky, A. R.; Cai, C.; Suzuki, K.; Singh, S. K. *J. Org. Chem.* **2004,** *69*, 811-814.

(6) (a) Katritzky, A. R.; Zhang, Y.; Singh, S. K. *Synthesis* **2003**, 2795-2798. (b) Katritzky, A. R.; Meher, N. K.; Cai, C.; Singh, S. K. *Rev. Soc. Quim. Mex.* **2004,** *48*, 275-278. (c) Katritzky, A. R.; Suzuki, K.; Wang, Z. *Synlett* **2005**, 1656-1665.
(7) Duangkamol, C.; Wangngae, S.; Pattarawarapan, M.; Phakhodee, W. *Eur. J. Org. Chem.* **2014,** *2014*, 7109-7112.
(8) Wet-osot, S.; Duangkamol, C.; Pattarawarapan, M.; Phakhodee, W. *Monatsh. Chem.* **2015**, *146*, 959-963.
(9) (a) Montalbetti, C. A. G. N.; Falque, V. *Tetrahedron* **2005,** *61*, 10827-10852. (b) Valeur, E.; Bradley, M. *Chem. Soc. Rev.* **2009,** *38*, 606-631.
(10) (a) Blotny, G. *Tetrahedron* **2006,** *62*, 9507-9522. (b) Kaminski, Z. J. *Biopolymers* **2000,** *55*, 140-164.
(11) (a) Bandgar, B.; Sawant, S. *Synth. Commun.* **2006,** *36*, 859-864. (b) Giacomelli, G.; Porcheddu, A.; de Luca, L. *Curr. Org. Chem.* **2004,** *8*, 1497-1519. (c) de Luca, L.; Giacomelli, G.; Taddei, M. *J. Org. Chem.* **2001,** *66*, 2534-2537. (d) Rayle, H. L.; Fellmeth, L. *Org. Process Res. Dev.* **1999,** *3*, 172-176. (e) Venkataraman, K.; Wagle, D. R. *Tetrahedron Lett.* **1979**, 3037-3040.
(12) Fierz-David, H. E.; Matter, M. *J. Soc. Dyers Colour.* **1937,** *53*, 424-436.
(13) Wu, C.; Li, N. J.; Chen, K. C.; Hsu, H.-F. *Res. Chem. Intermed.* **2014,** *40*, 2371-2379.
(14) General procedure: to a solution of saturated aqueous $NaHCO_3$ (5 mL) containing the carboxylic acid (0.54 mmol) was added TBAB (0.054 mmol) followed by a solution of TCT (0.36 mmol) in acetone (1 mL) and stirred for 30 min at 0 ^oC. BtH (0.59 mmol) was then added to the white turbid solution, followed by stirring at 25 ^oC for the specified time. The crude reaction mixture was washed with CH_2Cl_2. The combined organic layers were dried over anhydrous Na_2SO_4, filtered through a short pad of silica packed in a filter funnel fitted with a frit, followed by solvent evaporation under reduced pressure to afford the product.
(1H-Benzo[d][1,2,3]triazol-1-yl)(3-(dimethylamino)phenyl)methanone (Table 1, entry 7); Following the general procedure, the product was obtained as an orange liquid (0.1005 g, 70% yield). R_f 0.40 (10% EtOAc/hexanes,);^{1}H NMR (400 MHz, $CDCl_3$) δ 8.37 (d, *J* = 8.4 Hz, 1H), 8.16 (d, *J* = 8.4 Hz, 1H), 7.69 (t, *J* = 8.4 Hz, 1H), 7.58 – 7.45 (m, 3H), 7.41 (t, *J* = 8.4 Hz, 1H), 7.02 (ddd, *J* = 8.4, 2.8, 0.8 Hz, 1H), 3.03 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.6, 150.3, 145.8, 132.5, 132.1, 130.2, 129.0, 126.2, 120.1, 119.7, 117.5, 114.8, 40.5; HRMS (ESI-TOF) m/z calcd for $C_{15}H_{15}N_4O$ $[M + H]^+$ 267.1246, found 267.1245. *(1H-Benzo[d][1,2,3]triazol-1-yl)(2-(phenylamino)phenyl)methanone* (Table 1, entry 8); Following the general procedure, the product was obtained as a yellow oil (0.1068 g, 59% yield). R_f 0.36 (5% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.11 (s, 1H), 8.28 (d, *J* = 8.4 Hz, 1H), 8.17 (d, *J* = 8.4 Hz, 1H), 8.06 (dd, *J* = 8.4, 0.8 Hz, 1H), 7.68 (t, *J* = 7.6 Hz, 1H), 7.53 (t, *J* = 7.6 Hz, 1H), 7.43 (t, *J* = 7.6 Hz, 1H), 7.38-7.34 (m, 3H), 7.28 (d, *J* = 7.6 Hz, 2H), 7.11 (t, *J* = 7.6 Hz, 1H), 6.89 (t, *J* = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.5, 148.9, 145.8, 140.3, 135.2, 134.7, 132.6, 130.1, 129.5, 126.1, 124.0, 122.3, 120.2, 117.7, 115.3, 114.5, 114.2; HRMS (ESI-TOF) m/z calcd for $C_{19}H_{15}N_4O$ $[M + H]^+$ 315.1246, found 315.1249. *1-(1H-Benzo[d][1,2,3]triazol-1-yl)-2-(2,6-dichlorophenyl)ethanone* (Table 1, entry 15); Following the general procedure, the product was obtained as a light white solid (0.1379 g, 89% yield). mp 158.4-159.7^{o}C; R_f 0.57 (10% EtOAc/hexanes);^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (dd, *J* = 8.2, 0.8 Hz, 1H), 8.15 (dd, *J* = 8.2, 0.8 Hz, 1H), 7.64 (td, *J* = 8.2, 0.8 Hz, 1H), 7.52 (td, *J* = 8.2, 0.8 Hz, 1H), 7.40 (d, *J* = 8.0 Hz, 2H), 7.26 (t , *J* = 8.0 Hz, 1H), 5.17 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.0, 146.2, 136.4, 130.6, 130.0, 129.6, 128.2, 126.3, 120.3, 114.4, 38.2; HRMS (ESI-TOF) m/z calcd for $C_{14}H_{10}Cl_2N_3O$ $[M + H]^+$ 306.0201, found 306.0204.
(15) Katritzky, A. R.; Shobana, N.; Pernak, J.; Afridi, A. S.; Fan, W. Q. *Tetrahedron* **1992,** *48*, 7817-7822.
(16) Katritzky, A. R.; He, H.-Y.; Suzuki, K. *J. Org. Chem.* **2000,** *65*, 8210-8213.
(17) Fu, J.; Yang, Y.; Zhang, X.-W.; Mao, W.-J.; Zhang, Z.-M.; Zhu, H.-L. *Bioorg. Med. Chem.* **2010,** *18*, 8457-8462.
(18) Pardin, C.; Pelletier, J. N.; Lubell, W. D.; Keillor, J. W. *J. Org. Chem.* **2008,** *73*, 5766-5775.
(19) Wang, X.; Yu, H.; Xu, P.; Zheng, R. *J. Chem. Res.* **2005**, 595-597.
(20) Katritzky, A. R.; Yang, B.; Qian, Y. *Synlett* **1996**, 701-702.
(21) Katritzky, A. R.; Tala, S. R.; Abo-Dya, N. E.; Gyanda, K.; El-Gendy, B. E.-D. M.; Abdel-Samii, Z. K.; Steel, P. J. *J. Org. Chem.* **2009,** *74*, 7165-7167.

Graphical Abstract

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