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An expedient one-pot synthesis of benzophenone Schiff bases from benzene

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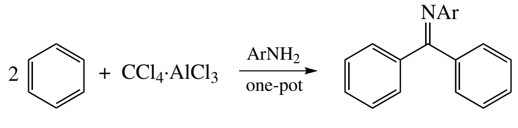
A simple and efficient one-pot synthesis of benzophenone Schiff bases from benzene, CCl_4 and aromatic amines was developed based on the the reaction of benzene with $CCl_4{\cdot}AlCl_3$ complex. This method affords Ph_2CCl_2 as well as the products of its subsequent reaction with aromatic amines, benzophenone Schiff bases, selectively and in good yields.



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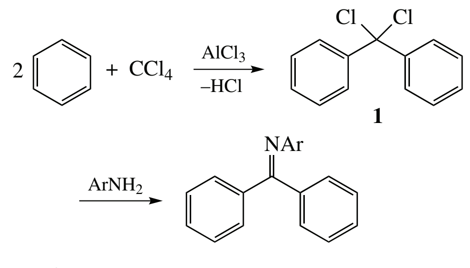
Benzophenone Schiff bases demonstrate promising activity against different bacterial and fungal strains[1] as well as are used as catalysts and multipurpose reactants.[2] Numerous methods have been developed for their synthesis.[1–3] Among them, the widely used ones originated from ketones and arylamines have definite drawbacks.[3(a)] Unlike the condensation of aldehydes and arylamines, the reactions of ketones require high temperatures as well as use of catalysts and specific techniques. A set of Brønsted or Lewis acids, dehydration agents as well as microwave, infrared or ultrasound irradiation have been employed to carry out the syntheses of ketone Schiff bases.[3(a)] Most of these procedures suffer from low yields, long reaction times, poor functional group tolerance, the need for elevated temperature, expensive substrates, toxic reagents, or have a limited scope. On the other hand, the application of a Lewis acid–base pair like $AlCl_3$–Et_3N provided products in good yields under mild conditions.[3(a)] However, this reaction required large amounts of $AlCl_3$ and Et_3N in a ratio of $[Ph_2C(O)]/[AlCl_3]/[Et_3N]$ 1 : 1.7 : 5.1 and failed to produce anils from sterically crowded anilines. Alternative procedures for the synthesis of Schiff bases were used rarely, notwithstanding their potential advantage.[1,3(b)–(f)] Generally, in more than 150 years since the first Schiff base had been obtained,[4] the development of milder and cheaper methods for their synthesis has remained a challenge.



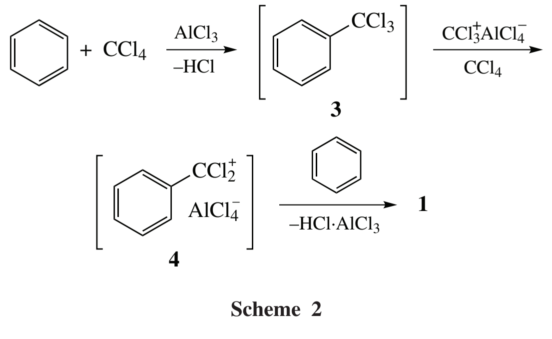
2a Ar = Ph
2b Ar = 4-MeC_6H_4
2c Ar = 4-$MeOC_6H_4$
2d Ar = 4-FC_6H_4
2e Ar = 4-ClC_6H_4
2f Ar = 2-ClC_6H_4
2g Ar = 4-BrC_6H_4
2h Ar = 4-$O_2NC_6H_4$
2i Ar = 2,6-$Me_2C_6H_3$
2j Ar = 2-$O_2NC_6H_4$
2k Ar = 2-Cl-4-MeC_6H_3

Scheme 1

In this work, we have developed a simple one-pot synthesis of benzophenone anils **2a**–**k** from benzene, $CCl_4{\cdot}AlCl_3$ complex and aromatic amines (Scheme 1) through *in situ* generated dichlorodiphenylmetane **1**. The reaction can be performed in CH_2Cl_2 or as a solvent-free one.

The reaction of benzene with CCl_4 in the presence of $AlCl_3$ has been known since the early 20th century (Scheme 2).[5] It involves the Friedel–Crafts alkylation of benzene with CCl_3^+ cation, generated from CCl_4 and $AlCl_3$ with formation of benzotrichloride **3**. In turn, compound **3** undergoes the abstraction of Cl^- ion by the electrophile resulting in cation **4** which can alkylate another benzene molecule affording compound **1**.

Willard reported that the exchange of chlorine atom of CCl_4 and $AlCl_3$ labeled with ^{35}Cl occurs even at –20 °C, thus indicating the ionization of CCl_4 to CCl_3^+ cation.[6] Complex $PhCCl_2^+AlCl_4^-$ **4** preceding the formation of dichloride **1** was found to possess definite stability and could be stored for two weeks at 25 °C.[7] The complication arises (see Scheme 2) since the electrophiles, namely $CCl_3^+AlCl_4^-$ if the reaction is carried out in excess CCl_4, or $HCl{\cdot}AlCl_3$ if CCl_4 is used in the equimolar ratio, can initiate the subsequent transformations of dichloride **1**. Depending on the reaction conditions, this process results in Ph_3CCl,[8(a)] Ph_2CCl_2,[5(b),(c)] Ph_3CH[8(a)] or $PhCCl_3$.[8(b),(c)] If the reaction is carried out in CH_2Cl_2 or $CHCl_3$, the yield of compound **1** decreases due to the side reactions of benzene and CH_2Cl_2[9(a)] or $CHCl_3$,[9(b)] respectively. Several works reported on the use of CS_2 as a solvent.[10] Examples of the preparative use of the reaction of



Scheme 2

benzene with CCl_4 are scarce.[5(c),11] On the other hand, dichloride **1** is widely used in organic synthesis, in particular, for the preparation of promising drugs.[12] Several benzophenone Schiff bases were obtained as well from compound **1**[1] whilst it was prepared by chlorination of benzophenone with PCl_5 and $POCl_3$[13] rather than from benzene and CCl_4. The one-pot synthesis of benzophenone imines from benzene, CCl_4 and amines has not been described.

We have found that an efficient synthesis of dichloride **1** as the key compound for the preparation of Schiff bases from benzene and CCl_4 in the presence of $AlCl_3$, does not require any solvent besides CCl_4. We carried out this reaction at molar ratio $[PhH]/[CCl_4]/[AlCl_3]$ of 1 : 1 : 0.5 or 1 : 1.5 : 0.5 at room temperature for 1 h. Under these conditions, compound **1** was formed selectively in yields of 82–87%. In CH_2Cl_2, this reaction leads to a decrease in both yield and selectivity, apparently due to formation of by-products form benzene alkylation with CH_2Cl_2. In our synthesis of dichloride **1**, CCl_4 acts as a reactant as well as a component of the catalyst[14] and a solvent.

To obtain the Schiff base, aromatic amine was introduced to *in situ* generated dichloride **1** at a molar ratio $[ArNH_2]/[C_6H_6]$ of 0.5 : 1. The reaction with $2,6\text{-}Me_2C_6H_3NH_2$ and $4\text{-}HalC_6H_4NH_2$ (Hal = Cl, F) was carried out at room temperature for 1.5–2 h, while the reactions with other amines (Table 1) were performed at 55–60 °C for 1–3 h. After an aqueous work up, Schiff bases **2a**–**k** were purified by recrystallization.

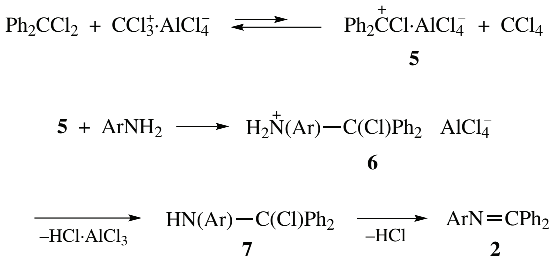
Note, the method developed makes it possible to obtain Schiff bases from sterically hindered anilines, whereas the reactions of benzophenone with such amines have been never accomplished previously. For example, a product from benzophenone and *o*-nitroaniline was obtained only in trace amounts and was not characterized.[3(a)] Similarly, attempts to obtain the Schiff bases from benzophenone and 2,6-dimethylaniline[8(d)] or 2-aminobenzonitrile[15(a)] as well as from aniline and 2-methyl-[15(b)] or 2-methoxybenzophenones[15(c),(d)] failed. For comparison, Schiff bases **2a**,**h** were prepared earlier by heating dichloride **1** with the corresponding amines at 110 °C for 24 h in toluene.[1] Compounds **2e**,**g**,**k** can be further transformed into functionally substituted benzophenone imines *via* the Suzuki cross-coupling.[4]

The reaction mechanism can involve the formation of cation **5** from dichloride **1** upon action of an electrophile, followed by the formation of ammonium salt **6** from cation **5** and aniline. Elimination of HCl from salt **6** leads to intermediate **7**, which converts into a Schiff base after elimination of the second HCl molecule (Scheme 3).

Our attempts to carry out this reaction with aliphatic amines were unsuccessful. The different behavior of aromatic and aliphatic amines here is apparently due to their diverse basicity. For example, pK_a of aniline is 4.6, while pK_a for aliphatic amines is 15.0 or higher.[16(a)] The formation of stable complexes of aliphatic amines with $CCl_4{\cdot}AlCl_3$[16(b),(c)] can be the reason for their inertness in this reaction.

Table 1 Preparation of Schiff bases by one-pot procedure from benzene, $CCl_4{\cdot}AlCl_3$ and aromatic amines.

Entry	$ArNH_2$	Schiff base	Yield (%)	Mp (lit. mp)/°C
1	$PhNH_2$	**2a**	77	103–105 [104–106[6(b)]]
2	$4\text{-}MeC_6H_4NH_2$	**2b**	73	47 [48–50[6(c)]]
3	$4\text{-}MeOC_6H_4NH_2$	**2c**	80	71–72 [70–72[6(b)]]
4	$4\text{-}FC_6H_4NH_2$	**2d**	62	106–108 [102–104[6(b)]]
5	$4\text{-}ClC_6H_4NH_2$	**2e**	80	88–89 [88–89[6(b)]]
6	$2\text{-}ClC_6H_4NH_2$	**2f**	69	87.5–89 [93–95[6(b)]]
7	$4\text{-}BrC_6H_4NH_2$	**2g**	85	80–82 [82–83[6(b)]]
8	$4\text{-}O_2NC_6H_4NH_2$	**2h**	83	156–157 [152–153[6(b)]]
9	$2,6\text{-}Me_2C_6H_3NH_2$	**2i**	75	90–92 [90–92[6(b)]]
10	$2\text{-}O_2NC_6H_4NH_2$	**2j**	40	106–108
11	$2\text{-}Cl\text{-}4\text{-}MeC_6H_3NH_2$	**2k**	76	72–74



$$Ph_2CCl_2 + CCl_3^+{\cdot}AlCl_4^- \rightleftharpoons Ph_2\overset{+}{C}Cl{\cdot}AlCl_4^- + CCl_4$$

$$\mathbf{5} + ArNH_2 \longrightarrow H_2\overset{+}{N}(Ar){-}C(Cl)Ph_2\ \ AlCl_4^-\ \ (\mathbf{6})$$

$$\xrightarrow[-HCl{\cdot}AlCl_3]{} HN(Ar){-}C(Cl)Ph_2\ (\mathbf{7}) \xrightarrow[-HCl]{} ArN{=}CPh_2\ (\mathbf{2})$$

Scheme 3

All the products were characterized by ^1H and ^{13}C NMR spectra, IR and MS spectrometry. The spectra and melting points for of products **2a**–**i** were identical to the known ones (see Online Supplementary Materials). The structures of new compounds **2j**,**k** were also proved by elemental analysis.

The attempted extension of the method developed towards other arenes than benzene turned impractical. In our hands, the empolyment of toluene or fluorobenzene gave poorly separable mixture of 2,2′-, 2,4′- and 4,4′-dimethylbenzophenone or difluorobenzophenone imines, respectively.

In summary, we have found that the well known reaction of benzene with CCl_4 in the presence of $AlCl_3$ provides good possibility for the easy preparation of benzophenone Schiff bases. Compared to the previously described methods, our approach comprise availability of the reactants, no need for inert atmosphere or strictly anhydrous conditions, simple one-pot procedure, good or moderate yields as well as compatibility with sterically crowded aromatic amines.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2020.03.037.

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