

New Heteroaromatic Azo Compounds Based on Pyridine, Isoxazole, and Benzothiazole for Efficient and Highly Selective Amidation and Mono-*N*-Benzylation of Amines under Mitsunobu Conditions

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4,4′-Azopyridine (**2c**) is used in conjunction with triphenylphosphine for the efficient conversion of carboxylic acids into amides via Mitsunobu reaction with primary and secondary aliphatic and aromatic amines. The highly selective amidation of only primary aromatic amines with new heterogeneous azo compounds based on benzothiazole **2d** and isoxazole **2e** is also described. These azo compounds **2c**–**2e** can also be applied for selective mono-*N*-benzylation of primary aromatic amines. The solid side product heteroaromatic hydrazines obtained under the developed Mitsunobu conditions are easily separated by simple filtration and can be reoxidized to azo compounds for further use.

Development of simple, efficient, and useful methods for the easy synthesis of organic compounds using readily available reagents is one of the major research demands in organic synthesis. Among these, C–N bond formation is one of the most significant transformations in organic synthesis. Amides and amines are significant classes of compounds owing to their versatility as building blocks and intermediate in organic synthesis and also in chemical industrial processes.[1] Some derivatives of amides exhibit biological properties such as antitumor, anthelmintic, antihistamine, antifungal, and antibacterial activity.[2] Synthesis of these compounds has mainly been achieved by classical chemical reactions, which generally involve the generation of a reactive carboxy derivative, either an acid chloride, anhydride, or acyl azide,[3] followed by aminolysis with an amine, due to the low activity of carboxylic acids. More recently, new systems were developed for facile synthesis of amides using carbonyl diimidazole,[4] isocyanides, and carboxylic acids in methanol,[5] Staudinger ligation,[6] microwave activation,[7] *N*-reductive alkylation followed by acylation,[8] and catalytic systems.[9] Besides, due to the synthetic utility of amines, reactions of amines have been a topic of immense research interest.[10] Also, the alkylation of primary amines to secondary or tertiary amines is one of the most fundamental reactions in organic synthesis. Alkylation with alkyl halides or similar alkylating agents is the most conventional and well-known method,[11] but it generates salts as by-products and exhibits often low chemical selectivity. In addition, other approaches that are employed to obviate this problem are the use of catalytic systems in the presence of alcohols, such as ruthenium, rhodium, iridium, zinc, palladium, γ-alumina, KF/Al_2O_3,[12–18] reductive amination of carbonyl compounds,[12a,19] and amide reduction.[20] In many cases direct *N*-monoalkylation of amines is either unsatisfactory or not possible because subsequent alkylation occurs and cannot be readily prevented. Moreover, toxicity of such alkylating agents can be problematic.[21] For these reasons, the expansion of new and more efficient methodologies to introduce a nitrogen moiety in a synthetic sequence will always be a major issue of interest. One chemical transformation that has received attention in organic synthesis is the Mitsunobu reaction. The Mitsunobu reaction provides an extremely useful and versatile synthetic method for a large array of products.[22] The Mitsunobu protocol involves activation of alcohols for attack by a range of acidic pronucleophiles NuH to form accumulation product RNu which contains the newly formed C–X bond (X = C, O, N, S, and halogens) using the combination of an azodicarboxylate and a phosphine. However, the use of this method is complicated by the resulting complex reaction mixtures containing product, triphenylphosphine oxide and the reduced azodicarboxylate, as well as unreacted starting material. Herein we wish to report a simple, convenient, and efficient method for amidation and selective *N*-monoalkylation of aromatic amines using hetero aryl azo compounds as new, easily prepared and stable reagents in the Mitsunobu reaction.

In spite of widespread use, the original Mitsunobu reaction employing diethyl azodicarboxylate (DEAD) and triphenylphosphine (TPP) has a serious drawback: the difficulty involved in isolating the pure product from a crude reaction mixture containing excess and spent reagents, specifically phosphine oxide, hydrazine from reduced azodicarboxylate, and unconsumed acidic substrate NuH. So an assortment of approaches has surfaced for tackling the separation problems in the Mitsunobu reaction[23] and these approaches have recently been reviewed.[24] Furthermore, DEAD is an explosive, photosensitive, toxic, shock sensitive, and thermally unstable reagent, which may cause cancer or mutation.[25] In order to diminish these complications and in connection with our ongoing project aiming at the development and alteration of Mitsunobu reactions,[26] we recently reported azo pyridines as new, efficient, and possible alternatives to standard Mitsunobu esterification reagents.[27] In continuation of our earlier work, we report herein an efficient method using azopyridine **2c** for amidation of

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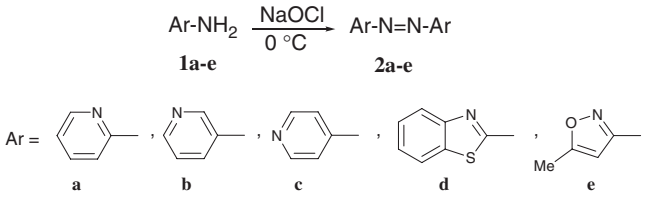


Scheme 1.

aliphatic and aromatic amines with carboxylic acids. In addition, the use of heterogeneous new hetero aryl azo compounds **2d** and **2e** for highly selective acylation and mono-*N*-benzylation of only primary aromatic amines is reported.

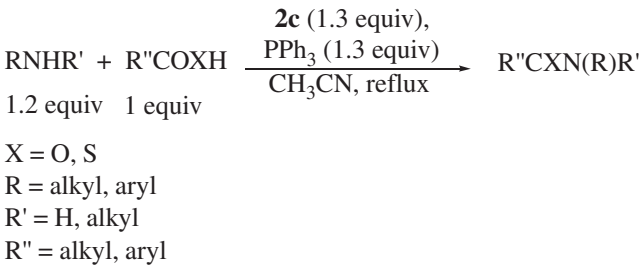
Results and Discussion

Our first attempts started with synthesis of 2,2′-, 3,3′-, and 4,4′-azopyridine (**2a**–**2c**) from oxidation of 2-, 3-, and 4-aminopyridine (**1a**–**1c**) with sodium hypochlorite solution 6–14% at 0 °C.[28] We then applied this condition to the synthesis of 2,2′-azobenzothiazole (**2d**) and 5,5′-dimethyl-3,3′-azoisoxazole (**2e**) from 2-aminobenzothiazole (**1d**) and 3-amino-5-methylisoxazole (**1e**) (Scheme 1).

To test the usefulness of these heterocyclic aryl azo compounds under Mitsunobu conditions for amidation of carboxylic acids, we found that the 2,2′- (**2a**) and 4,4′-azopyridines (**2c**) are nearly equally efficient reagents and are more reactive than their 3,3′-isomer **2b** for amidation of both aliphatic and aromatic amines with carboxylic acids. In comparison, it was observed that heterocyclic azo compounds based on benzothiazole **2d** and isoxazole **2e** are highly selective reagents for amidation of only primary aromatic amines.

Apart from the handling problems, a property that has restricted the Mitsunobu reaction somewhat is the isolation and purification of the desired product when contaminated by the produced diethyl hydrazinedicarboxylate by-product from DEAD. In addition, to the best of our knowledge, DEAD has not been employed for amidation reactions.[22,24] Although **2a** and **2c** were found to be equally efficient and acceptable alternatives for DEAD in the Mitsunobu reaction, since the yield for synthesis of **2c** is much higher than for **2a**, this compound was chosen as the reagent of choice for our study. 4,4′-Azopyridine (**2c**) can be simply purified by recrystallization and is very stable with easy handling. It should be noted that the 4,4′-hydrazopyridine by-product is solid and usually can be isolated from the reaction mixture by filtration. This makes the workup much easier compared to DEAD. Additionally, the resulting hydrazine by-product can also be recycled by oxidation with iodosobenzene diacetate in DMSO at room temperature to give the azo compound **2c**,[27] which can be reused. In the amidation process, the reaction of benzoic acid with aniline was chosen as a model reaction and carried out with different ratios of RCO_2H/amine/**2c**/PPh_3. Of the various stoichiometries, the ratio of 1.0/1.2/1.3/1.3 was the best and gave a high yield of benzanilide (86%). In designing our experiments we fixed the solvent as refluxing CH_3CN (Scheme 2).

With the optimized conditions in hand, a variety of carboxylic acids and aromatic amines were converted into the

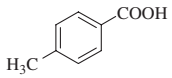
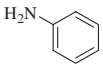
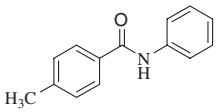
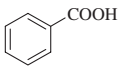
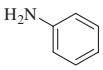
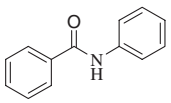
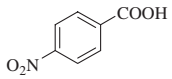
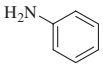
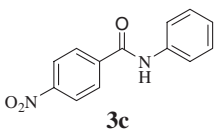
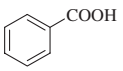
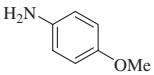
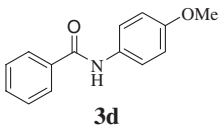
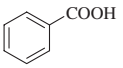
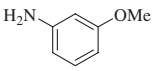
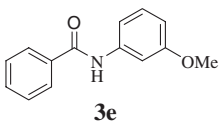
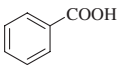
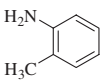
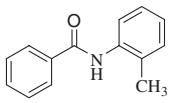
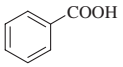
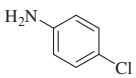
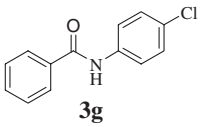
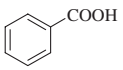
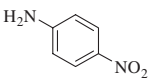
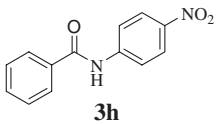
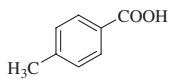
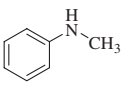
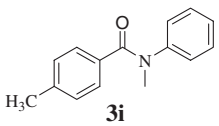
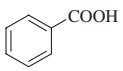
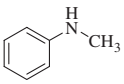
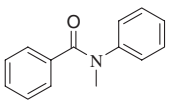
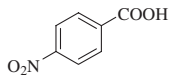
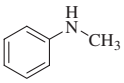
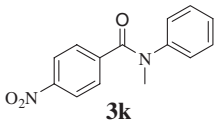
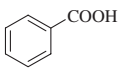
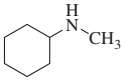
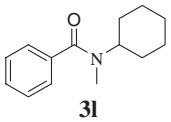


Scheme 2.

corresponding benzanilides, which indicated the procedure accommodates a wide range of substrates. The results are listed in Table 1.

The scope of this efficient reaction was explored with various electron-deficient and electron-rich acids and amines. Yields varied depending on the electronic nature of the substituents on both the acid and the amine. From Table 1 it was found that for most cases better results were observed for the reaction of electron-poor aromatic acids with activated aromatic amines carrying electron-donating substituents. For instance, reaction of *p*-methylbenzoic acid with aniline proceeded to afford the desired product **3a** in 77% (Table 1, Entry 1), while 86% and 94% yield of products **3b** and **3c** were obtained, respectively, when benzoic or *p*-nitrobenzoic acid were employed in the reaction (Table 1, Entries 2 and 3). As expected, anilines with an electron-donating group gave much better results. Treatment of *p*-methoxyaniline and benzoic acid led to a clean reaction affording the desired amide product **3d** in excellent yield (Table 1, Entry 4). The reaction of electron-deficient anilines such as *p*-chloro- and *p*-nitroaniline (Table 1, Entries 7 and 8) gave the corresponding amide **3g** and **3h** in lower yields of 85% and 70%, respectively. Also, a perceptible dependence of reaction durations on electronic factors is noteworthy. For the reactions in refluxing acetonitrile, the unsubstituted benzoic acid (Table 1, Entry 2) or acids that carry electron-withdrawing groups (Table 1, Entries 3 and 11), and also aniline (Table 1, Entry 3) and aniline derivatives that have electron-donating groups (Table 1, Entries 4 and 6) underwent approximately complete conversion in a comparable time (3–4.5 h), whereas *p*-methylbenzoic acid (Table 1, Entries 1 and 9) and *p*-nitroaniline (Table 1, Entry 8) were found to react in a relatively longer duration (6–8 h). The reaction of *N*-methylaniline with different substituted benzoic acid was found to afford the amides **3i**–**3k** in high yields (Table 1, Entries 9–11). In the case of synthesis of amides, the more nucleophilic *N*-methylaniline (91%) compared to poorly nucleophilic aromatic amines such as aniline (86%) gave the better yield (Table 1, Entry 10 compared to Entry 2). The intriguing reactivity observed with the variation of substituents in both acid and aromatic amine is clearly suggestive of the dependence of the reaction on acidity of benzoic acid derivatives and nucleophilicity of aromatic amines. As shown in Table 1, aliphatic amine (Entries 12 and 16) and both aliphatic (Entry 14) and aromatic acids (Entry 13) are suitable substrates for synthesis of the corresponding amides **3l**–**3p**. The successful transformation of both aliphatic and aromatic thiocarboxylic acids to their corresponding thioamides **3q** and **3r** was observed using the same reaction conditions as carboxylic acids (Table 1, Entries

Table 1. Synthesis of Amides under Condition of the Mitsunobu Reaction Using **2c**[a)]

Entry	Acid	Amine	Product[b)]	Time/h	Yield/%[c)]
1			 **3a**	6	77
2			 **3b**	4.5	86
3			 **3c**	3.5	94
4			 **3d**	4	91
5			 **3e**	4.5	82
6			 **3f**	4	89
7			 **3g**	5.5	85
8			 **3h**	8	70
9			 **3i**	6	88
10			 **3j**	5.5	91
11			 **3k**	3	94
12			 **3l**	4.5	87

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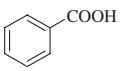
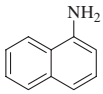
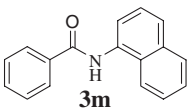
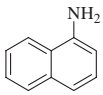
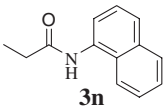
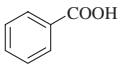
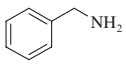
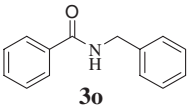
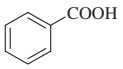
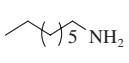
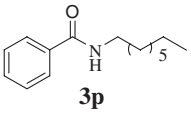
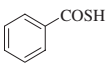
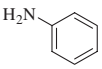
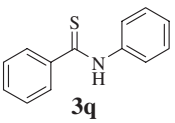
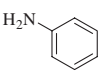
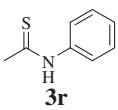
Continued.

Entry	Acid	Amine	Product[b)]	Time/h	Yield/%[c)]
13			 **3m**	5	87
14			 **3n**	5	84
15			 **3o**	3.5	89
16			 **3p**	3.5	90
17			 **3q**	4	84
18			 **3r**	4.5	83

a) The molar ratio of the reactants for $RCO_2H/ArNHR/PPh_3$/azpy in refluxing CH_3CN is 1.2/1.0/1.3/1.3. b) The products were identified by their spectral data. c) Isolated yield.

17 and 18). Taking advantage of the versatility and stability of azopyridines in the Mitsunobu reaction, we have synthesized two new azo compounds **2d** and **2e** that have more than one hetero atom in their aromatic ring and investigated their abilities in amidation reaction. First of all, we carried out a study of the proper conditions to carry out the amidation reaction between acids and amines. The optimized conditions such as solvent, ratio of reagents, and temperature were similar to the previously optimized conditions for azopyridines. On the basis of the optimized conditions, we probed their scope in the amidation of various aryl-substituted acids by substituted primary and secondary aliphatic and aromatic amines. Both 2,2′-azobenzothiazole (**2d**) and 5,5′-dimethyl-3,3′-azoisoxazole (**2e**) as well as 4,4′-azopyridine (**2c**) could be employed providing comparable isolated yields (Table 2).

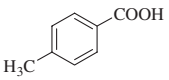
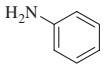
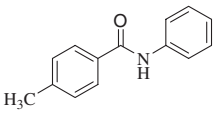
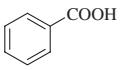
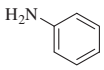
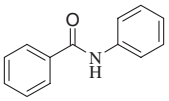
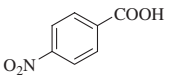
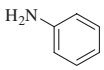
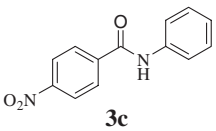
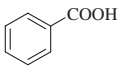
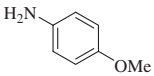
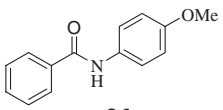
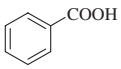
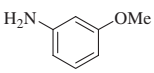
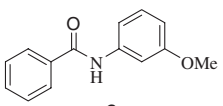
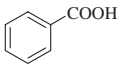
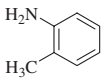
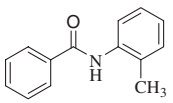
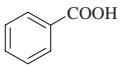
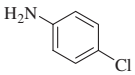
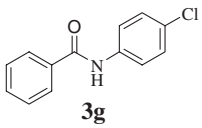
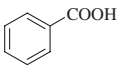
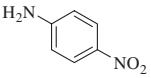
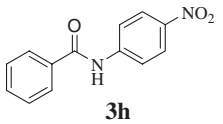
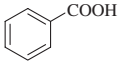
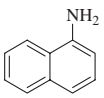
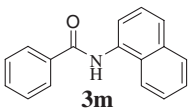
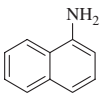
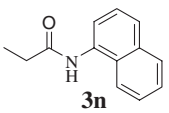
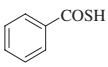
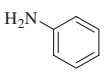
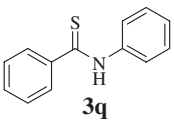
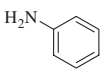
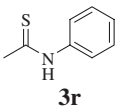
As shown in Table 2, under refluxing CH_3CN, a variety of primary aromatic amines were efficiently transformed into amides **3a**–**3h**, **3m**, and **3n** and the yields ranged from 66 to 93%. Both azo compounds **2d** and **2e** were applied for thioamide formation from aliphatic and aromatic thiocarboxylic acids. (Table 2, Entries 11 and 12). The process of amidation takes place as azopyridines, except that a longer reaction time was required (Table 2, Entries 1 and 2 compared to Table 1, Entries 1 and 2). The reaction tolerates electron-rich and electron-poor substituents in both acid and amines. The reaction of the aromatic and aliphatic carboxylic acids with electron-rich and -poor substituents on the aromatic amine such as –OMe, –Cl, and $–NO_2$ produced the corresponding amides with acceptable yields (Table 2). However, the use of aniline bearing an electron-withdrawing group such as the nitro (Table 2, Entry 8), lead to the desired product **3h** with lower yield due to the low nucleophilicity of amine. In addition to this, gratifyingly, from the results depicted in Table 2, it can be established that the amidation reaction that is performed with two azo compounds **2d** and **2e** was successful only for transformation of primary aromatic amines. Therefore, the use of azo compounds **2d** and **2e**, more electron deficient than azopyridines **2c**, permitted highly selective preparation of secondary aromatic amides **3a**–**3h**, **3m**, and **3n**.

To investigate the selectivity of reactions of these azo compounds **2d** and **2e**, we set up experiments using binary mixtures of equimolar amounts of aniline and different secondary aliphatic and aromatic amines with benzoic acid. NMR and TLC analysis of the reaction mixture showed that solely **3b** was formed and no **3k**, **3l**, **3o**, and **3p** were observed (Scheme 3).

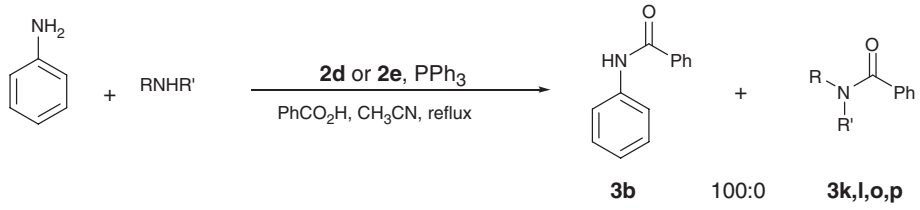
The results of this study are also summarized in Table 3. Crucially, treatment of a binary mixture of aniline and benzylamine under the optimized amidation conditions gave benzanilide (**3b**) as a single product, with none of the *N*-benzylbenzamide (**3o**) detectable in either the crude or purified products (76% yield for **2d** and 80% for **2e**, Table 3, Entry 2).

Reaction of benzoic acid with binary mixture including primary aromatic amine such as aniline and secondary aliphatic amines such as *N*-methyl-*N*-cyclohexylamine in the presence of azo compounds **2d** and **2e** showed complete selectivity for the aromatic amine over the secondary aliphatic amine, giving benzanilide (**3b**) in a yield of 82% and 77%, in the case of **2d** and **2e** respectively (Table 3, Entry 3). Reaction of the mixture of aniline and *N*-methylaniline under the above reaction

Table 2. Conversion of Various Primary Aromatic Amines to Corresponding Amides Using **2d** and **2e** under Mitsunobu Conditions[a)]

Entry	Acid	Amine	Product[b)]	2d		2e	
				Time/h	Yield/%[c)]	Time/h	Yield/%[c)]
1			 **3a**	9	73	10.5	71
2			 **3b**	7.5	75	8	80
3			 **3c**	5	88	5	85
4			 **3d**	7	93	8	90
5			 **3e**	7.5	77	9	79
6			 **3f**	5	84	4.5	89
7			 **3g**	6.5	87	6.5	90
8			 **3h**	11	70	12	66
9			 **3m**	5	90	6	91
10			 **3n**	6.5	90	7.5	86
11			 **3q**	6	85	6.5	83
12			 **3r**	6	82	7.5	82

a) The molar ratio of the reactants for $RCO_2H/ArNH_2/PPh_3$/azo in refluxing CH_3CN is 1.2/1.0/1.3/1.3. b) The products were identified by their spectral data. c) Isolated yield.



R = $PhCH_2$, *n*-Octyl, Cyclohexyl, Ph
R' = H, Me

Scheme 3.

Table 3. Selective Conversion of Various Amines with Benzoic Acid in Binary Mixtures to Corresponding Amides Using **2d** and **2e** under Mitsunobu Conditions[a)]

Entry	Binary mixture	Conversion /%[b)]	2d Time /h	2d Yield /%[c)]	2e Time /h	2e Yield /%[c)]
1	$PhNH_2$ / $CH_3(CH_2)_6CH_2NH_2$	**3b** 100 / **3p** 0	8.5	79	8.5	82
2	$PhNH_2$ / $PhCH_2NH_2$	**3b** 100 / **3o** 0	7.5	76	8	80
3	$PhNH_2$ / Cyclohex-NH-Me	**3b** 100 / **3l** 0	8	82	8.5	77
4	$PhNH_2$ / PhNHMe	**3b** 100 / **3k** 0	7	86	7.5	83

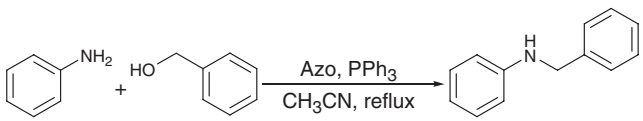
a) The molar ratio of Ph_3P/**2d** or **2e**/binary mixture/acid is 1.3/1.3/1.2/1.0. b) Analysis by TLC. c) Isolated yield.

conditions in acetonitrile resulted in a complete conversion, yielding **3b** as a single product selectively (Table 3, Entry 4). Despite versatility and significant improvements in the Mitsunobu reaction, attempts to apply DEAD and its derivatives to the alkylation of amines have not been satisfied by the low acidity of amines. In the case of amines, the yields are higher with lower pK_a of the amine component and due to the low acidity; aliphatic amines are usually resistant toward *N*-alkylation. According to our knowledge, there are very few examples in the literature where the Mitsunobu reaction has been used to form alkylated amines.[29] However, N–H acidic compounds, such as sulfonamides,[30] cyclic imides,[31] and amides[32] can be *N*-alkylated satisfactorily under Mitsunobu reaction conditions.

To extend the applicability of our methodology and find out the limitations encounter on using these novel azo compounds **2c**, **2d**, and **2e**, we sought conditions for performing *N*-alkylation of various amines. As expected, our attempts to alkylate aliphatic amines (e.g., *n*-butylamine) under the aforementioned conditions were unsuccessful. The reason for this observation is due to the fact that the Mitsunobu reactions generally proceed best with acidic nucleophiles.[33] However *N*-alkylation of primary aromatic amines with benzyl alcohols in the presence of **2c**, **2d**, and **2e** proceeded to give the corresponding *N*-benzylamines in good yields. The azo reagent optimization when aniline and benzyl alcohol were used as the starting material clearly indicated that **2c** is a more suitable azo reagent in terms of yield and reaction time (Table 4).

We found that this reaction has maximal yield when we use the molar ratios of 1.0/1.2/1.3/1.3 for ROH/ArNHR/**2c**/PPh_3 in refluxing CH_3CN (Scheme 4).

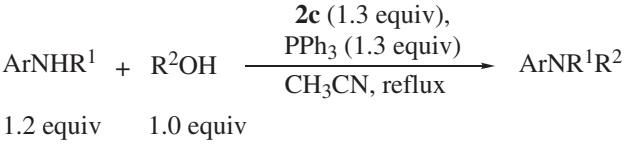
Table 4. Azo Reagent Optimization for *N*-Benzylation of Aniline



4a

Azo	Yield of **4a**/%[a)]	Time/h
2c	80	7
2d	71	11
2e	68	12

a) Isolated yield.



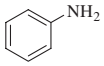
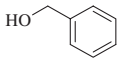
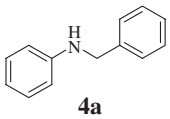
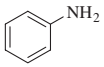
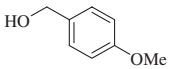
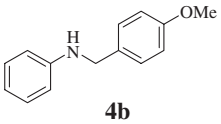
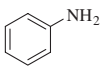
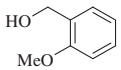
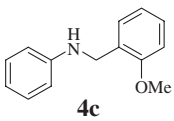
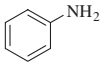
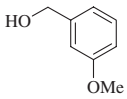
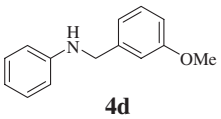
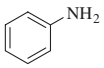
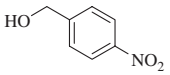
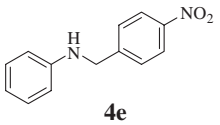
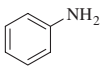
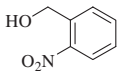
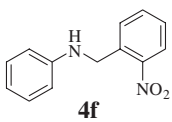
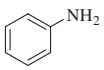
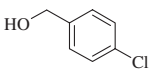
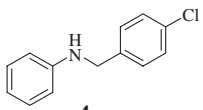
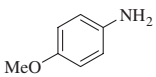
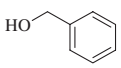
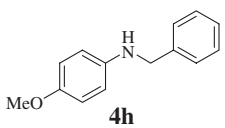
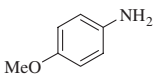
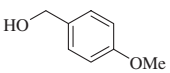
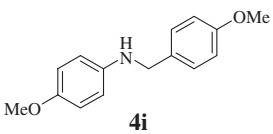
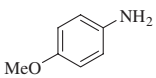
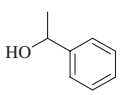
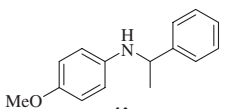
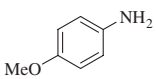
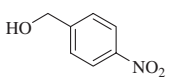
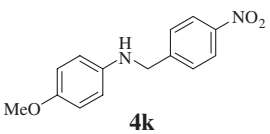
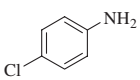
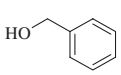
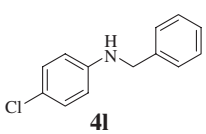
R^1= H, CH_3, $COCH_3$
R^2= $ArCH_2$

Scheme 4.

The obtained results are summarized in Table 5. As these data indicate, *N*-alkylation of disparate anilines with benzyl alcohols bearing electron-donating and electron-withdrawing substituents at the aromatic ring proceeded to give benzylanilines derivatives in good to excellent yields.

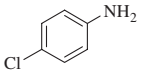
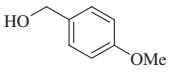
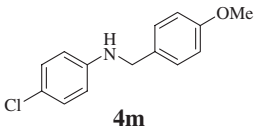
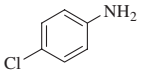
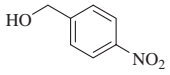
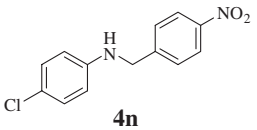
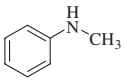
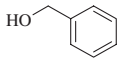
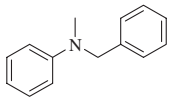
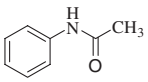
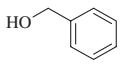
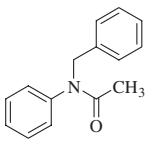
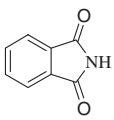
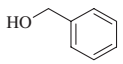
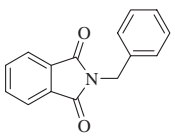
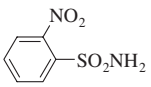
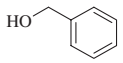
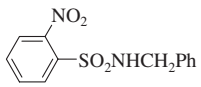
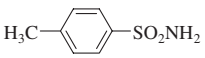
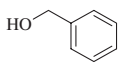
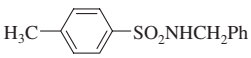
Anilines and benzyl alcohols substituted with an –OMe group resulted in a nearly complete conversion during their reactions, and the products **4h** and **4i** were obtained in 87% and 92% yields. Other primary, and secondary aliphatic and also secondary benzylic alcohols, such as 1-octanol, 2-octanol, and 1-phenylethanol were not applicable to this reaction. In the case of the less reactive (Table 5, Entries 5, 6, 11, and 14) and more hindered *ortho*-substituted alcohols (Table 5, Entries 3 and 6), the reaction did reach completion under the reaction conditions. *N*-alkylation of secondary aromatic amine was also examined. Reactions of *N*-methylaniline with benzyl alcohol proceeded to give its corresponding tertiary amine **4o** in moderate yield (77%, Table 5, Entry 15). The reaction of acetanilide with benzyl alcohol resulted in the formation of *N*-benzylacetanilide in good yield (84%, Table 5, Entry 16). We briefly also examined the reaction of imides and sulfonamides with benzyl alcohol under these condition and we found that this method

Table 5. Benzylamines Synthesized via Mitsunobu Reaction Using azpy **2c**[a)]

Entry	Alcohol	Amine	Product[b)]	Time/h	Yield/%[c)]
1			 **4a**	7	80
2			 **4b**	6	83
3			 **4c**	6.5	81
4			 **4d**	7.5	75
5			 **4e**	8.5	68
6			 **4f**	9	64
7			 **4g**	7.5	75
8			 **4h**	6	87
9			 **4i**	5.5	92
10			 **4j**	—	—
11			 **4k**	7	73
12			 **4l**	7.5	75

Continued on next page.

Continued.

Entry	Alcohol	Amine	Product[b)]	Time/h	Yield/%[c)]
13			 **4m**	6.5	78
14			 **4n**	8	74
15			 **4o**	6	77
16			 **4p**	6.5	84
17			 **4q**	6	90
18			 **4r**	6	81
19				6	5

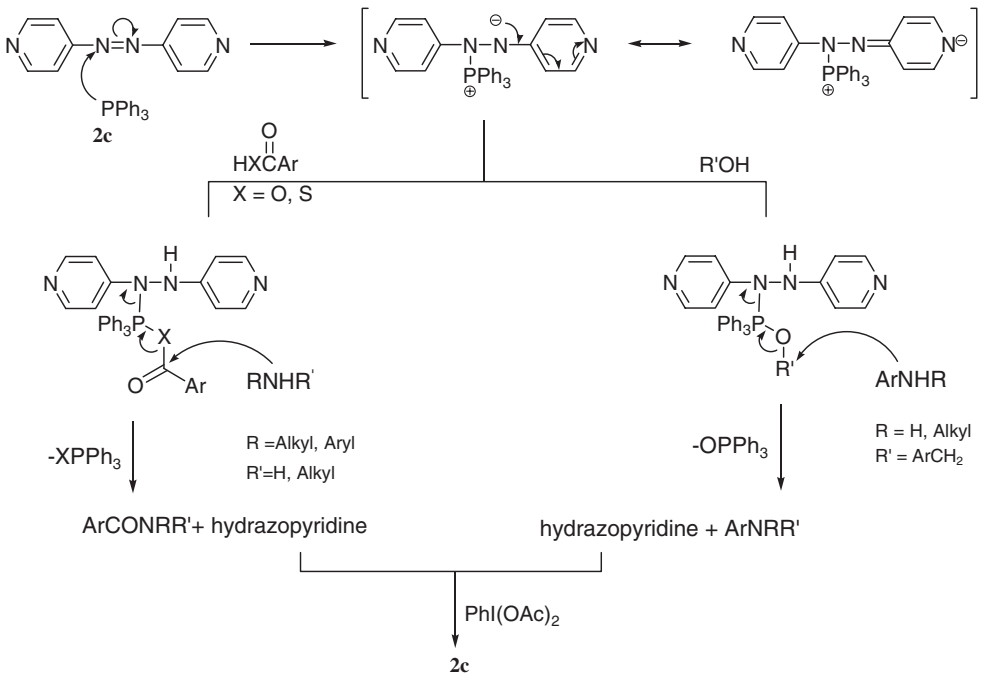
a) The molar ratio of the reactants for ROH/ArNHR/azpy/PPh_3 in refluxing CH_3CN is 1/1.2/1.2/1.2. b) The products were identified by their spectral data. c) Isolated yield.

can also be used for *N*-alkylation of imides and benzene sulfonamides having electron-withdrawing substitutents. In the case of phthalimide, the desired monoalkylated product, *N*-benzylphthalimide (**4q**), was isolated in excellent yield (90%, Table 5, Entry 17). 2-Nitrobenzenesulfonamide also took part in the reaction to afford the corresponding *N*-benzyl-2-nitrobenzenesulfonamide (**4r**) in good yield, while 4-methylbenzenesulfonamide remained almost intact (Table 5, Entries 18 and 19). Aliphatic amines were also tested for *N*-alkylation but our attempts at their alkylation under the aforementioned conditions were unsuccessful. This observation is conformable to the prior studies on *N*-alkylation of amines under condition of Mitsunobu reaction.[29a,29b]

To gain further insight about the reactivity of azo pyridine **2c**, an experiment was performed under intentionally harsh conditions. A mixture of primary aliphatic amine such as *n*-butylamine and *n*-butyllithium was treated with benzyl alcohol, in the presence of azpy **2c** and PPh_3 and the reaction was allowed to proceed overnight in refluxing acetonitrile in order to purposely perform the alkylation of inactive *n*-butylamine. Regretfully, no product was detected. When the reaction of aniline with benzyl alcohol was performed using an excess amount of benzyl alcohol (2.0 equiv) for 10 h, the di-alkylated product was obtained just in low yield of 10% as well as the mono-alkylated product (69%) indicating the high selectivity of the method for mono-alkylation reaction. A plausible mechanism that might explain these results is depicted in Scheme 5. Isolation of Ph_3PO and hydrazopyridine supports the suggested mechanism.

Conclusion

In summary, we have developed novel azo reagents **2c** for the efficient and robust amidation of carboxylic acids with different aromatic and aliphatic amines and **2d** and **2e** for the highly selective amidation of only primary aromatic amines. Selective *N*-benzylation of primary and secondary aromatic amines can also be achieved with all three heteroaryl azo compounds **2c**–**2e** using a Mitsunobu protocol. Apart from easy synthesis, stability and ease of handling of these azo compounds instead of DEAD, a clear advantage gained is that the side product hydrazine can be removed easily and reoxidized to the original azo. The excellent selectivity obtained in amidation reaction based on the different reactivity of these azo compounds and also their uses for the selective mono-*N*-benzylation of amines can be regarded as useful achievements in the Mitsunobu reaction.



Scheme 5.

Experimental

Solvents were dried and purified by standard procedures. Melting points were determined in open capillary tubes in a Buchi 530 circulating oil apparatus and are not corrected. FT-IR spectra were run on a Shimadzu FTIR-8300 spectrophotometer. NMR spectra were recorded on a Bruker Avance DPX-250 (^{1}H NMR 250 MHz, ^{13}C NMR 62.9 MHz) spectrometer in $CDCl_3$ or DMSO-d_6 solvents using TMS as an internal standard.

Determination of the purity of the products and the reaction monitoring were carried out on silica gel 254 analytical sheets or by GLC on a Shimadzu model GC-10A instrument. Column chromatography was carried out on silica gel 60 Merck (230–270). All compounds had been reported previously, and their identities were confirmed by comparison of their physical and spectroscopic data with those of known compounds. Characterization data for the compounds **3a**–**3d**, **3f**–**3h**, **3j**, **3k**, **3o**, **3p**, **4a**–**4e**, **4g**, **4h**, **4l**, **4o**, and **4q** are shown below.

General Procedure for Synthesis of Azo Compounds. Azo compounds **2a**–**2e** were prepared by oxidative coupling of aminopyridine by sodium hypochlorite solution. A 100-mL aliquot of a cold solution of aminopyridine (2.5 g) in water (aminobenzothiazole and aminooxazole were dissolved in THF) was added dropwise to 200 mL of a 6–14% NaOCl solution. The mixture was stirred at 0 °C as a precipitate formed. Filtration was performed a few minutes after the end of addition, and participates were collected and were used in our reactions without any purification.

Oxidation of Hydrazopyridine to Azopyridine by Iodobenzene Diacetate PhI(OAc)$_2$. Iodosobenzene diacetate (0.322 g, 1.0 mmol) was added in one portion to a stirred solution of pyridinehydrazine (0.186 g, 1.0 mmol) in 7 mL of DMSO and the reaction mixture was stirred at room temperature for 6 h. H_2O (20 mL) was then added and the reaction solution was extracted with EtOAc (3 × 20 mL). The organic extracts were combined together and dried over anhydrous $MgSO_4$. Upon concentrating the solution under vacuum, azopyridine **2a** was precipitated as orange crystals (127 mg, 69%).

Typical Procedure for the Conversion of Benzoic Acid to Benzanilide. To a stirred solution of 4,4′-azopyridine (1.3 mmol, 0.239 g) and PPh_3 (1.3 mmol, 0.338 g) in 3 mL of CH_3CN was added benzoic acid (1 mmol, 0.12 g) and aniline (1.2 mmol, 0.11 mL) successively. The reaction mixture was refluxed and completion of the reaction was monitored by TLC for the consumption of benzoic acid. After completion of the reaction, the reaction mixture was filtered to remove the precipitated hydrazopyridine. The residue was washed with 4% aq. HCl to remove the excess aniline and dried with anhydrous Na_2SO_4. Evaporation of the solvent followed by column chromatography of the crude mixture on silica gel using *n*-hexane and ethyl acetate (3:1) as eluent gave benzanilide (**3b**) in good yield (0.17 g, 86%). Mp 163 °C, mp 160–161 °C, Lit;[34a,34e] IR (neat, cm^{-1}): 3344, 3050, 2918, 1654, 1597. ^{1}H NMR (250 MHz, $CDCl_3$): δ 8.08–7.15 (m, 11H). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 165.8, 137.9, 133.6, 131.8, 128.8, 128.4, 127.0, 124.61, 120.3. Anal. Calcd for $C_{13}H_{11}NO$: C, 79.16; H, 5.62; N, 7.10%. Found: C, 79.10; H, 5.70; N, 7.13%.

4-Methyl-*N*-phenylbenzamide (3a): Mp 147 °C, mp 145 °C, Lit.[34h] IR (KBr, cm^{-1}): 3345, 3061, 1650. ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.90 (br s, 1H, NH), 7.68 (d, 2H, J = 8.0 Hz), 7.59 (d, 2H, J = 7.6 Hz), 7.42 (t, 2H, J = 7.8 Hz), 7.25 (d, 2H, J = 8.2 Hz), 7.23 (t, 1H, J = 7.4 Hz), 2.38 (s, 3H). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 167.2, 142.5, 138.3, 137.8, 131.6, 129.5, 129.1, 128.4, 124.6, 119.8, 21.3. Anal. Calcd for $C_{14}H_{13}NO$: C, 79.59; H, 6.20; N, 6.63%. Found: C, 79.52; H, 6.25; N, 6.62%.

4-Nitro-*N*-phenylbenzamide (3c): Mp 211–213 °C, mp 211–212 °C, Lit.[34i] IR (KBr, cm^{-1}): 3344, 3059, 1646. ^{1}H NMR (250 MHz, DMSO-d_6): δ 10.54 (br s, 1H, NH), 8.36 (d, 2H, J = 8.8 Hz), 8.16 (d, 2H, J = 8.8 Hz), 7.76 (d, 2H, J = 8.3 Hz), 7.36 (m, 2H), 7.15–7.10 (m, 1H). ^{13}C NMR (62.9 MHz, DMSO-d_6): δ 164.2, 157.5, 134.1, 133.8, 129.2, 128.7, 124.1, 123.5, 120.4. Anal. Calcd for $C_{13}H_{10}N_2O_3$: C, 64.46; H, 4.16; N, 11.56%. Found: C, 64.51; H, 4.15; N, 11.50%.

***N*-(4-Methoxyphenyl)benzamide (3d):** Mp 154 °C, mp 156–157 °C, Lit.[34c] IR (neat, cm^{-1}): 3335, 3054, 1645. ^1H NMR (250 MHz, $CDCl_3$): δ 7.77 (d, 2H, $J = 8.1$ Hz), 7.64 (br s, 1H, NH), 7.61–7.39 (m, 5H), 6.78 (d, 2H, $J = 8.5$ Hz), 3.85 (s, 3H). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 165.7, 155.9, 137.1, 132.3, 131.2, 128.9, 127.5, 122.0, 121.7, 114.9, 114.2, 55.4. Anal. Calcd for $C_{14}H_{13}NO_2$: C, 73.99; H, 5.77; N, 6.16%. Found: C, 73.97; H, 5.80; N, 6.13%.

***N*-(2-Methylphenyl)benzamide (3f):** Mp 144 °C, mp 142–143 °C, Lit.[34d] IR (KBr, cm^{-1}): 3325, 3050, 1648. ^1H NMR (250 MHz, $CDCl_3$): δ 7.81–7.78 (m, 3H), 7.65 (br s, 1H, NH), 7.47–7.40 (m, 3H), 7.17–7.13 (m, 2H), 7.06–7.03 (m, 1H), 2.24 (s, 3H). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 165.4, 135.8, 135.1, 134.0, 131.8, 130.6, 129.1, 128.8, 127.1, 126.9, 125.4, 123.2, 122.5, 17.8. Anal. Calcd for $C_{14}H_{13}NO$: C, 79.59; H, 6.20; N, 6.63%. Found: C, 79.60; H, 6.21; N, 6.60%.

***N*-(4-Chlorophenyl)benzamide (3g):** Mp 187 °C, mp 188–190 °C, Lit.[34e] IR (KBr, cm^{-1}): 3341, 3052, 1652. ^1H NMR (250 MHz, $CDCl_3$): δ 7.76 (d, 2H, $J = 7.0$ Hz), 7.70 (s, 1H), 7.65–7.52 (m, 5H), 7.44 (d, 2H, $J = 8.7$ Hz). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 163.9, 137.3, 132.2, 128.9, 127.6, 126.7, 126.1, 121.6, 120.8. Anal. Calcd for $C_{13}H_{10}ClNO$: C, 67.39; H, 4.35; N, 6.05%. Found: C, 67.44; H, 4.28; N, 6.06%.

***N*-(4-Nitrophenyl)benzamide (3h):** Mp 197 °C, mp 198–199 °C, Lit.[34f] IR (KBr, cm^{-1}): 3347, 3044, 1655. ^1H NMR (250 MHz, DMSO-d_6): δ 9.95 (br s, 1H, NH), 8.18–7.83 (d, 2H, $J = 7.2$ Hz), 7.76–7.69 (m, 3H), 7.55–7.39 (m, 4H). ^{13}C NMR (62.9 MHz, DMSO-d_6): δ 164.0, 143.1, 141.4, 131.6, 129.2, 128.6, 128.1, 123.3, 120.0. Anal. Calcd for $C_{13}H_{10}N_2O_3$: C, 64.46; H, 4.16; N, 11.56%. Found: C, 64.50; H, 4.14; N, 11.53%.

***N*-Methyl-*N*-phenylbenzamide (3j):** Mp 104–106 °C, mp 103–104 °C, Lit.[34g] IR (KBr, cm^{-1}): 3049, 1642. ^1H NMR (250 MHz, $CDCl_3$): δ 7.65 (d, 2H, $J = 7.1$ Hz), 7.47–7.14 (m, 3H), 6.93–6.71 (m, 5H), 3.52 (s, 3H). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 168.3, 142.7, 136.4, 129.1, 129.0, 128.7, 127.5, 126.7, 126.0, 39.6. Anal. Calcd for $C_{14}H_{13}NO$: C, 79.59; H, 6.20; N, 6.63%. Found: C, 79.54; H, 6.23; N, 6.59%.

***N*-Methyl-4-nitro-*N*-phenylbenzamide (3k):** Mp 109–111, mp 106–107 °C, Lit.[34h] IR (KBr, cm^{-1}): 3055, 1646. ^1H NMR (250 MHz, $CDCl_3$): δ 8.33–8.01 (m, 4H), 6.82–6.63 (m, 5H), 3.46 (s, 3H). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 165.7, 150.6, 144.3, 141.3, 132.6, 130.8, 130.2, 128.7, 124.5, 37.8. Anal. Calcd for $C_{14}H_{12}N_2O_3$: C, 65.62; H, 4.72; N, 10.93%. Found: C, 65.62; H, 4.69; N, 10.98%.

***N*-Benzylbenzamide (3o):** Mp 104–106 °C, mp 103–104 °C, Lit.[34b] IR (KBr, cm^{-1}): 3318, 1634. ^1H NMR (250 MHz, $CDCl_3$): δ 7.70 (d, 2H, $J = 8.4$ Hz), 7.40–7.21 (m, 8H), 6.53 (br s, 1H, NH), 4.54 (d, 2H, $J = 5.7$ Hz). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 167.4, 138.2, 134.4, 131.5, 128.8, 128.6, 127.9, 127.6, 127.0, 44.1. Anal. Calcd for $C_{14}H_{13}NO$: C, 79.59; H, 6.20; N, 6.63%. Found: C, 79.65; H, 6.21; N, 6.60%.

***N*-Octylbenzamide (3p):** IR (neat, cm^{-1}): 3313, 3041, 1635. ^1H NMR (250 MHz, $CDCl_3$): δ 7.68 (d, 2H, $J = 8.2$ Hz), 7.41–7.30 (m, 3H), 6.16 (br s, 1H, NH), 3.36 (t, 2H, $J = 8.3$ Hz), 1.59–1.39 (m, 2H), 1.25–1.09 (m, 10H), 0.84 (t, 3H, $J = 6.9$ Hz). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 167.3, 134.9, 131.8, 131.24, 128.5, 127.9, 126.8, 40.1, 31.8, 29.7, 29.3, 29.2, 27.0, 22.6, 14.1. Anal. Calcd for $C_{15}H_{23}NO$: C, 77.21; H, 9.93; N, 6.00%. Found: C, 77.19; H, 9.89; N, 6.05%.

Typical Procedure for the Conversion of Aniline to *N*-Phenylbenzylamine. To a flask containing a stirred mixture of 4,4′-azopyridine (1.3 mmol, 0.239 g) and PPh_3 (1.3 mmol, 0.338 g) in 3 mL of acetonitrile, was added benzyl alcohol (1 mmol, 0.1 mL). Aniline (1.2 mmol, 0.11 mL) was then added to the reaction mixture. The reaction mixture was refluxed for 7 h. The reaction mixture was then filtered to remove some of the produced hydrazopyridine. The solvent was then evaporated and the residue was chromatographed on a silica gel column using *n*-hexane and ethyl acetate (4:1) as eluent. *N*-Phenylbenzylamine (**4a**) was obtained in 80% yield (0.146 g). Mp 37 °C, Lit.,[34a,34k] mp 37.5 °C; IR (KBr, cm^{-1}): 3403, 1325. ^1H NMR (250 MHz, $CDCl_3$): δ 7.43–7.22 (complex, 8H), 6.79–6.68 (complex, 3H), 4.38 (s, 2H). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 148.2, 139.5, 129.3, 128.4, 127.6, 127.3, 117.6, 112.9, 48.4. Anal. Calcd for $C_{13}H_{13}N$: C, 85.21; H, 7.15; N, 7.64%. Found: C, 85.16; H, 7.20; N, 7.64%.

4-Methoxy-*N*-phenylbenzylamine (4b):[34j] ^1H NMR (250 MHz, $CDCl_3$): δ 7.31 (d, 2H, $J = 7.5$ Hz), 7.13–6.51 (m, 7H), 4.39 (s, 2H), 3.91 (br s, 1H, NH), 3.74 (s, 3H). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 157.8, 149.1, 131.8, 129.9, 129.6, 128.3, 118.6, 115.5, 114.1, 113.0, 56.1, 49.7. Anal. Calcd for $C_{14}H_{15}NO$: C, 78.84; H, 7.09; N, 6.57%. Found: C, 78.81; H, 7.07; N, 6.59%.

2-Methoxy-*N*-phenylbenzylamine (4c):[34k] ^1H NMR (250 MHz, $CDCl_3$): δ 7.24–7.02 (m, 4H), 6.79–6.53 (m, 5H), 4.40 (s, 2H), 4.05 (br s, 1H, NH), 3.80 (s, 3H). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 159.1, 146.7, 130.1, 129.6, 128.7, 127.9, 121.4, 118.5, 112.9, 110.8, 57.3, 45.4. Anal. Calcd for $C_{14}H_{15}NO$: C, 78.84; H, 7.09; N, 6.57%. Found: C, 78.85; H, 7.09; N, 6.60%.

3-Methoxy-*N*-phenylbenzylamine (4d):[34j] ^1H NMR (250 MHz, $CDCl_3$): δ 7.29–6.72 (m, 9H), 4.37 (s, 2H), 4.11 (br s, 1H, NH), 3.84 (s, 3H). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 159.7, 146.8, 140.4, 130.2, 129.6, 129.1, 118.8, 118.0, 112.9, 112.4, 112.0, 56.7, 49.3. Anal. Calcd for $C_{14}H_{15}NO$: C, 78.84; H, 7.09; N, 6.57%. Found: C, 78.88; H, 7.12; N, 6.56%.

4-Nitro-*N*-phenylbenzylamine (4e):[34k] IR (neat, cm^{-1}): 3412. ^1H NMR (250 MHz, $CDCl_3$): δ 8.18–8.13 (m, 2H), 7.71–7.56 (m, 2H), 7.37–7.23 (m, 2H), 6.84–6.68 (m, 3H), 4.38 (s, 2H), 4.11 (br s, 1H, NH). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 146.4, 144.9, 143.7, 130.5, 128.4, 124.5, 117.7, 113.5, 48.9. Anal. Calcd for $C_{13}H_{12}N_2O_2$: C, 68.41; H, 5.30; N, 12.27%. Found: C, 68.44; H, 5.36; N, 12.24%.

4-Chloro-*N*-phenylbenzylamine (4g):[34l] ^1H NMR (250 MHz, $CDCl_3$): δ 7.12–6.61 (m, 9H), 4.29 (s, 2H), 3.92 (br s, 1H, NH). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 148.6, 139.1, 133.4, 129.8, 128.3, 128.0, 119.2, 114.5, 48.3. Anal. Calcd for $C_{13}H_{12}ClN$: C, 71.72; H, 5.56; N, 6.43%. Found: C, 71.68; H, 5.60; N, 6.40%.

***N*-(4-Methoxyphenyl)benzylamine (4h):**[34j] ^1H NMR (250 MHz, $CDCl_3$): δ 7.17 (d, 2H, $J = 7.3$ Hz), 7.08–7.06 (m, 3H), 6.48 (d, 2H, $J = 8.0$ Hz), 6.34 (d, 2H, $J = 7.9$ Hz), 4.39 (s, 2H), 4.11 (br s, 1H, NH), 3.76 (s, 3H). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 153.5, 141.2, 140.7, 127.8, 127.6, 127.0, 117.1, 115.3, 50.1. Anal. Calcd for $C_{14}H_{15}NO$: C, 78.84; H, 7.09; N, 6.57%. Found: C, 78.83; H, 7.11; N, 6.52%.

***N*-(4-Chlorophenyl)benzylamine (4l):**[34j] ^1H NMR (250 MHz, $CDCl_3$): δ 7.14 (d, 2H, $J = 7.2$ Hz), 7.05–7.02 (m, 5H), 6.44 (d, 2H, $J = 7.1$ Hz), 4.37 (s, 2H), 4.08 (br s, 1H, NH). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 150.2, 141.4, 128.7, 127.3, 127.0, 125.3, 119.5, 49.2. Anal. Calcd for $C_{13}H_{12}ClN$: C, 71.72; H, 5.56; N, 6.43%. Found: C, 71.76; H, 5.51; N, 6.45%.

***N*-Methyl-*N*-phenylbenzylamine (4o):**[34m] IR (neat, cm^{-1}): 1349. ^1H NMR (250 MHz, $CDCl_3$): δ 7.27–7.02 (m, 7H), 6.86–6.71 (m, 3H), 4.33 (s, 2H), 3.11 (s, 3H). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 149.4, 135.9, 129.7, 128.7, 126.0, 125.2, 117.4, 112.6, 59.3, 38.1. Anal. Calcd for $C_{14}H_{15}N$: C, 85.24; H, 7.66; N, 7.10%. Found: C, 85.19; H, 7.65; N, 7.16%.

***N*-Benzylphthalimide (4q):** ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.75–7.72 (m, AA′, 2H), 7.61–7.58 (m, XX′, 2H), 7.36–7.16 (m, 5H), 4.75 (s, 2H). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 168.1, 136.4, 134.0, 132.1, 128.6, 127.6, 127.0, 123.3, 41.6. Anal. Calcd for $C_{15}H_{11}NO_2$: C, 75.94; H, 4.67; N, 5.90%. Found: C, 75.90; H, 4.68; N, 5.92%.

***N*-Benzyl-2-nitrobenzenesulfonamide (4r):**[34n] ^{1}H NMR (250 MHz, $CDCl_3$): δ 8.03 (dd, 1H, $J = 7.8$, 1.8 Hz), 7.83 (dd, 1H, $J = 7.9$, 1.8 Hz), 7.75–7.60 (m, 2H), 7.25–7.01 (m, 5H), 5.66 (br s, 1H, NH), 4.30 (s, 2H). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 147.5, 135.9, 134.2, 133.1, 132.6, 130.7, 129.1, 128.3, 127.7, 124.8, 47.6. Anal. Calcd for $C_{13}H_{12}N_2O_4S$: C, 53.42; H, 4.14; N, 9.58; S, 10.97%. Found: C, 53.37; H, 4.16; N, 9.53; S, 11.01%.

4,4′-Azopyridine (2c): Mp 106–107 °C (lit.[28] Mp 107–108 °C). IR (KBr, cm^{-1}): 3028, 1585. ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.7 (4H, m, AA′XX′), 8.7 (4H, m, AA′XX′). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 116.3, 151.5, 156.5. MS (m/z %): 184 (11.5), 106 (14.6), 92 (6.9), 78 (39.0). Anal. Calcd for $C_{10}H_8N_4$: C, 65.21; H, 4.38; N, 30.42%. Found: C, 65.19; H, 4.43; N, 30.39%.

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