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Subin Jaita, Pantitra Kaewkum, Wong Phakhodee and Mookda Pattarawarapan*

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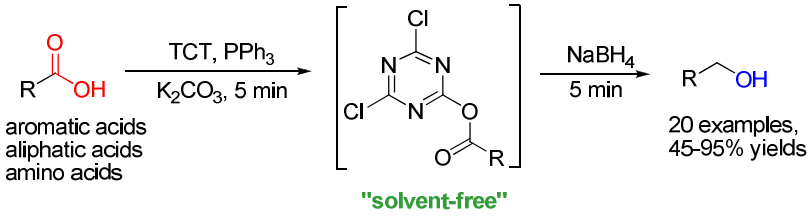

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COMMUNICATION

Solvent-free reduction of carboxylic acids to alcohols with $NaBH_4$ promoted by 2,4,6-trichloro-1,3,5-triazine and PPh_3 in the presence of K_2CO_3

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A simple, rapid, and eco-friendly method for $NaBH_4$ reduction of carboxylic acids to alcohols under solvent-free conditions was developed using a combination of 2,4,6-trichloro-1,3,5-triazine (TCT) with catalytic amount of triphenylphosphine as an acid activator. With the 1:0.2:1.5:2 mole ratio of TCT:PPh_3:K_2CO_3:$NaBH_4$, carboxylic acids including aromatic acids, aliphatic acids, and *N*-protected α-amino acids (Fmoc, Z) could readily undergo reduction to give the corresponding alcohols in good to excellent yields within 10 min.

Sodium borohydride ($NaBH_4$) is a versatile reducing agent possessing widespread applications in organic synthesis.[1] Due to its low cost, high stability, and ease of handling, $NaBH_4$ and its polymer bound analogs are routinely used in conversion of aldehydes and ketones to the respective alcohols.[2] Other functional groups such as acyl chlorides, esters, and imines could as well undergo reduction under the typical room temperature reactions.[3] Nevertheless, carboxylic acids are generally inert and unable to reduce directly without activation.

So far a number of methods have been developed particularly in attempts to convert carboxylic acids into alcohols with $NaBH_4$.[4] Carboxylic acids are commonly pre-activated *via* an *in-situ* formation of active species such as acyl halides, mixed anhydrides, or active esters prior to borohydride reduction. Acid activators such as $BF_3.Et_2O$,3a cyanuric fluoride,[5] BOP reagent,[6] 2,4,6-trichloro-1,3,5-triazine (TCT)/*N*-methylmorpholine (NMM),[7] 1,1'-carbonyldiimidazole,[8] sulfonylbenzotriazole derivatives,[4c, 9] 3,4,5-trifluorophenylboronic acids,[10] and 1-propanephosphonic acid cyclic anhydride[4h] have been applied in combination with $NaBH_4$ to achieve the direct reduction of carboxylic acids under mild conditions. Nevertheless, the methods still suffer from some of these limitations including the use of expensive reagents in excessive amount, long reaction times, and difficulty in work-up.

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Recently, due to the awareness of environmental problems, considerable efforts have been made toward the synthesis under solvent-free conditions. The methods are not only of interest from ecological point of view, but in many cases also offer several synthetic advantages in terms of yield, selectivity, and simplicity of the reaction procedure. For the reduction with $NaBH_4$, a number of solvent-free methods have been reported mostly for reduction of carbonyl compounds.[2c, 11] However, the protocol for carboxylic acids has yet to be reported.

Our interest in simple, low cost, and low environmental impact protocols has led us to develop a facile and efficient solvent-free method for direct reduction of carboxylic acids to alcohols with $NaBH_4$ using cheap and readily available TCT as an acid activator. Although TCT has previously been applied in combination with tertiary amines such as NMM[7b, 12] and triethylamine,[13] the acid activation step often requires cooling to 0 °C to avoid decomposition of the formed quaternary *N*-triazinylammonium chlorides intermediates.[14] Such conditions, however, are not easily amendable under solvent-free conditions.

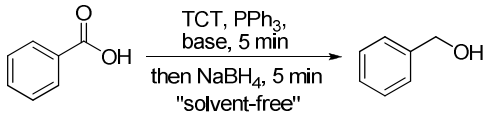
Since triphenylphosphine (PPh_3) is considered a phosphorus analog of tertiary amine exhibiting high stability and good nucleophilicity.[15] It was envisaged that PPh_3 could be used to activate TCT providing a more stable triazinylphosphonium intermediate which enables the acid activation to be carried out at room temperature in an absence of organic solvent.

In our preliminary studies, solvent-free reduction of benzoic acid with $NaBH_4$ promoted by TCT-PPh_3 system was investigated as a model reaction. The reduction was carried out by grinding using mortar and pestle at room temperature, while TLC was used to follow the progress of the reaction. The effect of the amount of reagents used was first examined using potassium carbonate which was inert toward TCT as base. The reaction time was kept constant for the ease of comparison. Typically, a specified amount of PPh_3, benzoic acid (1 equiv), and K_2CO_3 (1.5 equiv) were added to TCT (1 equiv). Since the reactant and reagents are all solid, a few drops of CH_2Cl_2 were added to the mixture to facilitate homogeneous mixing and grinding. After grinding for 5 min in which TLC showed completed disappearance of the acid, $NaBH_4$ (2 equiv) was then added with continuous grinding for further 5 min. The product was isolated by column chromatography.

According to Table 1, it was found that in the absence of PPh_3 (entry 1), no appreciable amount of the corresponding alcohol was detected. Using 10 mol% of PPh_3 gave the expected alcohol in 59% yield (entry 2). When the amount of PPh_3 was increased to 20 mol% (entry 3), the yield of the reaction improved significantly and this amount was further applied as the

optimal value for PPh_3. Since the three chloride atoms on the triazine ring of TCT are known to be reactive toward nucleophiles,[16] it seems possible to perform the acid activation using TCT in less than stoichiometric amount. However, it was found that upon decreasing the amount of TCT from 1 to 0.66 (entry 4), the reaction yield dramatically reduced. This result implied that monoacylated triazine was the key intermediate in reacting with $NaBH_4$. To determine the effect of the counterion of the carbonate base on the outcome of the reaction, the reduction was carried out using 1 equiv of TCT and 20 mol% of PPh_3 with cesium, sodium, and calcium carbonate. Since solubility of carbonate bases in organic solvent increases as the ionic radius of the metal within a group increases,[17] Cs_2CO_3 is thus expected to be the most effective base, followed by K_2CO_3, Na_2CO_3, and $CaCO_3$, respectively. However, as shown in Table 1, using Cs_2CO_3 gave relatively low yield of benzyl alcohol (entry 5), while the uses of Na_2CO_3 and $CaCO_3$ led to complex mixtures with significant amount of starting materials remained (entries 6-7). It is thus possible that Cs_2CO_3 may be too reactive under the applied condition leading to partial decomposition of the generated intermediates before subsequence reduction.

Table 1 Optimization of benzoic acid reduction with $NaBH_4$ promoted by TCT-PPh_3.[a]



entry	TCT (equiv)	PPh_3 (equiv)	base	% yield
1	1	0	K_2CO_3	-
2	1	0.1	K_2CO_3	59
3	1	0.2	K_2CO_3	90
4	0.66	0.2	K_2CO_3	39
5	1	0.2	Cs_2CO_3	34
6	1	0.2	Na_2CO_3	nd
7	1	0.2	$CaCO_3$	nd

[a]All reactions were carried out with benzoic acid (0.271 mmol), TCT, PPh_3, base (0.406 mmol), and $NaBH_4$ (0.541 mmol). nd = not determined.

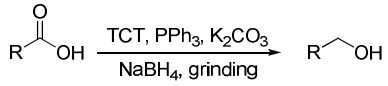
We next turned our attention to investigate substrate compatibility to obtain the scope and generality of the method. The best reaction condition (Table 1, entry 3) was applied with aromatic acids, aliphatic acids, and *N*-protected α-amino acids.[18] For direct comparison, the reaction time again was fixed equally for all substrates without further optimization, except for the less reactive substrates. After product isolation, ^1H NMR, ^{13}C NMR and GC-MS data were recorded and compared with those reported in literature to confirm product formation.

According to Table 2, aromatic carboxylic acids especially benzoic acid and its electron-rich derivatives reduced readily to provide the expected alcohols in good to excellent yields (entries 1-6). Only the case of 3-(dimethylamino)benzoic acid, the product was obtained in moderate yield (entry 7). Benzoic acid derivatives containing halogen substituents (Cl or I) gave the corresponding products in slightly lower yields (entries 8-10), while poor results were obtained with the less reactive substrates having strong electron-withdrawing NO_2 group (entries 11-12). Obviously, longer time is required for activation of the less reactive 4-nitrobenzoic acid since the yield of the alcohol increased with prolonged acid activation step as indicated in parenthesis.

For conjugated acid, cinnamic acid (entry 13) was reduced smoothly to give the expected allylic alcohol as the major product along with 20% of the saturated alcohol derived from the competitive C=C reduction based on GC-MS analysis. This result was in consistent with the previously reported works on borohydride reduction with the TCT/NMM system.[7b] Aliphatic acids including 1-napthylacetic acid and 5-phenylvaleric acid were less reactive than aromatic carboxylic acids and gave the corresponding alcohols in moderate yields (entries 14-15).

For *N*-protected α-amino acids (entries 16-20), the method was less effective possibly due to sterric hindrance of these substrates. Amino acids having 9-fluorenylmethyloxycarbonyl (Fmoc) and benzyloxycarbonyl (Z) as the amino protecting groups were reduced to the corresponding amino alcohols in moderate yields without loss of their optical purities indicating no racemization occurred under the applied condition. Upon increasing the time of the first grinding step from 5 min to 10 min, the yields of the corresponding amino alcohols were greatly improved indicating that for the less reactive or steric hindered substrates, the acid activation times need further adjustment to enhance the product yields.

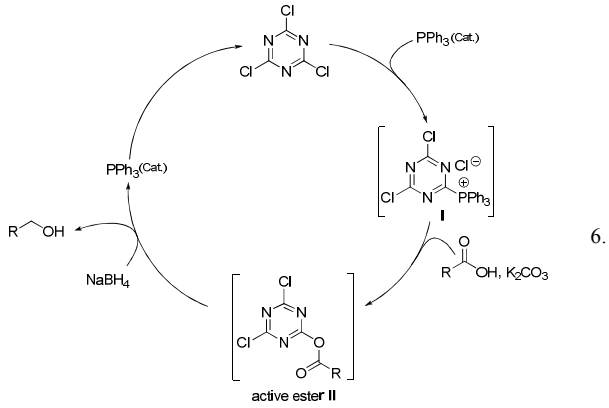
Table 2 Solvent-free reduction of carboxylic acids with $NaBH_4$ promoted by TCT-PPh_3.[a]



entry	carboxylic acid	% yield[Ref]
1	R = C_6H_5	90[19a]
2	R = 3-$CH_3C_6H_4$	91[19b]
3	R = 4-$CH_3C_6H_4$	91[19c]
4	R = 2-$CH_3OC_6H_4$	89[19d]
5	R = 4-$CH_3OC_6H_4$	92[19e]
6	R = 3,4-$(CH_3O)_2C_6H_3$	95[19f]
7	R = 3-$(CH_3)_2NC_6H_4$	75[19g]
8	R = 2-ClC_6H_4	88[19h]
9	R = 2-IC_6H_4	85[19i]
10	R = 4-ClC_6H_4	89[19j]
11	R = 3-$NO_2C_6H_4$	71[19k]
12	R = 4-$NO_2C_6H_4$	45(70)[19a]
13	R = cinnamyl	81[19l]
14	R = 1-naphthylacetyl	76[19m]
15	R = 5-phenylvaleryl	74[19n]
16	Fmoc-Gly-OH	77(87)[19o]
17	Fmoc-Ala-OH	64(80)[19p]
18	Fmoc-Val-OH	66(83)[19q]
19	Fmoc-Ile-OH	61(78)[19q]
20	Z-Phe-OH	75(84)[19r]

[a]Unless otherwise specified, a mixture of TCT (0.271 mmol), PPh_3 (0.054 mmol), carboxylic acid (0.271 mmol), and K_2CO_3 (0.406 mmol) was ground for 5 min before adding $NaBH_4$ (0.541 mmol), followed by grinding for further 5 min. The yields in parenthesis were obtained with 10 min acid activation, followed by 5 min reduction.

Based on the above results, reaction mechanism for the TCT-PPh_3 mediated carboxylic acid activation prior to borohydride reduction was proposed according to Scheme 1. Since the reaction requires 1 equiv of TCT to achieve high conversion, the reaction is believed to proceed *via* nucleophilic displacement of one chloride atom of TCT with PPh_3 to provide a triazinephosphonium chloride **I.** This highly reactive intermediate then undergoes rapid substitution with a carboxylic acid to give an acylated triazine **II** prior to reduction with $NaBH_4$.



Scheme 1 Proposed mechanism for $NaBH_4$ reduction of carboxylic acid mediated by TCT-PPh_3.

It is important to note that in contrast to the reduction of carboxylic acids activated by the TCT/NMM system where aliphatic acids were more favorable,[7] our system was more effective with aromatic carboxylic acids. This could presumably due to the π-π stacking interactions between the benzene ring of the aromatic acids with those of phosphonium salt **I** which accelerates the rate of formation of an active ester **II**.

In summary, this work reported the first solvent-free method for reduction of carboxylic acids to alcohols with $NaBH_4$. Using TCT in combination with catalytic amount of PPh_3 as an acid activator, a range of carboxylic acids could be readily reduced to the corresponding alcohols in good to excellent yields within short reaction times. This protocol offers several benefits over the existing methods including the use of inexpensive reagents, reduction of volatile organic solvent with time and energy efficiency. Applications of the developed reagent system on other functional group transformations are currently underway and outcome will be reported shortly.

Acknowledgements

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