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Simple Formylation of Aromatic Compounds Using a Sodium Formate/Triphenylphosphine Ditriflate System

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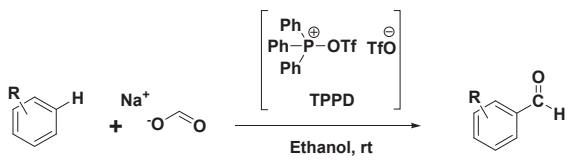
A new procedure was developed for formylation of arenes to produce aromatic aldehydes using a sodium formate/triphenylphosphine ditriflate system in ethanol at room temperature in good yields. The simplicity of the procedure, short reaction times, and mild reaction conditions are the other advantages of this metal- and carbon monoxide-free protocol.

Keywords: Formylation of arene | Metal- and CO-free protocol | Aromatic aldehyde

Formylation is an important strategy to form aromatic aldehydes as intermediates in organic synthesis. These compounds are widely used in pharmaceutical and fine-chemical industries.[1] Classical methods for synthesis of carboxaldehydes are Vilsmeier and Haack,[2] Gatermann and Koch,[3] Reimer and Tiemann,[4] and Duff reactions.[5] Direct formylating reagent systems using aryl formate,[6a] formamidine acetate,[6b] triethyl orthoformate,[6c] triformamide,[7a] *N*,*N*,*N*′,*N*′-tetraformylhydrazine,[7b] *N*-methyl formanilide,[7c] dimethylformamide,[7d] formyl fluoride,[8a] and formic acid[8b] have been reported. Some of these methods suffer from some disadvantages such as multisteps reactions, production of large amounts of noxious waste, need for excess reagents, use of strongly toxic compounds, low selectivity, and need for low temperature. Aromatic aldehydes have also been synthesized using methods such as oxidation of alcohols,[9] and reduction of acids and their derivatives.[10] The organometallic compounds were reacted with CO,[11] and CO_2[12] to form aromatic aldehydes. In one of these approaches syngas (CO/H_2 1:1) was applied as formylating agent of aromatic compounds.[13] This approach is also very useful on an industrial scale but, utilization of CO is not desirable because of its toxicity. Hence, CO-free formylation protocols have attracted much attention. Aryl halides as substrates have also been used in formylation reactions.[14] The aim of this work was synthesis of aromatic aldehydes from aromatic compounds using a triphenylphosphine ditriflate/sodium formate system in ethanol at room temperature (Scheme 1).

Initially, triphenylphosphine ditriflate (TPPD) was produced as a white precipitate from the reaction of trifluoromethanesulfonic anhydride (Tf_2O) and triphenylphosphine oxide in



R= H, Cl, NO_2, Br, Me, OH, OMe, F

Scheme 1. Synthesis of aromatic aldehydes.

Table 1. Optimization of the reaction conditions for formylation of mesitylene[a]

Entry	Solvent	Promoter	The amount of promoter /mmol	Time /min	Yield[b] /%
1	EtOH	Tf_2O	1.2	70	0
2	EtOH	DMSD	1.2	70	50
3	EtOH	TPPD	0.0	70	0
4	**EtOH**	**TPPD**	**1.2**	**65**	**82**
5	EtOH	TPPD	0.6	65	44
6	EtOH	TPPD	2.0	65	83
7	H_2O	TPPD	1.2	65	5
8	H_2O–EtOH (1:1)	TPPD	1.2	65	27
9	CH_2Cl_2	TPPD	1.2	65	0
10	$CHCl_3$	TPPD	1.2	65	5
11	CH_3CN	TPPD	1.2	65	20

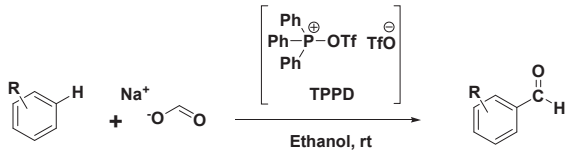
[a]Conditions: Mesitylene (1 mmol), sodium formate (1 mmol), TPPD (1.2 mmol), EtOH (3 mL), room temperature. [b]Isolated yields.

dichloromethane at 0 °C to room temperature.[15] Then, we focused on finding suitable conditions for optimization of the efficient and mild reaction of aromatic compound with sodium formate in the presence of promoter. Thus, mesitylene was chosen as a model substrate and next, the reaction was carried out using HCOONa as formylaing agent and Tf_2O as promoter in EtOH at room temperature (Table 1). When 1.2 equivalent of Tf_2O was applied, no corresponding product was obtained (Entry 1). We decided to test dimethyl sulfide ditriflate (DMSD) for the formylation reaction. This salt was produced from dropwise addition of one equivalent of Tf_2O to one equivalent of Me_2SO at 0 °C.[16] This promoter was tested to formylate mesitylene and it was found that the reaction proceeded and the corresponding aldehyde obtained after 70 min in 50% yield (Entry 2). We further examined TPPD as the promoter for this reaction under the same reaction conditions. The results indicated that TPPD is the best promoter with respect to the yield of the product (82%) (Entry 4).

To optimize solvent, H_2O was used instead of EtOH and the result shows water was not effective as a solvent due to its inability to solvate the arene and as a result a decreased yield of the product was obtained (5%) (Entry 7). The reaction in H_2O–EtOH (1:1) solution leaded to a lower yield of the product (27%) (Entry 8). Other solvents such as CH_2Cl_2, $CHCl_3$, and CH_3CN were also tested and resulted in lower yields of the products (0%, 5%, and 20%, respectively) (Entries 9–11).

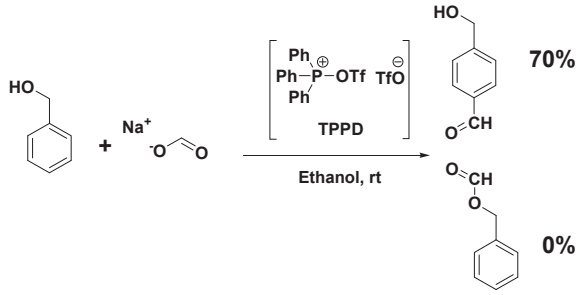
The effect of amount of TPPD on the reaction was also examined and it was found that 1.2 equiv of TPPD was the best choice. When up to 2 equiv of TPPD were used, the results did not show any noticeable differences with respect to the yield and reaction time. However, the reaction using lower than 1.2 equiv of the promoter was not complete. Therefore, the optimized

Table 2. Synthesis of aromatic aldehydes with sodiom formate using TPPD



Entry	ArH	Product	Time /min	Yield[a] /%
1	C_6H_5Cl	2- and 4-Cl-C_6H_4-CHO	80	65 (*o*/*p*:9/91)[b]
2	$C_6H_5NO_2$	3-NO_2-C_6H_4-CHO	120	20
3	C_6H_5Br	2- and 4-Br-C_6H_4-CHO	80	60 (*o*/*p*:12/88)[b]
4	$C_{10}H_8$	1-$C_{10}H_7$-CHO	75	55
5	$C_6H_5CH_3$	2- and 4-CH_3-C_6H_4-CHO	90	60 (*o*/*p*:10/90)[b]
6	C_6H_5OH	4-HO-C_6H_4-CHO	75	70
7	$C_6H_5OCH_3$	4-CH_3O-C_6H_4-CHO	70	65
8	C_6H_6	C_6H_5-CHO	90	55
9	C_5H_5N	3-C_5H_4NCHO	120	20
10	1,3-$C_6H_4Cl_2$	2,4-$Cl_2C_6H_3$CHO	80	60
11	1,3,5-$C_6H_3(CH_3)_3$	2,4,6-$(CH_3)_3C_6H_2$CHO	65	82
12	1,4-$C_6H_4(CH_3)_2$	2,5-$(CH_3)_2C_6H_3$CHO	70	75
13	1,2-$C_6H_4(CH_3)_2$	3,4-$(CH_3)_2C_6H_3$CHO	72	76
14	1,3-$C_6H_4(CH_3)_2$	2,4-$(CH_3)_2C_6H_3$CHO	70	75
15	C_6H_5F	2- and 4-F-C_6H_4-CHO	120	30 (*o*/*p*:25/75)[b]

[a]Isolated yield. [b]Based on ^{1}H NMR determination.



Scheme 2. Chemoselective formylation of benzyl alcohol.

Table 3. Comparison of tolualdehyde formation from toluene under different conditions

Entry	Condition	Temp /°C	Time /h	Yield /%	Ref.
1	$C_6H_{12}N_4$, CF_3COOH	83–90	12	61	17
2	HCl/NaCN/$AlCl_3$	100	7	39	18
3	$AlCl_3$/HCl/$CHCl_2OCH_3$	0	2	80	19
4	CO/HCl/$AlCl_3$/CuCl	50	7	50	20
5	HCOF/BF_3/CS_2	0–10	3	75	8a
6	$AlCl_3$/$Zn(CN)_2$	100	7	65	8a
7	$AlCl_3$/$(CH_3)_2C(OH)CN$	111	5	40	21
8	TPPD/HCOONa/EtOH	rt	1.5	60	This work

reaction conditions for this reaction are TPPD (1.2 equiv) in EtOH at room temperature (Table 1). A control experiment conducted without TPPD indicated that the reaction did not take place, and the mesitylene remained unreacted at the end of the reaction.

To study the generality of this procedure, we examined the reaction using several arenes under the optimized conditions. The results are summarized in Table 2. The arenes with electron-releasing groups reacted with shorter reaction times and good yields, while the reactions of arenes with electron-withdrawing groups proceeded with longer reaction times and lower yields. The formylation of nitrobenzene with an electron-acceptor group occurred and 3-nitrobenzaldehyde was obtained in 20% yield (Entry 2). This shows that the formylation agent is highly reactive and can formylate nitrobenzene with a strong electron-acceptor group. The formylation of low reactive pyridine occurred and pyridine-3-carboxaldehyde was obtained in 20% yield (Entry 9). Of course, the yields of these two products were low due to the low reactivities of the substrates and incomplete reaction. The reaction of anisole was carried out with high regioselectivity in 65% yield (Entry 7). The formylation of chlorobenzene, bromobenzene, and toluene under the present reaction conditions afforded a mixture of *o*- and *p*-isomers in 65, 60, and 60% yields, respectively (Entries 1, 3, and 5). Benzene was formylated under the same reaction conditions, and benzaldehyde obtained in 55% yield (Entry 8). In addition, the reaction of naphthalene with sodium formate occurred with high regioselectivity and 1-naphthaldehyde was obtained as the only product in 55% yield, (Entry 4). It seems that steric effects have an important role in the regioselectivity of these reactions under the present reaction conditions. This selectivity might be due to the highly hindered formylating reagent which prefers *para* position to be mainly or completely formylated. The room temperature (not high temperature) may also another reason accounting for the regioselectivity. The formylation reaction of phenyl acetate as an acid-sensitive compound under the reaction conditions was not complete and about half of the substrate remained intact. Phenol (<5%) and 4-hydroxybenzaldehyde (10%) as side products plus the corresponding aromatic aldehyde (15%) were obtained.

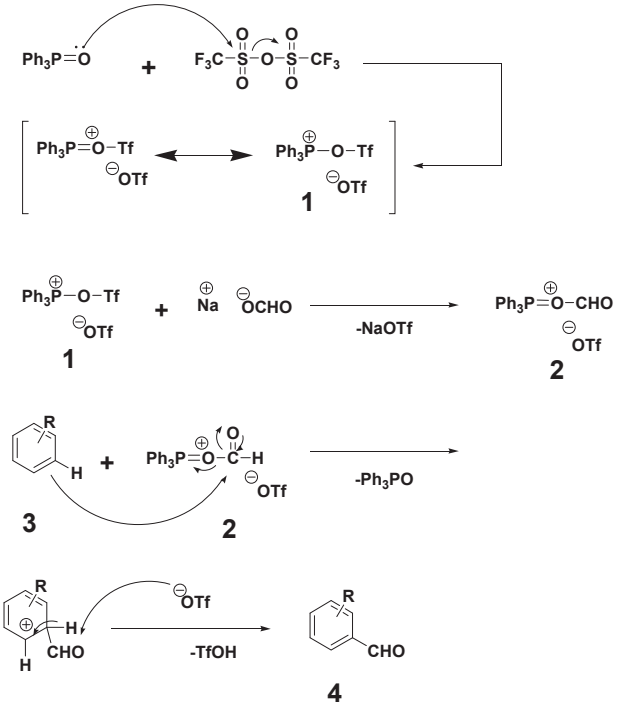
The reaction of benzaldehyde under the same reaction conditions was not complete and was accompanied by the formation of several unidentified products. Efforts to obtain the corresponding product were not successful in this case. Formylation of benzyl alcohol was chemoselectively led to 4-hydroxymethylbenzaldehyde in 70% yield and no alcohol formylation occurred (Scheme 2). It seems that the formylating agent is soft and hence it prefers to be attacked by aromatic rings as a soft nucleophile.

To assess the capability of applying this method on a preparative scale, the formylation reaction of mesitylene with sodium formate was carried out on a 10 mmol scale (Supporting Information).

In order to show the efficiency of this method, the results of toluene formylation by our method are compared with those reported in the literature. The results show that this method is comparable to some previously reported methods in terms of reaction times, temperatures, and yields (Table 3).

Interestingly, TPPD reacts with sodium formate and produces the formylating agent, while EtOH as a solvent is present in the reaction. It seems that ethanol as a nucleophile can be a competitor for sodium formate and attack TPPD to produce an alkylating agent for the aromatic compounds. But, it was found that EtOH cannot act as a nucleophile.

In our previous work, it was indicated that benzylation of arenes can be carried out in the presence of TPPD in CH_2Cl_2.[22] In fact benzyl alcohol reacted with TPPD and produced alkoxy-triphenylphosphonium triflate intermediate which converted to



Scheme 3. Plausible mechanism for the synthesis of aromatic aldehydes.

relatively stable benzyl cation as a benzylating reagent of the arenes, while EtOH as a nucleophile cannot form a relatively stable carbocation and thus it acts as a solvent.

To obtain more information about the reaction path of formylation reaction, we tried to isolate formylating agent **2** [$(PPh_3\text{-}OCHO)^+$ ^-OTf] from TfONa. Unfortunately, our efforts were not successful. Thus, the intermediate **2** was characterized by FT-IR and NMR spectra in the presence of TfONa (Supporting Information). The presence of intermediate **2** during the process of formylation reaction might be confirmed by the observation of FT-IR peak at 1700 cm^{-1} related to the stretching vibrations of the carbonyl group and the peaks at 2734 and 2814 cm^{-1} corresponded to C–H stretching of aldehyde group. In the ^1H NMR spectrum of the mixture, a peak at 10 ppm ascribed to the formyl proton in intermediate **2** was observed. Furthermore, the ^{13}C NMR spectrum also confirmed the presence of formylating agent **2** by the peak of carbon at 193 ppm related to a carbonyl group. Therefore, the formation of intermediate **2** during the process of reaction was confirmed.

As a result of this observation, the following mechanism indicated in Scheme 3 was proposed for the synthesis of aromatic aldehydes promoted by triphenylphosphine ditriflate. The reagent was prepared via a two-step process at low temperature. In the first step, a nucleophilic substitution reaction between triphenylphosphine oxide and triflic anhydride leads to the promoter **1**. The produced phosphonium cation accepts a nucleophilic sodium formate and the triflate leaving group exits simultaneously. Replacement of triflate with the oxygen of the sodium formate generates intermediate **2**. The resulting reagent (compound **2**) was used for successful formylation of a broad range of arenes via an ordinary electrophilic aromatic substitution reaction.

In conclusion, we have developed a simple salt-promoted, clean, mild, rapid, and efficient method for direct formylation of arenes to produce aromatic aldehydes.[23] This protocol uses readily available aromatic compounds as the substrates, TPPD as a promoter, and EtOH as the solvent. This CO and CO_2-free method could tolerate various functional groups and be performed at room temperature.

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Supporting Information is available on http://dx.doi.org/10.1246/cl.170152.

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23 **Typical procedure for the formylation of arenes:** To a solution of TPPD (0.673 g, 1.2 mmol) in EtOH (3 mL), sodium formate (0.068 g, 1 mmol) was added and the mixture allowed stirring for 30 min. Then, mesitylene (0.139 mL, 1 mmol) was added to this solution and the mixture was stirred for 60 min at room temperature. After 65 min, the solvent was removed under reduced pressure and then the saturated sodium bicarbonate solution (10 mL) was added. The mixture was extracted with chloroform (3 × 5 mL) and the organic layer washed with water and dried over anhydrous $MgSO_4$. The filtrate was evaporated and the crude product purified by silica gel column chromatography using ethyl acetate/*n*-hexane (3:7) as eluent to afford 2,4,6-trimethylbenzaldehyde (0.121 g, 82%). The products are all known compounds.

