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Tantalum(V) Fluoride-catalyzed *N*-Alkylation of Arylamines with Benzyl Alcohols

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This paper describes a simple and efficient protocol for the *N*-alkylation of arylamines with benzyl alcohols using tantalum(V) fluoride as the catalyst.

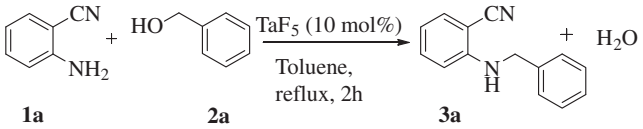
The formation of C–C and C–N bonds is important reactions in organic synthesis. *N*-Alkylated amines are good synthons for drug intermediates, agrochemicals, natural products, and various biologically active compounds.[1] Conventional *N*-alkylation of amines was performed with alkyl halides[2] in the presence of stoichiometric amounts of base, or with carbonyl compounds[3] using strong reducing agents. Over a period of time, alternate methods were developed such as hydroamination of olefins[4] or alkynes.[5]

Alcohols are interesting alkylating agents for the selective monoalkylation of amines, though the reactions are somewhat sluggish. Classical methods for the *N*-alkylation of amines with alcohols using catalysts such as iridium,[6] rhodium,[7] and ruthenium[8] complexes have been reported. These transition-metal complexes act as redox reagents for *N*-alkylation based on the hydrogen autotransfer mechanism. The initial reaction was the oxidation of alcohols followed by imine formation with amine. The subsequent reduction of imine leads to the *N*-monoalkylated product. Heterogeneous catalysis[9] received attention for the *N*-alkylation of amines using alcohols. Zhao and co-workers developed new ligands[10] for the *N*-alkylation of amines using alcohols in the presence of iron, which proceeds via a nucleophilic substitution (SN) type reaction.

In accordance with our goal to develop new synthetic procedures such as the Lewis acid-catalyzed *N*-formylation of amines with formic acid under microwave irradiation,[11] we have developed for the first time an elegant method for the monoalkylation of amines with alcohols using tantalum(V) fluoride as the catalyst. Lewis acid catalysts have been extensively used for various chemical transformation reactions previously.

We have investigated the reaction of 2-aminobenzonitrile and benzyl alcohol in the presence of Lewis acids such as zinc(II) chloride, aluminum(III) chloride, aluminum(III) fluoride, copper(II) fluoride, copper(II) triflate, lanthanum(III) triflate, gadolinium(III) triflate, titanium(IV) chloride, and tantalum(V) fluoride under refluxing toluene. With the exception of tantalum(V) fluoride, none of the other Lewis acids induced any reaction. Therefore, tantalum(V) fluoride has been identified as a suitable catalyst for the formation of 2-(benzylamino)benzonitrile from 2-aminobenzonitrile and benzyl alcohol (Scheme 1).[12] Tantalum(V) fluoride is volatile but exists as an oligomer in the solid state and is used for some fluorination reactions.[13]

The versatility of the alkylation reaction was proved by employing a variety of alcohols **2a**–**2l**, and using TaF_5 as the catalyst in refluxing toluene. In this study, the efficient *N*-alkylation with benzyl alcohols **2a**–**2j** furnished corresponding *N*-alkylamines **3a**–**3j** as exclusive products in 65–86% yields. We did not find any dialkylated product. Aliphatic alcohols such as propargyl alcohol (**2k**), isoamyl alcohol (**2l**), and allylic alcohol (**2m**) remained unreactive as shown in Table 1.



Scheme 1. Reaction of 2-aminobenzonitrile with benzyl alcohol.

We studied the *N*-alkylation of a variety of amines **1a**–**1o** with 4-methoxybenzyl alcohol using TaF_5 as the catalyst in refluxing toluene. Arylamines **1a**–**1m** were found to undergo *N*-alkylation and furnished the corresponding *N*-alkylamines **4a**–**4m** in 56–96% yields, as shown in Table 2. Aliphatic amines such as morpholine **1n** and butylamine **1o** remained unreactive under these reaction conditions.

TaF_5 might form a complex with alcohol (Scheme 2). Then, amine, acting as a nucleophile, replaces the OH functional group in the form of H_2O and TaF_5. We observed that amino-containing electron-withdrawing groups were more favorable for this reaction. However, greater electron density on the nitrogen-containing compounds (aliphatic amines) did not give the desired product as the amine first formed a complex with TaF_5 instead of alcohol.

The nucleophilic displacement mechanism was further confirmed by carrying out the reaction of aniline (**1b**) with 2-(2-methoxyphenyl)propan-2-ol (**2n**) under the same reaction conditions, furnished *N*-[2-(2-methoxyphenyl)propan-2-yl]aniline (**4p**) in good yield (Scheme 3).

It was further supported by the reaction of 4-methoxyaniline (**1d**) with 9-methyl-9*H*-fluoren-9-ol (**2o**), which yielded *N*-(4-methoxyphenyl)-9-methyl-9*H*-fluoren-9-amine (**4q**) (Scheme 4).

The above-mentioned products **4p** and **4q** were characterized based on ^{1}H NMR and ESI-Mass spectral data. The formation of compounds **4p** and **4q** indicate that the benzylation reaction followed the nucleophilic substitution type mechanism and not the hydrogen autotransfer mechanism.

In conclusion, the present work shows that tantalum(V) fluoride-catalyzed the efficient *N*-alkylation of arylamines with benzyl alcohols. In this study, a variety of arylamines and benzyl alcohols were shown to react efficiently to give *N*-alkylamines in high yields in the presence of tantalum(V) fluoride as the catalyst.

We are thankful to the Director, IICT for constant encouragement and we are also thankful to Council of Scientific and Industrial Research (CSIR), India for the financial assistance in the form of SRF fellowship.

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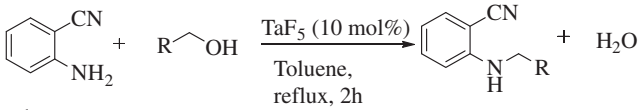
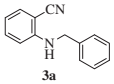
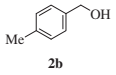
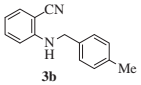
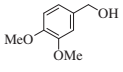
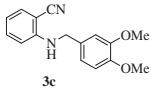
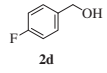
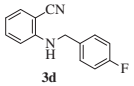
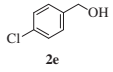
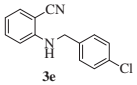
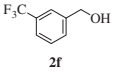
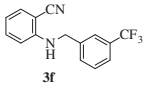
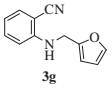
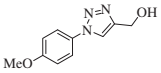
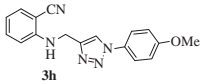
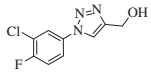
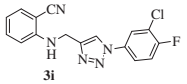
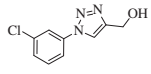
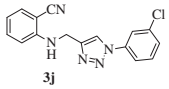
Table 1. Tantalum(V) fluoride-promoted *N*-alkylation of 2-aminobenzonitrile with various alcohols

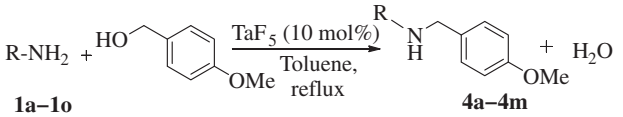


1a **2a–2l** **3a–3j**

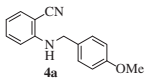
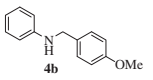
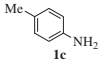
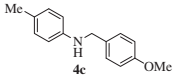
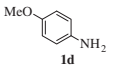
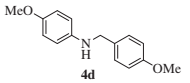
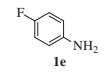
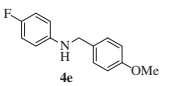
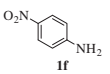
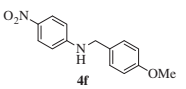
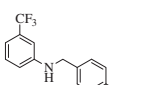
Entry	Alcohol **2**	*N*-Alkylamine **3**	Reaction time/h	Yield[a] /%	Mp /°C
1	 **2a**	 **3a**	2.5	80	118–120
2	 **2b**	 **3b**	2.5	83	121–123
3	 **2c**	 **3c**	2.0	85	103–104
4	 **2d**	 **3d**	3.0	86	88–89
5	 **2e**	 **3e**	4.5	72	114–116
6	 **2f**	 **3f**	3.5	68	117–119
7	 **2g**	 **3g**	4.0	80	liquid
8	 **2h**	 **3h**	3.0	77	107–109
9	 **2i**	 **3i**	4.5	70	80–82
10	 **2j**	 **3j**	4.0	65	111–113
11	 **2k**	N.R.	24	—	—
12	 **2l**	N.R.	24	—	—
13	 **2m**	N.R.	24	—	—

[a]Isolated yields. All products gave satisfactory ^{1}H, ^{13}C NMR, IR, and mass spectral data.

Table 2. TaF_5-catalyzed reaction of 4-methoxybenzyl alcohol with an various amines



1a–1o **4a–4m**

Entry	Amine **1**	*N*-Alkylamine **4**	Reaction time/h	Yield[a] /%	Mp /°C
1	 **1a**	 **4a**	2.25	95	89–91
2	 **1b**	 **4b**	2.5	90	liquid
3	 **1c**	 **4c**	3.25	86	70–72
4	 **1d**	 **4d**	2.75	84	97–99
5	 **1e**	 **4e**	3.0	80	liquid
6	 **1f**	 **4f**	1.75	96	148–150
7	 **1g**	 **4g**	3.25	70	liquid
8	 **1h**	**4h**	3.75	65	liquid
9	**1i**	**4i**	4.5	70	80–82
10	**1j**	**4j**	6.0	56	liquid
11	**1k**	**4k**	3.75	85	194–196
12	**1l**	**4l**	3.25	70	liquid
13	**1m**	**4m**	3.5	86	170–171
14	**1n**	N.R.	24	—	—
15	**1o**	N.R.	24	—	—

[a]Isolated yields. All products gave satisfactory ^{1}H, ^{13}C NMR, IR, and Mass spectral data.

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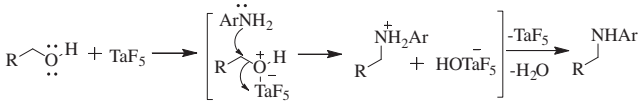
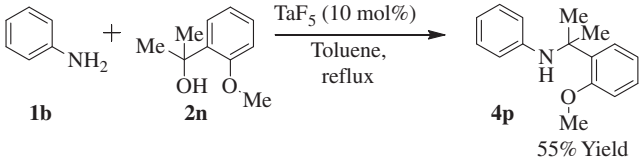
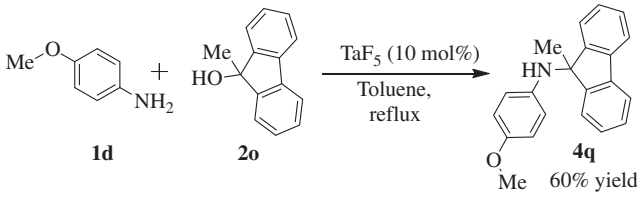


Scheme 2. Plausible mechanism for the monoalkylation of aromatic amines with alcohols.



Scheme 3.



Scheme 4.

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12 **Typical procedure for *N*-alkylation under tantalum(V) fluoride catalysis**: 2-Aminobenzonitrile (**1a**) (0.2 g, 1.69 mmol), benzyl alcohol (**2a**) (0.183 g, 1.69 mmol), dry toluene (5 mL), and TaF_5 (0.046 g, 0.169 mmol) were taken into a 50-mL round-bottomed flask fitted with a condenser and calcium chloride guard tube. The reaction mixture was stirred at 110 °C for 2 h and after completion of the reaction (judged by TLC), the reaction mixture was concentrated under reduced pressure and the residue was purified by column chromatography (60–120 mesh silica gel, ethyl acetate:hexane = 1:20) afforded the corresponding *N*-alkylamine **3a** in the form of white solid (0.282 g, 80%, mp 118–120 °C). Experimental details and characterization data are in the Supporting Information. Supporting Information is available electronically on the CSJ-Journal Web site, http://www.csj.jp/journals/chem-lett/index.html.

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