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PII: S0040-4039(14)01310-0
DOI: http://dx.doi.org/10.1016/j.tetlet.2014.07.124
Reference: TETL 44967

To appear in: *Tetrahedron Letters*

Received Date: 13 May 2014
Revised Date: 31 July 2014
Accepted Date: 31 July 2014

Please cite this article as: Rajbongshi, K.K., Sarma, M.J., Phukan, P., A catalyst-free protocol for direct oxidative esterification of alcohols and aldehydes, *Tetrahedron Letters* (2014), doi: http://dx.doi.org/10.1016/j.tetlet.2014.07.124

Graphical Abstract

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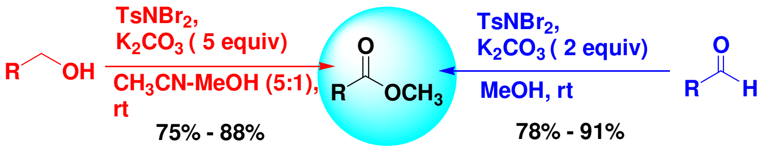

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A catalyst-free protocol for direct oxidative esterification of alcohols and aldehydes

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ARTICLE INFO

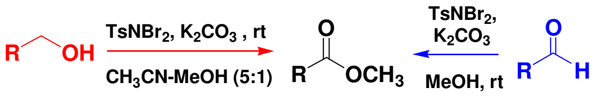
Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
$TsNBr_2$
Oxidation
Methyl Esterification
Alcohol
Aldehyde

ABSTRACT

A fast, simple and efficient protocol for the direct conversion of alcohols and aldehydes to methyl ester has been developed using $TsNBr_2$ without any catalyst. The one pot reaction proceeds in presence of a base at room temperature in methanol, to produce the corresponding methyl ester with high yield within a short time.

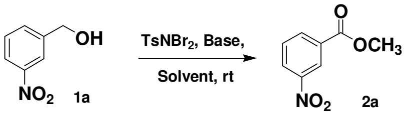
Esters belong to a class of organic compounds which are widely used in industry, medicine, synthetic chemistry and in biology.[1] In particular, methyl esters have high synthetic value in terms of its biological activity.[1] Classically, methyl esters are generated from carboxylic acid by treating with methanol under acidic or basic conditions.[2] Synthesis of methyl esters can also be achieved by reacting diazomethane with carboxylic acid.[3] Although direct oxidative methyl esterification of alcohol is a convenient approach, a limited method has been reported. Recently, Mao *et al.* carried out methyl esterification of alcohol using TBHP as oxidant at 120 °C in presence of a copper catalyst.[4] Another protocol was developed by Ishii *et* al. using acetone as acceptor under the influence of $[Cp^*IrCl_2]_2$ combined with 2-(methylamino)ethanol as catalyst.[5] Ruthenium catalyzed hydrogen transfer process has also been used for methyl esterification of alcohols.[6] Some other metal catalysts based on Pd[7], Au[8], Zn[9], Rh[10] have been developed for similar process. Use of TCCA,[11] iodine,[12] hypervalent iodine (III)[13] as oxidizing agent were also reported for such processes. Very recently, Beller developed a heterogeneous cobalt catalyst for oxidative esterification of alcohols.[14] Thus, most of the methods reported so far requires some drastic condition such as high temperature, expensive metal as a catalyst and long reaction time. Therefore, development of a methodology which proceeds rapidly under mild reaction condition, without using metal catalyst is of high demand. Recently, we found that *N,N*-dibromo-*p*-toluenesulfonamide ($TsNBr_2$) is a very reactive and efficient reagent for various organic transformations.[15] In continuation of our work on this particular reagent, we report herein a very simple and efficient method of direct oxidative esterificaiton of alcohol and aldehydes using $TsNBr_2$ under mild condition (Scheme 1).



Scheme 1: Methyl esterification of alcohols and aldehydes

Initially, the reaction was examined by using *m*-nitrobenzyl alcohol (**1a**). When **1a** (1 mmol) was treated with $TsNBr_2$ (2.5 mmol) and K_2CO_3 (2 mmol) in MeOH (2 mL) at room temperature (25-30°C), methyl 3-nitro benzoate (**2a**) was produced in 43% yield (Table-1, entry1) after 2h of reaction. Yield could be improved up to 50 % by increasing the amount of $TsNBr_2$ to 2.7 mmol. Further reaction in 5 mL of methanol could improve the yield to 65%. Next, we examined the reaction using different amount of K_2CO_3. We observed that the use of 5 equiv of base could improve both the yield and rate of the reaction. Reaction yield was found to be 70% in 80 min of reaction (Table 1, entry 7). On further investigation by changing the solvent system from methanol to a mixture of acetonitrile (2 mL) and methanol (1 mL) gave better result with 87 % yield within 45 minutes (Table1, entry 8). Interestingly, when the reaction was examined by reducing the volume of methanol to 0.4 mL, the rate of reaction was found to increase. In this case, the reaction was found to complete within 30 min with 88% yield of the corresponding methyl ester (Table 1, entry 9). The reaction in absence of base gave very poor yield of the product (Table 1, entry 10).

Table 1. Methyl esterification using $TsNBr_2$[a]



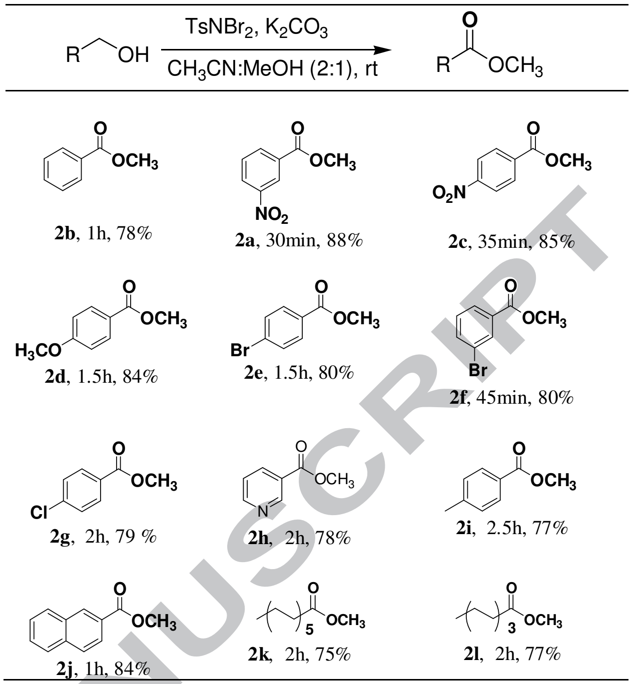
Entry	Solvent (mL)	Base (equiv)	$TsNBr_2$ (equiv)	Time	Yields (%)[b]
1	MeOH (2mL)	K_2CO_3 (2)	2.5	2h	43
2	MeOH (2mL)	K_2CO_3 (2)	2.7	2h	50
3	MeOH (2mL)	K_2CO_3 (2)	3.0	2h	51
4	MeOH (4mL)	K_2CO_3 (2)	2.7	2h	55
5	MeOH (5mL)	K_2CO_3 (2)	2.7	2h	65
6	MeOH (5mL)	K_2CO_3 (4)	2.7	80 min	65
7	MeOH (5mL)	K_2CO_3 (5)	2.7	80 min	70
8	CH_3CN-MeOH (2:1) (3 mL)	K_2CO_3 (5)	2.7	45 min	87
9	**CH_3CN-MeOH (5:1) (2.4 mL)**	**K_2CO_3 (5)**	**2.7**	**30 min**	**88**
10	CH_3CN-MeOH (2:1) (3 mL)	–	2.7	6h	27
11	CH_3CN-MeOH (2:1) (3 mL)	DBU (4)	2.7	2h	77
12	CH_3CN-MeOH (2:1) (3 mL)	DBU (4)	2.7	2h	80
13	CH_3CN-MeOH (2:1) (3 mL)	Na_2CO_3 (5)	2.7	3h	57
14	CH_3CN-MeOH (2:1) (3 mL)	KOH (5)	2.7	2.5h	57
15	CH_3CN-MeOH (2:1) (3 mL)	NaOH (5)	2.7	3h	55
16	CH_3CN-MeOH (2:1) (3 mL)	$(Et)_2NH$ (5)	2.7	3h	61

[a]Reaction conditions. Alcohol (1 mmol), rt. [b]Isolated yields.

Thereafter, we examined the reaction with different bases (Table 1). Although DBU could produce similar yield after 2h of reaction, addition of other bases such as Na_2CO_3, KOH, NaOH and $(Et)_2NH$ could not improve the reaction to a better extent. Finally, the use of 2.7 equiv of $TsNBr_2$, 5 equiv of K_2CO_3 and 2.4 mL of a mixture of acetonitrile and methanol (5:1) was found to be the best choice in terms of yield and reaction time.

After optimizing the reaction condition, we have extended the reaction to various alcohols which is summarized in the Table 2.[19] It is observed that the rate of reaction is very fast for benzyl alcohols with electron withdrawing group such as nitro benzyl alcohol. However, in case of other aromatic alcohols and aliphatic alcohols, the reaction requires about 2h for appreciable yield.

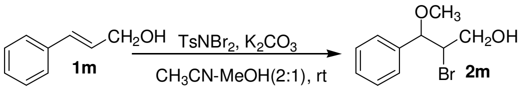
Table 2. Esterification of different alcohols using $TsNBr_2$[a]



2b, 1h, 78%
2a, 30min, 88%
2c, 35min, 85%
2d, 1.5h, 84%
2e, 1.5h, 80%
2f, 45min, 80%
2g, 2h, 79 %
2h, 2h, 78%
2i, 2.5h, 77%
2j, 1h, 84%
2k, 2h, 75%
2l, 2h, 77%

[a]Reaction condition: $TsNBr_2$ (2.7 mmol) , alcohol (1 mmol), K_2CO_3 (5 mmol), CH_3CN-MeOH (5:1, 2.4 mL)

We intended to extend the process to an alcohol bearing a double bond. When reaction was carried out using cinnamyl alcohol, corresponding 2-bromo-3-methoxy-3-phenylpropan-1-ol was produced as the major product (Scheme 2). This may be due to the fact that, $TsNBr_2$ reacts with olefins very fast to produce corresponding methoxy bromide.[15a]

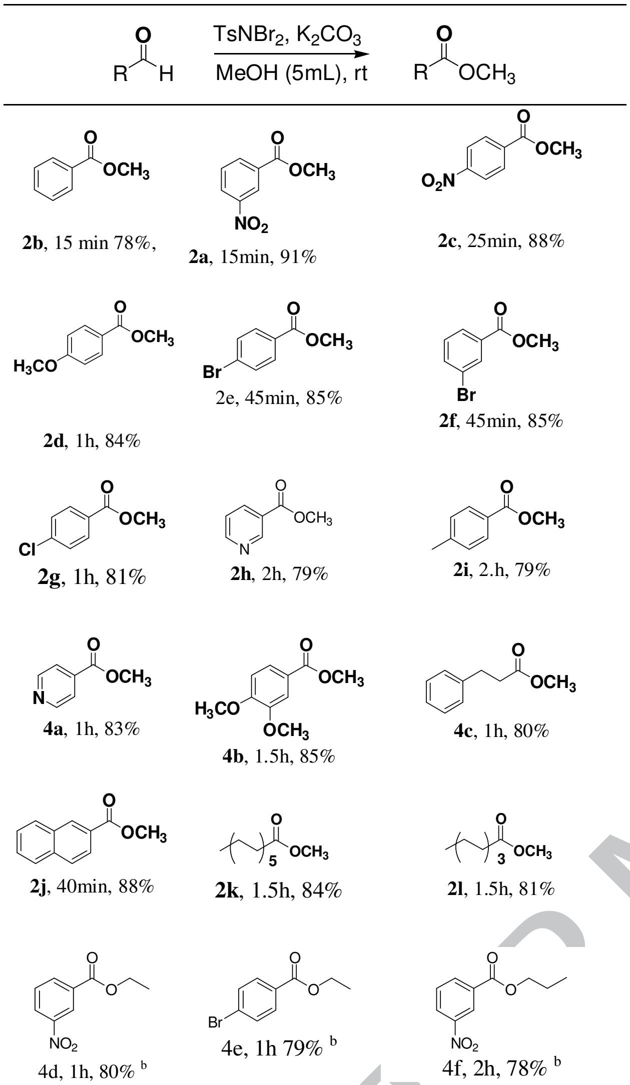


Scheme 2: Reaction with cinnamyl alcohol.

Recently, oxidative methyl esterification of aldehyde has also receiving a great deal of attention. Different metal catalysts have been employed for direct oxidative methyl esterification of aldehyde.[16] Other reagents such as NHC,[17] oxone,[18a] $NaIO_4$,[18b] H_2O_2,[18c] mCPBA,[18d] KI–TBHP,[18e] NBS-Pyridine,[18f] NIS[18g] and I_2[12] are also reported for oxidative esterification of aldehydes.

After successful completion of the reaction with alcohol the process was extended to a variety of aldehydes and to our expectation, the reaction occurred more rapidly with aldehyde compared to alcohol. We have carried out the reaction with aldehyde using 1.5 equiv of $TsNBr_2$ with K_2CO_3 (2 equiv) as a base in 5 mL of methanol. The reaction could be carried out even without bases though the yield is low compared to that with K_2CO_3. The results are summarized in Table 3. In most cases, the reaction is very fast to produce the corresponding ester in excellent yield. The reaction was further investigated using other alcohols such as ethanol and n-propanol. In this case, the use of a 5:1 mixture of acetonitrile and alcohol produced maximum yield (Table 3).

Table 3. Oxidative esterification of aldehyde[a]



2b, 15 min 78%,
2a, 15min, 91%
2c, 25min, 88%
2d, 1h, 84%
2e, 45min, 85%
2f, 45min, 85%
2g, 1h, 81%
2h, 2h, 79%
2i, 2.h, 79%
4a, 1h, 83%
4b, 1.5h, 85%
4c, 1h, 80%
2j, 40min, 88%
2k, 1.5h, 84%
2l, 1.5h, 81%
4d, 1h, 80% [b]
4e, 1h 79% [b]
4f, 2h, 78% [b]

[a]Reaction Condition : TSNBr$_2$ (1.5 mmol), aldehyde (1 mmol), K$_2$CO$_3$ (2 mmol), MeOH (5 mL), rt; [b] alcohol (0.4 mL), CH$_3$CN (2 mL).

In summary, we have developed a very simple, efficient and fast method for the direct synthesis of methyl ester from both alcohol as well as aldehyde using TsNBr$_2$ in presence of K$_2$CO$_3$ as base. The reaction could be extended to other alcohols such as ethanol and n-propanol also. The reaction is convenient as it proceeds at room temperature within a very short time with high yield.

Acknowledgement: Financial support from DST (Grant No. SR/S1/OC-43/2011) is gratefully acknowledged.

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19. **General Procedure for synthesis of methyl ester:** To a solution of alcohol (1mmol) in a mixture of MeCN and MeOH (5:1, 2.4 mL) was added TsNBr$_2$ (2.5 mmol) and K$_2$CO$_3$ (5 mmol) and stirred at room temperature. After completion of the reaction (TLC) sodium thiosulfate was added and the reaction mixture was stirred for 10 min. The reaction mixture was extracted in diethyl ether and hexane (1:1), dried (Na$_2$SO$_4$) and concentrated. Purification of the crude product by flash chromatography on silica gel (230-400mesh) with petroleum ether –EtOAc as eluent gave the pure product.

    In case of methyl ester synthesis from aldehydes, reaction was carried out using 1.5 mmol of TsNBr$_2$ and 2 mmol of K$_2$CO$_3$ was used for 1 mmol of substrate. For methyl ester synthesis, methanol (5 mL) was used as solvent and for other alkyl ester synthesis 5:1 mixture of MeCN-ROH (2.4 mL) was used as the reaction medium. Work-up procedure remains same.

Highlight

Title of the manuscript: A catalyst-free protocol for direct oxidative esterification of alcohols under mild condition

Authors: Kamal Krishna Rajbongshi, Manas Jyoti Sarma and Prodeep Phukan

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1. Fastest method for direct esterification of alcohols.
2. The process does not require any catalyst.
3. This protocol is simple, mild and high yielding.
4. Applicable for both benzylic and aliphatic alcohols.
5. Extended for direct esterificaiton of aldehydes.