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Base-induced rearrangement of tritylamines to imines: discovery and investigation of the mechanism

Vassiliki Theodorou,* Konstantinos Skobridis and Aris Karkatsoulis

Department of Chemistry, Section of Organic Chemistry and Biochemistry, University of Ioannina, GR-451 10 Ioannina, Greece

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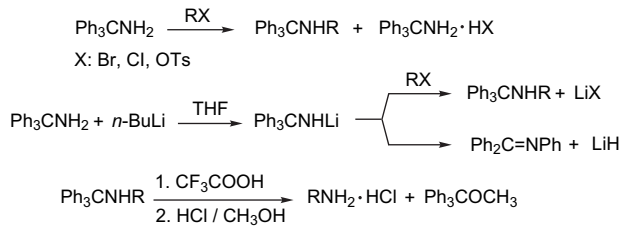
Abstract—An unexpected compound, the aniline derived benzophenone imine, was isolated when tritylamine was treated with *n*-BuLi and alkyl halides, during the formation of *N*-alkyl tritylamines, in the process of preparing primary amines. A nucleophilic attack of the nitrogen anion of tritylamide on the adjacent C-bonded phenyl, either substituted or not, involving a bridging anionic intermediate, is proposed for this base-induced tritylamine rearrangement to produce the corresponding imine. Electron-withdrawing groups in the aromatic ring, favoring the negative charge development, affect the relative migratory tendencies.

1. Introduction

The conversion of alkyl halides, alcohols or other similar alkylating agents to their corresponding primary amines is a very useful organic transformation. In the search for a mild, simple, and convenient method for such a conversion, we reported the application of triphenylmethylamine or tritylamine[1] (Ph_3CNH_2 or $TrNH_2$) as an ammonia synthon. Primary alkyl halides react smoothly in CH_3CN solution with 2 equiv of tritylamine to give *N*-tritylamines (TrNHR) and the salt of $TrNH_2 \cdot HX$. Alkyl tosylates react faster in refluxing toluene, giving the desired TrNHR. Such amines are also successfully derived from alkyl halides and lithium tritylamide formed by the reaction of $TrNH_2$ and *n*-BuLi in THF (Scheme 1).



Scheme 1. The synthesis of primary amines using tritylamine.[1]

Due to the high symmetry of the bulky trityl group, most of the *N*-alkylated tritylamines, obtained almost quantitatively in the reaction mixture, are easily separated and purified by recrystallization, while the byproducts can be easily separated, recycled, and reused. Trityl moiety is a valuable acid-labile sterically bulky protecting group for peptide, carbohydrate, and nucleotide chemistry, which can be selectively removed.[1] The extremely mild acidic conditions, under which the *N*-trityl group can be removed, make tritylamine a very useful ammonia equivalent in synthesis.

Recently, we have reported[2] that during the preparation of *N*-alkyl tritylamines by the reaction of lithium tritylamide and primary alkyl halides in THF, an unexpected compound was isolated, the imine $Ph_2C{=}NPh$ (benzophenone phenylimine or benzophenone anil), formed by phenyl migration and hydride loss from the tritylamide anion.

In view of these results, we tried to examine the mechanism of this transformation. To our delight, we realized that the formation of the imine was taking place regardless of the addition, or not, of alkyl halide.

After that, we tried to explore the mechanistic details for the above-mentioned base-induced rearrangement.

Previous reports related to this type of rearrangements have appeared in the literature. The well-known Stieglitz rearrangement[3] of *N*-substituted amines involves the migration of an aryl group from carbon to nitrogen through a bridging cationic intermediate to form the corresponding imine. The base-promoted rearrangement of tertiary benzylic amines, demonstrated by Eisch et al.,[4] involves an intramolecular

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* Corresponding author. Tel.: +30 26510 98591; fax: +30 26510 98682; e-mail: vtheodor@cc.uoi.gr

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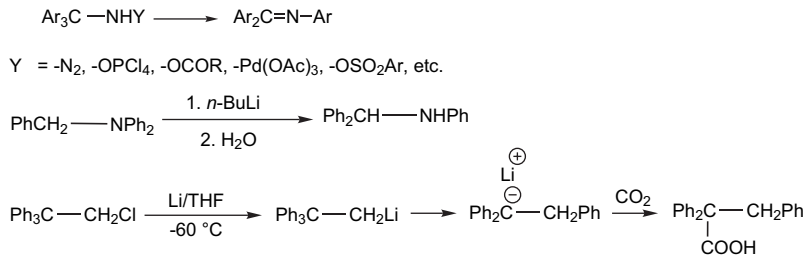


Scheme 2. Related 1,2-intramolecular aryl rearrangements.

shift of a phenyl or aryl group from nitrogen to carbon through a bridging anionic intermediate, leading to the formation of benzhydrylamines. Alternatively, the rearrangement of triphenylethyl lithium, described by Grovenstein and Williams,[5] takes place via a phenyl migration from carbon to carbon and a resonance stabilized carbanion. Confirmation of these results was provided with the formation of the subsequent addition product, through carboxylation to the corresponding propanoic acid (Scheme 2).

We are not aware, until now, of any reports on analogous reactions or related systems undergoing base-promoted phenyl migration and hydride loss.

Herein, we reveal our preliminary efforts in this area,[1,2] demonstrating the ability of the tritylamides to undergo intramolecular rearrangement, and we propose a mechanism for this rearrangement on the basis of the electronic properties of the migrating group and trapping experiments. Evidence was provided for the preferential migration, suggesting the presence of an anionic bridged intermediate. The migrating group moves without its electron pair, after a nucleophilic attack of the nitrogen anion on an adjacent *C*-bonded phenyl or aryl, forming the cyclic intermediate.

Loss of a hydride and subsequent phenyl rearrangement lead to the formation of the imine. Readdition reactions with CH_3I and H_2O or D_2O excluded the possibility of an intermediate carbanion, since no other products, except $TrNHCH_3$, were identified.

2. Results and discussion

2.1. Mechanism: substituent effects

The principal mechanistic questions were (i) whether the rearrangement is truly cationotropic/electrophilic (where the migrating group moves without its electron pair) or, maybe, anionotropic/nucleophilic (where the migrating group moves with its electron pair), and (ii) what the electronic requirements are for the migration of an aryl group from the C to the N center. It was critical to learn, also, whether an intramolecular 1,2-aryl shift occurs, by way of a bridging anionic or cationic intermediate, or whether an anionic process through a resonance stabilized carbanion.[2]

In order to determine the influence of the substituents on the mechanism of the rearrangement, we examined a series of monosubstituted tritylamines. Substituents of *p*-OCH_3, *p*-CH_3, and *p*-CF_3 were chosen, because of their compatibility with the strong basic and nucleophilic reaction conditions and because they provide varying electronic demands. Furthermore, the electron-withdrawing *p*-Br was attempted, even though it is not compatible with the reaction conditions, since halogen–metal exchange is also carried out in the presence of the butyllithium reagent.[6]

2.2. Preparation of the tritylamines and imines

The *p*-monosubstituted tritylamines were synthesized by the reaction of ammonia and the corresponding tritylchloride, according to a modification of the published procedures.[1,3c] The synthesis of the tritylchlorides was achieved by a Grignard reaction of the appropriate benzophenone and phenyl magnesium bromide to the respective trityl alcohol, followed by reaction of the alcohol with thionyl chloride to the corresponding tritylchloride (Scheme 3, Eq. 1).

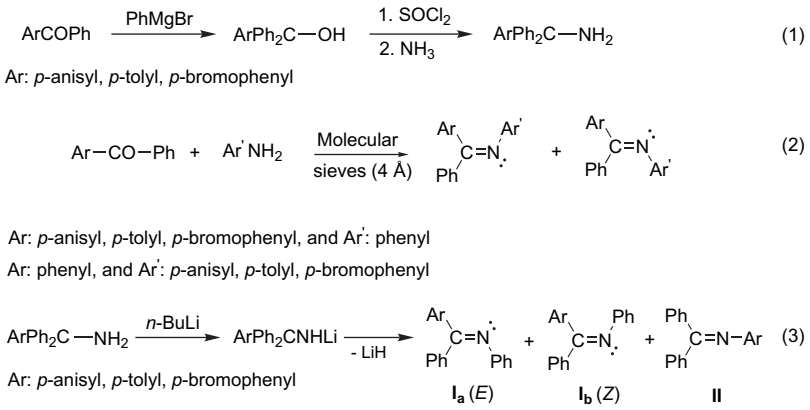
In addition, to characterize the products of the various tritylamines rearrangement, it was necessary to synthesize all the potentially formed ketimines, according to the published methods,[7–9] as samples of comparison, in order to analyze them directly by ^1H NMR. They were prepared from the appropriate benzophenone and aniline in the presence of molecular sieves[7] (Scheme 3, Eq. 2). After completion of the reaction and purification by column chromatography on alumina, the imines, as a mixture of *E* and *Z* geometric isomers, were isolated as yellow oils in relatively low yields (65–75%). This is due to their instability[8] to both silica and alumina.

2.3. Rearrangement reactions: analysis of products

The rearrangement reactions of tritylamines were readily performed in THF at −75 °C.

A mixture of two structurally isomeric imines **I** (as a mixture of *E* and *Z* isomers) and **II** is expected in all the rearrangement reactions. The relative abundance of these two products is sensitive to the electronic properties of the phenyl substituents (Scheme 3, Eq. 3).

We realized that the mixture of the expected isomeric imines was efficiently hydrolyzed during the purification by column chromatography on silica gel or alumina, in different rates, and thus it was not possible to establish their real composition. Thus, in order to obtain the formed imines at their representative composition, preparative chromatography on alumina plates was immediately performed.



Scheme 3. Synthesis of tritylamines and imines (Eqs. 1–3).

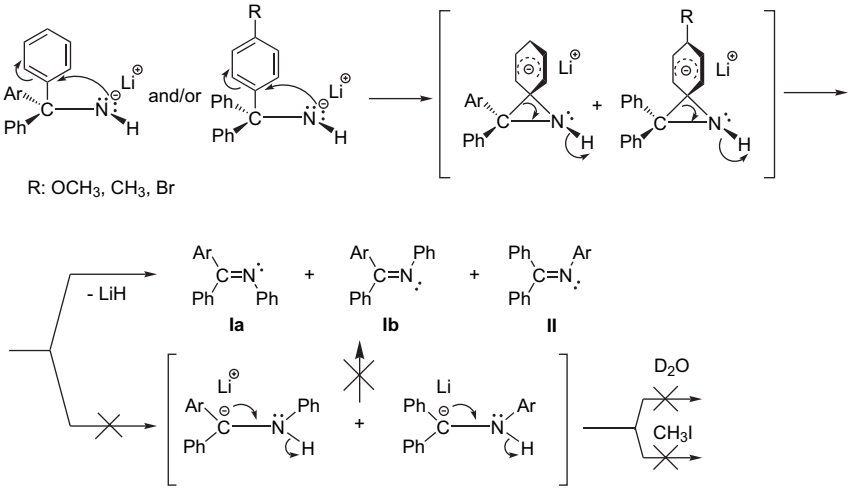
The products obtained from the rearrangement reactions suggest the formation of special intermediates, as illustrated in Scheme 4.

First of all, *p*-methoxytritylamine was examined, as *p*-OCH_3 was considered to be a strong electron-donating group, compatible with the reaction conditions, so that a direct comparison of the migratory tendencies of the unsubstituted phenyl ring and the *p*-OCH_3 substituted phenyl ring would be possible. A mixture of two structural isomers **I** and **II** was produced, in a ratio of ~3:1, as estimated macroscopically by the TLC picture.

We attempted to determine their ratio using the chemical shifts of the methoxy protons. ^{1}H NMR analysis of the imine mixture, after purification with preparative chromatography on alumina, revealed that imine **I** was about three times as much as imine **II**, showing that phenyl ring rearrangement was favored over the *p*-OCH_3 substituted phenyl ring. Obviously, migration of one of the two phenyls was faster, compared with the *p*-OCH_3 substituted phenyl ring, due to the greater stabilization of the bridged anionic intermediate in the first case. Imine **I** exists as a mixture of two geometrical isomers *E* and *Z* ($\mathbf{I_a}$ and $\mathbf{I_b}$), in a ratio of 1.7:1, as determined by ^{1}H NMR, while imine **II** exists only in one isomer. Three signals for the aromatic *p*-methoxy group protons were observed, indicating the occurrence of the three isomers ($\mathbf{I_a}$, $\mathbf{I_b}$, **II**) and confirming their identity (3.70, 3.75, and 3.83 ppm, respectively). Relative integration of the above three isomers gave a ratio of 2.1:1.2:1.

With *p*-methyltritylamine and the weakly electron-donating *p*-CH_3 group, imine **I** was slightly favored, yielding a ratio of imines: **I**:**II** of 2.1:1, while the two geometrical isomers *E* and *Z* were 1:1, as revealed from the ^{1}H NMR spectra of the imine mixture, obtained through preparative chromatography. Thin layer chromatography does not distinguish the two imines (**I** and **II**). Three signals for the *p*-tolyl methyl protons were observed, indicating the occurrence of the three isomers ($\mathbf{I_a}$, $\mathbf{I_b}$, **II**) and confirming their identity (2.23, 2.29, and 2.39 ppm, respectively). Relative integration of the above three isomers gave a ratio of 1:1:0.95.

In the case of *p*-bromotritylamine, which is not consistent with the reaction conditions, the expected debromination product[6] aniline derived benzophenone imine, $Ph_2C{=}NPh$ (^{1}H NMR spectrum identical with that of authentic sample), was isolated, at the same time with the *p*-bromoaniline derived benzophenone imine. However, the aniline derived bromobenzophenone imine was not detected by the ^{1}H NMR analysis. It seems that, only the *p*-bromophenyl group was rearranged, since *p*-Br stabilizes the intermediate



Scheme 4. Proposed mechanism for the imines formation.

anionic species. It is not certain whether the bromine to proton exchange occurs before or after the rearrangement.

Finally, our attempts to obtain the rearrangement products of *p*-trifluoromethyltritylamine were not successful. With the strongly electron-withdrawing *p*-CF_3 phenyl substituent, we failed to isolate any imine, but we obtained benzophenone and trifluoromethylaniline, which are the hydrolysis products of *p*-trifluoromethylaniline derived benzophenone imine, together with unreacted tritylamine (~40%) and other not identified minor byproducts (<5%). The above result indicates that only the *p*-substituted phenyl group was rearranged, as *p*-CF_3 is strongly stabilizing the intermediate anion. Moreover, it seems that the *p*-trifluoromethyl imines are very unstable and are easily decomposed to their hydrolysis products. Due to their great instability,[8] we failed to prepare pure *p*-CF_3-substituted imines, by the reaction of the respective benzophenone and aniline over molecular sieves.

3. Conclusion

From all these results, a cationotropic or electrophilic rearrangement of tritylamines upon treatment with *n*-BuLi is suggested. The base-promoted 1,2-intramolecular phenyl migration from the benzylic carbon of the tritylamide to the nitrogen occurs via a bridging anionic intermediate. Loss of a hydride and simultaneous aryl rearrangement leads to the formation of imines. The driving force for the phenyl migration and the hydride abstraction seems to be the release of steric strain from tritylamine relative to the imine.

The nitrogen anion of tritylamide attacks the adjacent aryl, affording, preferably, the better stabilized anion. The development of the negative charge on the migrating aryl group is influenced by the electronic nature of the substituents, being favored with electron-withdrawing groups (Br, CF_3). On the other hand, the electron-donating *p*-OCH_3 group does not favor the development of the negative charge and phenyl migration is preferred. The weakly electron-donating *p*-CH_3 group seems to slightly affect the composition of the reaction products (Table 1). This substituent effect can be explained by consideration of the mechanism of Scheme 4, excluding the rearrangement through a cationic intermediate. The relative amounts of imines **I** and **II** are dependent on the electron-withdrawing nature of the migrating aryl. The overall order of migratory tendencies (migratory aptitudes) is considered to be the following: CF_3>Br>H~CH_3>OCH_3 (Table 1).

Table 1. Reaction of *n*-BuLi with $ArPh_2C–NH_2$ (Eq. 3)

Amine (Ar)	Relative yield[a] **II**:**I**	M.A.[b]
p-Anisyl	1:3.34	0.60
p-Tolyl	1:2.1	0.95
p-Bromophenyl	1:n.d.[c]	≫1
p-Trifluromethylphenyl	1:n.d.	(≫1)[d]

[a] The ratios of **I** and **II** were obtained from the imine mixture by ^{1}H NMR analysis.
[b] M.A (migratory aptitudes) were calculated on the basis of the statistical preference factor of 2 for the phenyl migration versus the *p*-substituted phenyl: **II**:**I/2**.
[c] Not detected (n.d.).
[d] Only the hydrolysis products of the respective imine **II** were detected.

Confirmation of these results was provided by a direct attempt of readdition reactions. A rearranged carbanion could be trapped by any relatively good electrophile. When the reaction was quenched with D_2O, after a short period of time, no deuterated products corresponding to addition reaction have been identified. Addition of CH_3I to the reaction mixture did not give any other product, but the expected *N*-methyl tritylamine, TrNHMe.[1] This negative trapping result excludes the occurrence of any intermediate carbanion and supports the proposed mechanism.

While the mechanism depicted in Scheme 4 is consistent with experimental evidence, further theoretical and experimental exploration of other mechanistic possibilities for this type of migrations is continuing.

4. Experimental

4.1. General

All solvents were dried and distilled by standard methods. Tetrahydrofuran was purified by fresh distillation over sodium/benzophenone. Commercially available reagents were used without further purification. Analytical thin layer chromatography and preparative scale chromatography were performed on silica gel 60 F_{254} (Merck) and aluminum oxide 150 F_{254} neutral (Typ T, Merck), respectively. Column chromatography was performed either on silica gel (230–400 mesh) or on aluminum oxide neutral (type 507 C, Fluka). ^{1}H NMR spectra were recorded on Bruker AMX 400 and AMX 250 spectrometers (400 MHz and 250 MHz, respectively), at ambient temperature using tetramethylsilane (TMS) as an internal standard and deuterated chloroform as the solvent. Chemical shifts are reported in ppm (δ) referenced to TMS.

4.2. General synthetic procedures

4.2.1. Synthesis of *p*-monosubstituted tritylcarbinols. To a solution of phenyl magnesium bromide (11 mmol) in 30 mL of diethyl ether, prepared from equivalent quantities of bromobenzene and magnesium turnings, a solution of the monosubstituted benzophenone (10 mmol) in 20 mL of diethyl ether was added dropwise under an atmosphere of argon over a period of several minutes. Spontaneous boiling started and the reaction mixture, after being refluxed for 1 h, was diluted with additional 20 mL of diethyl ether and left under stirring at room temperature for about 2 h. At this point, the mixture was cooled in ice and quenched with a saturated aqueous solution of NH_4Cl (10 mL). The organic phase was separated, washed with H_2O (2×25 mL), dried over Na_2SO_4, evaporated, and the residue was recrystallized from ether/hexane. Total yields: 65–90% colorless solids. Their identity was confirmed by comparing their melting points with those of the literature[10] (98–99, 73–74, and 78–79 °C for the *p*-Br, *p*-CH_3, and *p*-OCH_3 carbinol derivatives, respectively).

4.2.2. Synthesis of *p*-monosubstituted tritylchlorides. To a solution of the *p*-substituted tritylcarbinol (10 mmol) in 50 mL of anhydrous CCl_4, freshly distilled thionyl chloride (4 mL, 55 mmol) was added under an atmosphere of argon

and the mixture was stirred at room temperature for 5 h.[11] After that, the mixture was concentrated in vacuo to give the corresponding chlorides as white solids, which were used without further purification.

4.2.3. Synthesis of *p*-monosubstituted tritylamines. To a solution of the *p*-substituted tritylchloride (10 mmol) in 15 mL CH_2Cl_2, ammonium hydroxide (15 mL, 28% in water) was added and the mixture was stirred vigorously for about two days. After that, it was extracted with CH_2Cl_2 (2×20 mL) and washed with water (2×25 mL). The organic layer was concentrated in vacuo and the resulting amine was purified by column chromatography on silica using CH_2Cl_2 as eluent (yield: 70–80%). The ^{1}H NMR spectra of the respective compound confirmed its identity.[3c]

4.2.3.1. *p*-Bromophenyldiphenylmethylamine *p*–Br–C_6H_4–Ph_2C–NH_2. ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.05 (2H, s, N*H*$_2$), 7.19 (2H, d, Ar*H*), 7.29 (10H, m, Ar*H*), 7.44 (2H, d, Ar*H*); white solid.

4.2.3.2. Diphenyl-*p*-tolylmethylamine *p*-CH_3–C_6H_4–Ph_2C–NH_2. ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.17 (2H, s, N*H*$_2$), 2.33 (3H, s, C*H*$_3$), 7.13 (4H, m, Ar*H*), 7.26 (10H, m, Ar*H*); oil.

4.2.3.3. *p*-Anisyldiphenylmethylamine *p*-CH_3O–C_6H_4–Ph_2C–NH_2. ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.19 (2H, s, N*H*$_2$), 3.75 (3H, s, OC*H*$_3$), 6.78 (2H, d, Ar*H*), 7.13 (2H, d, Ar*H*), 7.23 (10H, m, Ar*H*); oil.

4.2.3.4. Diphenyl-*p*-trifluoromethylphenylmethylamine *p*-CF_3–C_6H_4–Ph_2C–NH_2. ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.16 (2H, s, N*H*$_2$), 7.12 (2H, d, Ar*H*), 7.24 (12H, m, Ar*H*); oil.

4.3. Rearrangement of tritylamines

To a solution of 1 mmol of the respective tritylamine in 10 mL of THF, cooled to about −75 °C, 1 mmol of a solution of *n*-BuLi in hexane (1.6 M) was added under an argon atmosphere. A deep red-colored solution was obtained. The solution was left at this temperature for about 1 h, then the solvent was removed, CH_2Cl_2 was added (20 mL), and the solution filtered and concentrated. The crude mixture[8] was directly absorbed on neutral preparative alumina plates and eluted with a mixture of dichloromethane/hexane (1:1). The obtained ^{1}H NMR spectra confirmed the identity of the products, in each case, by comparison with the pure synthesized compounds.

(Yield: ∼50–60% of imines, hydrolysis products of the imines about 5% and other, not identified, minor byproducts <2%, as well as unreacted tritylamines).

4.4. Synthesis of imines

To a solution of the respective benzophenone (10 mmol) in ether or toluene (10 mL), aniline (11 mmol) was added. The reaction mixture was refluxed upon 5 g of 4 Å molecular sieves for 12–24 h. After completion of the reaction, monitored by TLC, the solution was filtered and concentrated in vacuo. After purification by column chromatography on alumina, using the eluent dichloromethane/hexane (1:1), the imines were isolated as yellow oils. Their ^{1}H NMR spectra were acquired and determined as a mixture of *E* and Z geometric isomers.

4.4.1. Benzophenone phenylimine (or benzophenone anil) Ph_2C=N–Ph. ^{1}H NMR (250 MHz, $CDCl_3$) δ 6.72 (2H, dd, Ar*H*), 6.92 (1H, dt, Ar*H*), 7.10–7.27 (7H, m, Ar*H*), 7.37–7.48 (3H, m, Ar*H*), 7.75 (2H, dd, Ar*H*) (lit.[2]).

4.4.2. *p*-Bromobenzophenone phenylimine Br–C_6H_4–PhC=N–Ph. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.69 (2H, dd, Ar*H*), 6.89 (1H, m, Ar*H*), 6.95 (2H, d, Ar*H*), 7.05–7.24 (5H, m, Ar*H*), 7.34–7.50 (3H, m, Ar*H*), 7.59 (1H, m, Ar*H*), 7.69 (1H, m, Ar*H*) (lit.[3e,12a]).

4.4.3. Benzophenone *p*-bromophenylimine Ph_2C=N–C_6H_4–Br. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.60 (2H, dt, Ar*H*), 7.10 (2H, dd, Ar*H*), 7.23–7.31 (5H, m, Ar*H*), 7.38–7.42 (2H, t, Ar*H*), 7.46–7.51 (1H, m, Ar*H*), 7.74 (2H, dd, Ar*H*) (lit.[6]).

4.4.4. *p*-Methylbenzophenone phenylimine CH_3–C_6H_4–PhC=N–Ph. ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.29 and 2.39 (3H, s, C*H*$_3$, as a mixture of *E*/*Z* isomers, ∼1:1), 6.72 (2H, dt, Ar*H*), 6.88–7.26 (9H, m, Ar*H*), 7.36–7.47 (1H, m, Ar*H*), 7.64 (1H, d, Ar*H*), 7.72–7.75 (1H, m, Ar*H*) (lit.[9a]).

4.4.5. Benzophenone *p*-tolylimine Ph_2C=N–C_6H_4–CH_3. ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.23 (3H, s, C*H*$_3$), 6.60 (2H, d, Ar*H*), 6.91 (2H, d, Ar*H*), 7.08–7.12 (2H, m, Ar*H*), 7.22–7.26 (3H, m, Ar*H*), 7.34–7.44 (3H, m, Ar*H*), 7.69–7.72 (2H, m, Ar*H*) (lit.[9b,c]).

4.4.6. *p*-Methoxybenzophenone phenylimine CH_3O–C_6H_4–PhC=N–Ph. ^{1}H NMR (250 MHz, $CDCl_3$) δ 3.75 and 3.83 (3H, s, OC*H*$_3$ as a mixture of *E*/*Z* isomers, ∼1:1.7), 6.68–7.47 (12H, m, Ar*H*), 7.69–7.75 (2H, m, Ar*H*) (lit.[3c,9e,12b]).

4.4.7. Benzophenone *p*-anisylimine Ph_2C=N–C_6H_4–OCH_3. ^{1}H NMR (250 MHz, $CDCl_3$) δ 3.70 (3H, s, OC*H*$_3$), 6.69 (4H, ∼s, Ar*H*), 7.10–7.14 (2H, m, Ar*H*), 7.26–7.29 (3H, m, Ar*H*), 7.38–7.45 (3H, m, Ar*H*), 7.72–7.76 (2H, dt, Ar*H*) (lit.[9d]).

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