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Transition Metal-Free Oxidative Coupling of Primary Amines in Polyethylene Glycol at Room Temperature: Synthesis of Imines, Azobenzenes, Benzothiazoles and Disulfides

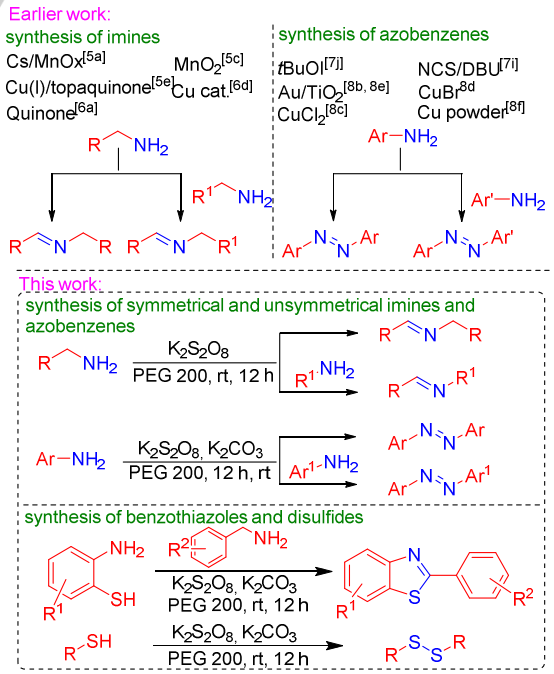
Abhinandan D. Hudwekar,[a,b] Praveen K. Verma,[a] Jaspreet Kour,[a,b] Shilpi Balgotra,[a,b] and Sanghapal D. Sawant*[a,b]

Abstract: A transition metal-free protocol has been developed for the oxidative coupling of primary amines to imines and azobenzenes, thiols to disulfides and 2-aminothiophenols to benzothiazoles offering excellent yields. The advantageous features of the present environmentally benign methodology includes the usage of biocompatible and green reaction conditions like solvent, room temperature reactions, transition metal-free approach and moreover, it offers broader substrate scope.

Introduction

Imines[1] and azobenzenes[2] are very important functional moieties having diverse applications in the fields of pharmaceuticals, biologicals, agrochemicals, dyes, polymerization, and as electrophiles for various transformations. These are also perceived as imperative intermediates during some chemical conversions and as synthones for the preparation of complex molecules.[3] Recent applications[3] of azo compounds included as radical initiator in photodynamic therapy, photochromics, prodrugs, drugs coating materials, chemosensors, non-linear optics, as directing group in catalysis for C-H functionalizations, and in biotechnology (artificial muscle, molecular machines, bistable memory devices etc.). Condensation of aldehydes and amines with azeotropic removal of water is the traditional approach for the synthesis of imines.[4] Oxidation of amines is the important transformation to access various nitrogen containing molecules such as imines, oximes, amides, nitriles etc.[5] Imines can be obtained by the self oxidative coupling of amines employing metal catalysts and oxidants (Scheme 1).[5] Some transition metal-free methods have also been furnished for the oxidative coupling of amines to imines[6] such as mesoporus carbon derived from natural vitamin B_{12} with molecular oxygen or air,[6i] photooxidative self coupling of amines using methylene blue,[6j] enzyme mediated oxidation of benzylamine with H_2O_2 oxidant,[6k] and also observed in some extent using $K_2S_2O_8$ during the oxidation of aliphatic amines to oximes.[6l] Similarly, vital routes[7] have been developed for the synthesis of azobenzenes from amines including stoichiometric amount of reagents with toxic transition metals, or through diazonium coupling using stoichiometric amounts of nitrite salts. Numerous metal promoted methodologies have also been developed for the synthesis of azo compounds (Scheme 1).[8] It has been observed that sometime the redox pathway of nitro and amino compounds proceed via azo compounds as one of the intermediates, hence, it is a challenging task to control the selectivity for azo intermediates.[8f]

Herein, we have developed a new transition metal-free approach for the oxidative coupling of alkyl amines to imines and aryl amines to azobenzenes in a green solvent system, polyethylene glycol (PEG 200) at room temperature. In recent years, PEG has attracted special interest as a biodegradable, thermally stable, non-volatile, environment friendly, biocompatible, green, inexpensive reaction medium.[9] The remarkable finding of the present protocol is the synthesis of symmetrical as well as unsymmetrical imines and azobenzenes. In extension to this, the oxidative coupling of benzylamines with *ortho*-thio substituted anilines leads to the formation of corresponding benzothiazoles and oxidative self coupling of thiols afforded disulfides under same reaction conditions. Thus, present methodology extends broader scope and applications in the area of organic synthesis.



Scheme 1. State of art on synthesis of imines, azobenzenes and present work.

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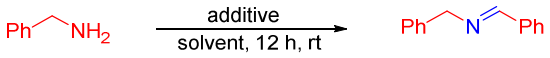
Results and Discussion

We began our studies using benzyl amine as model substrate for the optimization of reaction conditions. Initially, reaction was performed with various additives in ACN, at rt. Reaction proceeded well in case of TBHP and *m*-CPBA, however, poor selectivity was observed (Table 1, entries 1 and 6). Reaction with H_2O_2, NaO*t*Bu, KO*t*Bu and H_2O get started however, the conversion and selectivity for the desired product were low (Table 1, entries 2-5). In case of $K_2S_2O_8$ high conversion and selectivity was observed (Table 1, entry 7). Atmospheric oxygen was also not effective for the reaction (Table 1, entry 8). Hence, $K_2S_2O_8$ was selected for further optimization studies. Solvent plays a critical role for the present reaction. Excellent conversion was observed in case of H_2O, PEG 200, DMSO, DMF and ethylene glycol, however, best result was observed in PEG 200 (Table 1, entries 9, 11-13 and 15). C_2H_5OH and 1,4-dioxane gave the less conversion and selectivity (Table 1, entries 10 and 14).

Table 1. Screening of additives and solvents.[a, d]



Entry	Additive	Solvent	Con./Sel.[b]
1[c]	TBHP	ACN	82/19
2	H_2O_2	ACN	24/9
3	NaO*t*Bu	ACN	16/5
4	KO*t*Bu	ACN	11/3
5	H_2O	ACN	8/7
6	*m*-CPBA	ACN	48/17
7	$K_2S_2O_8$	ACN	87/84
8	Open air	ACN	13/4
9[c]	$K_2S_2O_8$	H_2O	>99/17
10	$K_2S_2O_8$	C_2H_5OH	63/70
11	$K_2S_2O_8$	PEG 200	>99/>99
12[c]	$K_2S_2O_8$	DMSO	>99/7
13[c]	$K_2S_2O_8$	DMF	>99/54
14	$K_2S_2O_8$	1,4-Dioxane	37/31
15	$K_2S_2O_8$	Ethylene glycol	82/82

[a] Reaction conditions: benzyl amine (1 mmol), additive (1 equiv.), solvent (5 mL), 12 h, rt. [b] GC conversion and selectivity for imine product. Benzaldehyde was also observed. [c] Benzaldehyde was formed as major product. [d] Reactant remains unreacted if not specified.

The quantity of additive, $K_2S_2O_8$, was also optimized for the present reaction (Figure 1). 0.5 equiv. of $K_2S_2O_8$ gave moderate amount of the desired product, albeit, yield increased upto 92% with 1 equiv. of additive. However, further increment in the quantity of $K_2S_2O_8$ did not increase the reaction yield, rather, decreased to some extent.

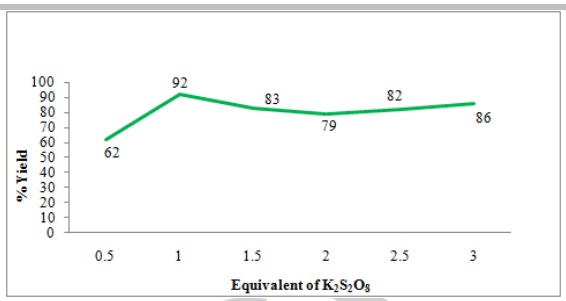
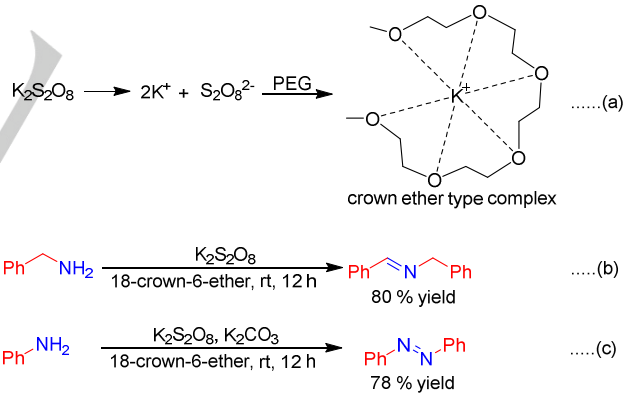


Figure 1. Optimization of $K_2S_2O_8$ quantity.

During optimization studies PEG was found to be superior over other solvents (Table 1). To understand its reason, we have gone through literature reports and found that PEG have possibilities of forming half open crown ether type complexes with potassium ions through self assembling (Scheme 2a) and also provide stability to the reagent.[9c-9g] To further confirm this we have carried out controlled reactions for the formation of self coupled imine and azobenzene in the presence of 18-crown-6 ether instead of PEG 200 as solvent under standard conditions and found that reaction proceed smoothly with high yields of product (Scheme 2b and 2c). It indicated that, PEG plays a critical role for the enhancement of the present reaction, probably, by promoting the availability of the persulfate anion and increase the basicity of the reaction.[9c-9g] The possibilities of any metallic contamination in the PEG were also ruled out by carrying out its elemental analysis using atomic absorption spectroscopy.



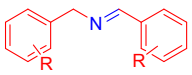
Scheme 2. Role of PEG 200 in the present reaction.

With best reaction conditions in hand, the scope of the present developed protocol was explored for the synthesis of homo coupled as well as hetero coupled imines (Table 2). Homo coupling of benzyl amine, -F, -Cl, $-CH_3$, $-OCH_3$ substituted benzyl amines gave the corresponding imines in excellent yields (2a-2g). We also thought to inflate the scope of present protocol for the cross coupling of benzyl amines with other amines. In this regard, initially, the reaction of equimolar amount of benzyl amine with aniline gave cross coupled product in 30% yield (2h). However, on increasing the amount of aniline to 3 equivalents, the reaction shifts towards desired cross coupled product in 99%

yield (2i). Reaction of methoxy, methyl and bromo substituted anilines with benzyl amine and *p*-methoxybenzyl amine afforded the corresponding cross coupled imines in excellent yields (2j-2o). Reaction of benzylamine with *p*-nitroaniline (strong electron withdrawing nitro group) could not proceed under present conditions (results not shown). To our delight, homo coupled imines were also observed in case of aliphatic amines with variable chain length (2p-2r). Present protocol was also applicable for the synthesis of imines in heterocyclic ring systems (2s and 2t), however, low selectivity was observed in case of cyclic secondary amines (2u).

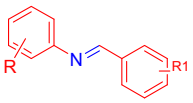
Table 2. Synthesis of symmetrical and unsymmetrical imines via oxidative coupling of amines.

homo coupling of benzylamines[a, d]



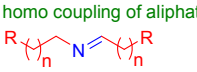
2a, R = H; 99% (82%)
2b, R = *m*-F; 99% (76%)
2c, R = *p*-F; 99%
2d, R = *m*-Cl; 94% (79%)
2e, R = *p*-CH_3; 99% (81%)
2f, R = *m*-OCH_3; 91%
2g, R = p-OCH_3; 99%

cross coupling of benzylamines with anilines[b, d]



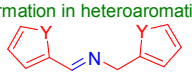
2h, R, R^1 = H; 30%[e, f]
2i, R, R^1 = H; 99%
2j, R = *o*-CH_3, *o'*-CH_3, R^1=H; 99%
2k, R = *m*-CH_3, *m'*-CH_3, R^1= H; 99%
2l, R = *o*-CH_3, *m*-CH_3, R^1= H; 99%
2m, R = *p*-OCH_3, R^1= H; 99%
2n, R= *p*-CH_3, R^1= *p*-OCH_3; 99%
2o, R= *p*-Br, R^1= *p*-OCH_3; 75%

homo coupling of aliphatic amines[c, d]

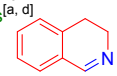


2p, R = CH_3, n = 3; 99%
2q, R = CH_3, n = 4; 99%
2r, R = CH_3, n = 5; 99%

imine formation in heteroaromatic substrates[a, d]



2s, y = S, 99%; 2t, y = O, 99%



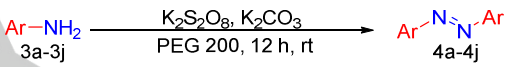
2u, 64%[g]

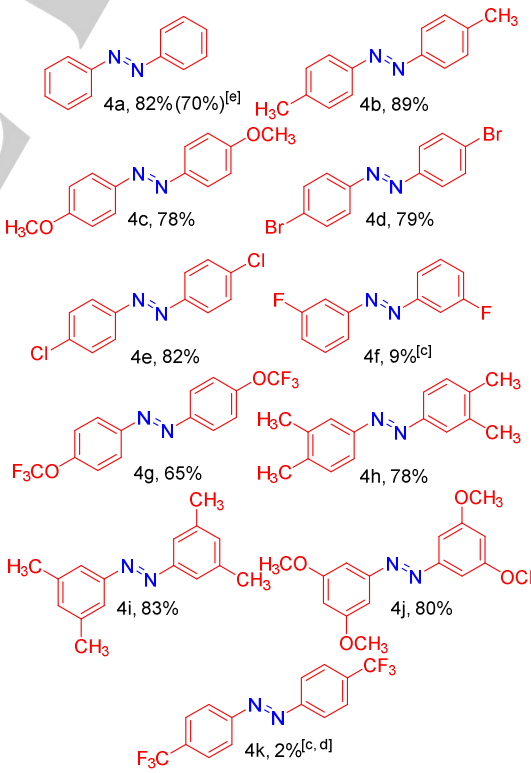
[a] Reaction conditions: amine (1 mmol), $K_2S_2O_8$ (1 equiv.), PEG 200 (5 mL), 12 h, rt. [b] Reaction conditions: benzyl amine (1 mmol), amine (3 equiv.), $K_2S_2O_8$ (1 equiv.), PEG 200 (5 mL), 12 h, rt. Yields based on benzyl amine. [c] Reaction conditions: amine (1 mmol), $K_2S_2O_8$ (1 equiv.), PEG 200 (5 mL), 12 h, rt. [d] GC yields (isolated yields in parentheses). [e] Reaction with 1 equiv. of aniline. [f] Benzaldehyde and homo coupled azobenzene were also observed. [g] 20% of isoquinoline was also observed.

After the synthesis of imines, next we successfully applied the developed protocol for the synthesis of symmetrical and unsymmetrical aromatic azo compounds, with additional requirement of inexpensive and easily available base, K_2CO_3 (Table 3 and 4). The reaction of methyl, methoxy, halides (Cl, Br), trifluoromethoxy, dimethyl, dimethoxy and unsubstituted anilines afforded the corresponding symmetrical azo compounds in good to excellent yields (4a-4e and 4g-4j). Albeit, 3-fluoroaniline (4f) and 4-(trifluoromethyl)aniline (4k) gave the corresponding product in very low yields and remains unreacted under present conditions. The gram scale applicability of the method was also tested by carrying out the reaction of aniline at 5g scale, slightly low yield of product was observed (4a). Our efforts towards synthesis of unsymmetrical azo compounds provided three different products under present conditions i.e., two corresponding symmetrical products (B and C) from each reactant and one cross coupled product (A). However, desired unsymmetrical azo compounds were observed as major product in almost all examples (Table 4). Very high conversion was observed for the reaction of chloro, bromo, methyl and methoxy substituted anilines with aniline providing fair selectivities for desired unsymmetrical azo compounds (5a-5i).

In addition to synthesis of imines and azobenzenes, present protocol was also applicable for the synthesis of highly valuable benzothiazoles.[10] Recently, various methods have been developed for the synthesis of benzothiazoles.[11] Herein, the reaction of 2-aminothiophenol with different benzylamines afforded the corresponding 2-arylbenzothiazoles in high yields (Table 5). Reaction of benzylamine afforded the 2-phenylbenzothiazole in high yield (6a). Halogens (Cl, CF_3), methyl, and methoxy functional groups were tolerated under the present conditions (6b-6e). Reaction of 4-pyridinylamine and naphthylamine gave the desired benzothiazoles in high yields (6f, 6g).

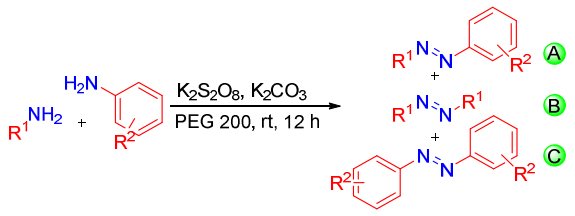
Table 3. Synthesis of symmetrical azoarenes.[a, b]

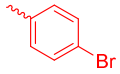
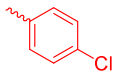
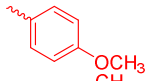
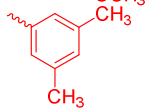
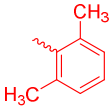
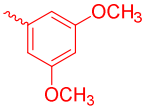
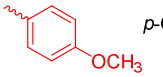
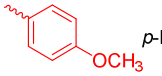
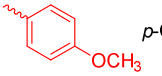




[a] Reaction conditions: amine (1 mmol), $K_2S_2O_8$ (1 equiv.), K_2CO_3 (1 equiv.) PEG 200 (5 mL), 12 h, rt. [b] Isolated Yields. [c] Reactant remains unreacted. [d] GC Yield. [e] Reaction at 5 g scale in parenthesis

Table 4. Synthesis of unsymmetrical azoarenes.[a]

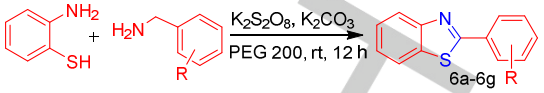


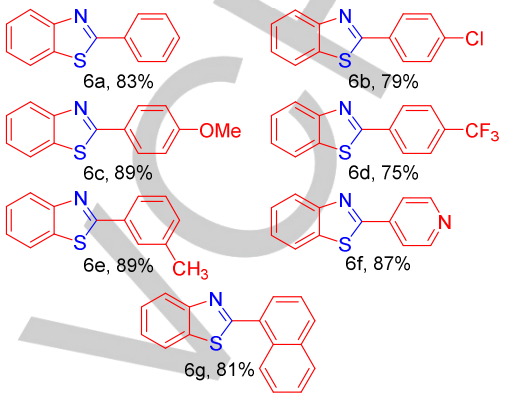
Entry	R^1	R^2	Con. (%)[b]	Sel. (%)[b] A	B	C
5a		H	>99	37 (30)	5 (5)	58 (51)
5b		H	>99	46 (41)	16	38 (29)
5c		H	>99	58 (52)	23	19
5d		H	92	50	27	23
5e		H	>99	59	21	20
5f		H	>99	73 (67)	0	27
5g		*p*-CH_3	>99	55 (48)	29	16
5h		*p*-Br	>99	95 (84)	0	5
5i		*p*-Cl	>99	55 (50)	40	5

[a] Reaction conditions: amine (1 mmol), aniline (1 mmol), $K_2S_2O_8$ (1 equiv.), K_2CO_3 (1 equiv.), PEG 200 (5 mL), 12 h, rt. [b] GC based conversion and selectivity (isolated yields in parentheses).

Disulfides belong to biologically important class of molecules, as reported in literature.[12] As an extension of the current method, disulfides were also prepared using current protocol from thiophenols under optimized conditions in excellent yields (Table 6). Reaction of unsubstituted, methyl, methoxy and amine substituted thiophenols afforded the corresponding disulfide products in high yields (7a-7c and 7e). Reactions with thiol bearing activated methylene moiety in aromatic as well as heteroaromatic compound also gave the desired disulfide in high yields (7d and 7f). Reaction of aliphatic cyclic and acyclic thiols have also afforded the corresponding disulfides in good yields (7g and 7h). Interestingly, the reaction of 4-methylthiophenol with 4-methoxythiophenol gave the cross coupled disulfide as the major product in good yield (7i), which gives scope for generating diverse asymmetric disulfides.

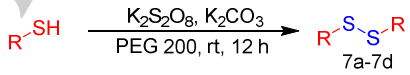
Table 5. Synthesis of benzothiazoles.[a, b]

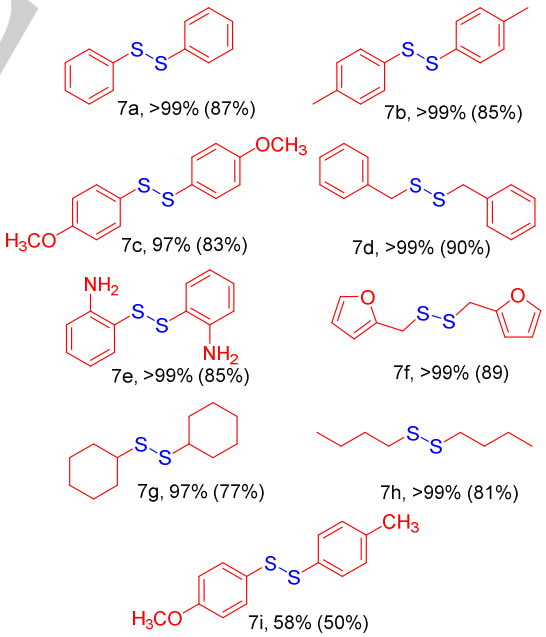




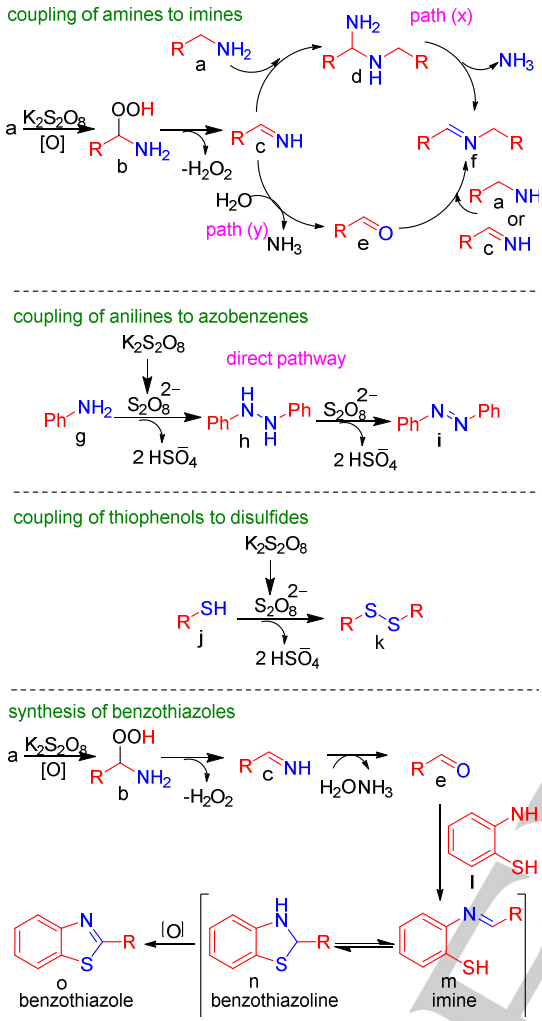
[a] Reaction conditions: 2-aminothiophenol (1 mmol), amine (1 mmol), $K_2S_2O_8$ (1 equiv.), K_2CO_3 (1 equiv.), PEG 200 (5 mL), 12 h, rt. [b] Isolated yields.

Table 6. Synthesis of disulfides.[a, b]





[a] Reaction conditions: thiophenol (1 mmol), $K_2S_2O_8$ (1 equiv.), K_2CO_3 (1 equiv.), amine (1 mmol), PEG 200 (5 mL), 12 h, rt. [b] GC yields (Isolated yields in parentheses).



Scheme 3. Proposed reaction pathways.

On the basis of observed results and earlier developed methodologies[5e, 11g, 11h, 11n, 16] the mechanistic pathways for present protocols are illustrated in Scheme 3. Benzyl amine gets converted into peroxide intermediate[11n, 16] (b) by $K_2S_2O_8$ which subsequently transformed into imine intermediate (c) with the removal of H_2O_2. After the formation of imine intermediate (c), two different paths (x and y)[5e] are known for the imine (f) formation. In path (x), the intermolecular nucleophilic attack of benzyl amine (a) on the imine (c) intermediate gave N-alkylated diamine intermediate (d), which is converted into desired imine (f) product with the removal of ammonia. Alternatively, in path (y), the imine intermediate (c) get converted into aldehyde (e), which on condensation either with imine (c) or benzyl amine (a) molecule provide the desired imine (f) product. The observation of aldehydes as byproduct during some of the reactions indicated the path (y) for the present protocol, although, the possibilities of path (x) cannot be ruled out under the present conditions. Preferentially, for the synthesis of azobenzenes, the well established direct route for the oxidation of anilines (g) to nitro compounds[13] was followed and under the conditions the reaction get stopped at the intermediate stage to give the desired azo compounds (i). During GC-MS analysis of reaction mixtures, the diphenyl hydrazine intermediate (h) was also observed in some cases. Similarly, persulfate anion promotes the synthesis of disulfides (k) from thiophenols (j) via abstraction of protons. For the synthesis of benzothiazoles (o), the in situ oxidation of benzylamine to benzaldehyde/imine formation/cyclization/oxidation pathway was followed.[14, 11g] $K_2S_2O_8$ promoted the formation of benzaldehyde (e) which immediately form imines (m), which remain in equilibrium with the cyclized product (n),[14, 11g] which is then oxidized either by $K_2S_2O_8$ or oxygen[15] to the desired benzothiazoles (o).

Conclusions

In summary, we have developed an efficient, environment friendly, transition metal-free protocol for the synthesis of imines and azobenzenes using PEG 200 as biocompatible and green reaction solvent at room temperature. Present protocol is applicable to the synthesis of symmetrical as well as unsymmetrical imines and azobenzenes from primary amines. Diverse functional groups were well tolerated under the developed conditions and yielding the desired product in high selectivities and yields. Present protocol was also applicable for the synthesis of highly valuable benzothiazoles and disulfides. Present method provide an effective alternative to the existing transition metal based methodologies to access highly valuable intermediate stage molecules which can be further utilized in numerous fields.

Experimental Section

General Information: All solvents were purified and dried as per standard protocols. All reagents were obtained from commercial sources and used without purification. ^{1}H NMR spectra were obtained at 400 MHz or 500 MHz and recorded relative to tetramethylsilane signal (0 ppm). ^{13}C NMR spectra were obtained at 100 MHz or 125 MHz and chemical shifts were recorded relative to the $CDCl_3$ (77.0 ppm). Data for ^{1}H NMR are recorded as follows, chemical shift (δ, ppm). Multiplicity (s = singlet, d = doublet, t = triplet, m = multiplet, br = broad singlet, coupling constant(s) in Hz, integration). Data for ^{13}C NMR were reported in terms of chemical shift (δ, ppm). The HRMS spectra were recorded on Agilent 6540 Ultra-High-Definition (UHD) Accurate-Mass Quadrupole Time-of-Flight (Q-TOF) liquid chromatography/mass spectrometry (LC/MS) system. GC-MS analysis was performed on a VARIAN GC-MS-MS instrument.

General procedure for synthesis of homo coupled imines: A dry round bottom flask (25 mL) was charged with benzyl amine (1 mmol), $K_2S_2O_8$ (1 equiv.) in PEG 200 (5 mL) at room temperature and stirred for 12 h. After completion (monitored by TLC), the reaction mixture was dissolved in a mixture of ethyl acetate: *n*-hexane (30:70) and washed with H_2O (3 times). The organic phases were combined and concentrated on rotary evaporator. The crude residue was analyzed by GC or purified using Silica gel (ethyl acetate: *n*-hexane) to give the desired product.

General procedure for synthesis of cross coupled imines: A dry round bottom flask (25 mL) was charged with benzyl amine (1 mmol),

other amine (3 equiv.), $K_2S_2O_8$ (1 equiv.) in PEG 200 (5 mL) at room temperature and stirred for 12 h. After completion (monitored by TLC), the reaction mixture was dissolved in a mixture of ethyl acetate: *n*-hexane (30:70) and washed with H_2O (3 times). The organic phases were combined and concentrated on rotary evaporator. The crude residue was analyzed by GC.

General procedure for synthesis of symmetrical azobenzenes: A dry round bottom flask (25 mL) was charged with amine (1 mmol), $K_2S_2O_8$ (1 equiv.), K_2CO_3 (1 equiv.) in PEG 200 (5 mL) at room temperature and stirred for 12 h. After completion (monitored by TLC), the reaction mixture was dissolved in a mixture of ethyl acetate: *n*-hexane (30:70) and washed with H_2O (3 times). The organic phases were combined and concentrated on rotary evaporator. The crude residue was analyzed by GC or purified using Silica gel (ethyl acetate: *n*-hexane) to give the desired product.

General procedure for synthesis of unsymmetrical azobenzenes: A dry round bottom flask (25 mL) was charged with aniline (1 mmol), other amine (1 mmol), $K_2S_2O_8$ (1 equiv.), K_2CO_3 (1 equiv.) in PEG 200 (5 mL) at room temperature and stirred for 12 h. After completion (monitored by TLC), the reaction mixture was dissolved in a mixture of ethyl acetate: *n*-hexane (30:70) and washed with H_2O (3 times). The organic phases were combined and concentrated on rotary evaporator. The crude residue was analyzed by GC or purified using Silica gel (ethyl acetate: *n*-hexane) to give the desired product.

General procedure for synthesis of benzothiazoles: A dry round bottom flask (25 mL) was charged with 2-aminothiophenol (1 mmol), amine (1 mmol), $K_2S_2O_8$ (1 equiv.), K_2CO_3 (1 equiv.) in PEG 200 (5 mL) at room temperature and stirred for 12 h. After completion (monitored by TLC), the reaction mixture was dissolved in a mixture of ethyl acetate: *n*-hexane (30:70) and washed with H_2O (3 times). The organic phases were combined, concentrated on rotary evaporator and purified using Silica gel (ethyl acetate: *n*-hexane) to give the desired product.

General procedure for synthesis of disulfides: A dry round bottom flask (25 mL) was charged with thiophenols (1 mmol), $K_2S_2O_8$ (1 equiv.), K_2CO_3 (1 equiv.) in PEG 200 (5 mL) at room temperature and stirred for 12 h. After completion (monitored by TLC), the reaction mixture was dissolved in a mixture of ethyl acetate: *n*-hexane (30:70) and washed with H_2O (3 times). The organic phases were combined, concentrated on rotary evaporator. The crude residue was analyzed by GC or purified using Silica gel (ethyl acetate: *n*-hexane) to give the desired product.

Spectral Data

Table 2, Entry 2a:[17] Yellow liquid; ^{1}HNMR (400 MHz, $CDCl_3$): δ = 8.43 (s, 1H), 7.80-7.83 (m, 2H), 7.49-7.50 (m, 2H), 7.44-7.46 (m, 3H), 7.37-7.38 (m, 3H), 4.86 (s, 2H); EI-MS (*m/z*): 195.3 $[M]^+$, 117, 91, 65, 51.

Table 2, Entry 2b:[18] Yellow liquid; ^{1}HNMR (400 MHz, $CDCl_3$): δ = 8.40 (s, 1H), 7.54-7.59 (m, 2H), 7.40-7.45 (m, 1H), 7.31-7.35 (m, 1H), 7.14-7.19 (m, 2H), 7.08-7.10 (m, 1H), 6.97-7.01 (m, 1H), 4.84 (s, 2H); EI-MS (*m/z*): 231.4 $[M]^+$, 135, 109, 83, 75.

Table 2, Entry 2c:[17] EI-MS (*m/z*): 231.3 $[M]^+$, 183, 135, 109, 83, 76, 57.

Table 2, Entry 2d:[19] Yellow liquid; ^{1}HNMR (400 MHz, $CDCl_3$): δ = 8.37 (s, 1H), 7.84 (s, 1H), 7.65-7.67 (m, 1H), 7.36-7.45 (m, 3H), 7.24-7.31 (m, 4H, mixed with solvent signal), 4.82 (s, 2H); EI-MS (*m/z*): 263.4 $[M]^+$, 228, 151, 125, 99, 89, 75.

Table 2, Entry 2e:[17] White solid; ^{1}HNMR (400 MHz, $CDCl_3$): δ = 8.37 (s, 1H), 7.68-7.70 (m, 2H), 7.22-7.25 (m, 4H), 7.16-7.18 (m, 2H), 4.79 (s, 2H), 2.41 (s, 3H), 2.36 (s, 3H); EI-MS (*m/z*): 223.4 $[M]^+$, 165, 131, 105, 89, 77, 65.

Table 2, Entry 2f:[3] EI-MS (*m/z*): 255.3 $[M]^+$, 224, 132, 122, 107, 91, 78, 51.

Table 2, Entry 2g:[17] EI-MS (*m/z*): 255.4 $[M]^+$, 147, 132, 121, 77, 51.

Table 2, Entry 2h and 2i:[11g] EI-MS (*m/z*): 180.2 $[M]^+$, 104, 77, 50.

Table 2, Entry 2j:[20] EI-MS (*m/z*): 209.3 $[M]^+$, 194, 165, 132, 117, 77, 51.

Table 2, Entry 2k:[21] EI-MS (*m/z*): 209.3 $[M]^+$, 132, 105, 77, 51.

Table 2, Entry 2l:[11g] EI-MS (*m/z*): 210.3 $[M]^+$, 132, 103, 77.

Table 2, Entry 2m:[6b] EI-MS (*m/z*): 211 $[M]^+$, 196, 167, 141, 115, 89, 63.

Table 2, Entry 2n:[22] EI-MS (*m/z*): 225 $[M]^+$, 207, 181, 91, 65.

Table 2, Entry 2o:[22] EI-MS (*m/z*): 289 $[M]^+$, 253, 207, 156, 76.

Table 2, Entry 2p:[23] EI-MS (*m/z*): 156.2 $[M]^+$, 126, 112, 98, 84, 70, 56, 41.

Table 2, Entry 2q:[17] EI-MS (*m/z*): 184.5 $[M]^+$, 140, 112, 84, 70, 41.

Table 2, Entry 2r:[24] EI-MS (*m/z*): 212.4 $[M]^+$, 154, 126, 98, 70, 41.

Table 2, Entry 2s:[17] EI-MS (*m/z*): 207.4 $[M]^+$, 123, 97, 69, 45.

Table 2, Entry 2t:[25] EI-MS (*m/z*): 175.1 $[M]^+$, 147, 118, 94, 81, 53.

Table 2, Entry 2u:[25] EI-MS (*m/z*): 130.3 $[M]^+$, 103, 78, 51.

Table 3, Entry 4a:[26] Red solid; ^{1}HNMR (400 MHz, $CDCl_3$): δ = 8.03 (d, *J* = 8Hz, 4H), 7.57 (m, 6H); ^{13}C (126 MHz, $CDCl_3$): δ = 152.7, 131.1, 129.2, 123.0; HRMS (ESI) *m/z*: calcd. for $C_{12}H_{11}N_2$ $[M+H]^+$ 183.0922; found: 183.0911.

Table 3, Entry 4b:[26] Yellow solid; ^{1}HNMR (400 MHz, $CDCl_3$): δ = 7.83 (d, *J* = 8Hz, 4H), 7.32 (d, *J* = 8Hz, 4H), 2.44 (s, 6H); ^{13}C (126 MHz, $CDCl_3$): δ = 150.8, 141.2, 129.7, 122.7, 21.4; HRMS (ESI) *m/z*: calcd. for $C_{14}H_{14}N_2Na$ $[M+Na]^+$ 233.1055; found: 233.1066.

Table 3, Entry 4c:[26] Yellow solid; ^{1}HNMR (400 MHz, $CDCl_3$): δ = 7.83 (d, *J* = 8Hz, 4H), 7.32 (d, *J* = 8Hz, 4H), 2.44 (s, 6H); ^{13}C (126 MHz, $CDCl_3$): δ = 150.8, 141.2, 129.7, 122.7, 21.4; HRMS (ESI) *m/z*: calcd. for $C_{14}H_{15}N_2O_2$ $[M+H]^+$ 243.1134; found: 243.1126.

Table 3, Entry 4d:[27] Red solid; ^{1}HNMR (400 MHz, $CDCl_3$): δ = 7.80 (m, 4H), 7.66 (m, 4H); ^{13}C (126 MHz, $CDCl_3$): δ = 151.1, 132.4, 125.7, 124.4; HRMS (ESI) *m/z*: calcd. for $C_{12}H_9N_2Br_2$ $[M+H]^+$ 340.9112; found: 340.9101.

Table 3, Entry 4e:[27] Yellow solid; ^{1}HNMR (400 MHz, $CDCl_3$): δ = 7.87 (d, *J* = 8Hz, 4H), 7.49 (d, *J* = 8Hz, 4H); ^{13}C (126 MHz, $CDCl_3$): δ = 150.8, 137.2, 129.4, 124.2; HRMS (ESI) *m/z*: calcd. for $C_{12}H_9N_2Cl_2$ $[M+H]^+$ 251.0143; found: 251.0122.

Table 3, Entry 4f:[7i] Red solid; ^{1}HNMR (400 MHz, $CDCl_3$): δ = 7.87 (d, *J* = 8Hz, 4H), 7.49 (d, *J* = 8Hz, 4H); ^{13}C (126 MHz, $CDCl_3$): δ = 164.2, 162.3, 153.8, 153.7, 130.3, 130.3, 120.8, 120.8, 118.3, 118.1, 108.2, 108.0; HRMS (ESI) *m/z*: calcd. for $C_{12}H_9N_2F_2$ $[M+H]^+$ 219.0734; found: 219.0717.

Table 3, Entry 4g:[28] Red solid; ^{1}HNMR (400 MHz, $CDCl_3$): δ = 7.97 (m, 4H), 7.36 (d, *J* = 8Hz, 4H); ^{13}C (126 MHz, $CDCl_3$): δ = 151.1, 150.4, 124.4, 121.2; HRMS (ESI) *m/z*: calcd. for $C_{14}H_9F_6N_2O_2$ $[M+H]^+$ 351.0568; found: 350.0561.

Table 3, Entry 4h:[26] Orange solid; ^{1}HNMR (400 MHz, $CDCl_3$): δ = 7.69 (s, 2H), 7.66 (d, *J* = 8Hz, 2H), 7.27 (d, *J* = 8Hz, 2H), 2.36 (s, 6H), 2.34, (s, 6H); ^{13}C (126 MHz, $CDCl_3$): δ = 151.2, 139.8, 137.3, 130.2, 123.3, 120.7, 19.8, 19.8; HRMS (ESI) *m/z*: calcd. for $C_{16}H_{19}N_2$ $[M+H]^+$ 239.1548; found: 239.1554.

Table 3, Entry 4i:[27] Orange solid; ^{1}HNMR (400 MHz, $CDCl_3$): δ = 7.55 (s, 4H), 7.13 (s, 2H), 2.34, (s, 12H); ^{13}C (126 MHz, $CDCl_3$): δ = 152.9, 138.7, 132.5, 120.5, 21.2; HRMS (ESI) *m/z*: calcd. for $C_{16}H_{19}N_2$ $[M+H]^+$ 239.1548; found: 239.1529.

Table 3, Entry 4j: Yellow solid; ^{1}HNMR (400 MHz, $CDCl_3$): δ = 7.13 (d, *J* = 5Hz, 4H), 6.61 (t, *J* = 5Hz, 2H), 3.88, (s, 12H); ^{13}C (126 MHz, $CDCl_3$): δ = 161.1, 154.3, 104.0, 100.9, 55.6; HRMS (ESI) *m/z*: calcd. for $C_{16}H_{19}N_2O_2$ $[M+H]^+$ 303.1345; found: 303.1344.

Table 3, Entry 4k:[7i] EI-MS (*m/z*): 318.10 $[M]^+$, 144.90, 95.14.

Table 4, Entry 5a:[29]

A: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.37 – 8.28 (m, 1H), 8.21 (dd, J = 8.4, 7.2 Hz, 2H), 8.12 (dd, J = 9.2, 2.2 Hz, 1H), 7.70 – 7.39 (m, 5H); EI-MS (*m/z*): 260.4 $[M]^+$, 183, 155, 105, 77, 51.

B: ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.20 (d, J = 8.9 Hz, 2H), 8.13 – 8.07 (m, 2H), 7.70 – 7.60 (m, 4H).

C: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.42 – 8.30 (m, 2H), 8.21 (dd, J = 8.5, 0.9 Hz, 2H), 7.61 – 7.49 (m, 5H), 7.43 (dd, J = 8.3, 6.5 Hz, 1H).

Table 4, Entry 5b:[29]

A: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.39 – 8.30 (m, 2H), 8.25 – 8.16 (m, 2H), 7.66 – 7.49 (m, 4H), 7.43 (dd, J = 8.3, 6.4 Hz, 1H); EI-MS (*m/z*): 216.3 $[M]^+$, 139, 111, 77, 51.

B: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.28 (d, J = 8.7 Hz, 2H), 8.19 (d, J = 8.7 Hz, 2H), 7.49 (dd, J = 13.0, 8.8 Hz, 4H).

C: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.31 (t, J = 8.4 Hz, 2H), 8.26 – 8.16 (m, 2H), 7.70 – 7.39 (m, 6H).

Table 4, Entry 5c:[29]

A: Yellow solid; ^{1}HNMR (400 MHz, $CDCl_3$): δ = 7.93 (d, J = 8Hz, 2H), 7.88 (d, J = 8Hz, 2H), 7.50 (m, 2H), 7.44 (m, 1H), 7.03 (m, 2H), 3.90 (s, 3H); ^{13}C (126 MHz, $CDCl_3$): δ = 162.0, 152.7, 147.0, 130.3, 129.0, 124.7, 122.5, 114.2, 55.6; HRMS (ESI) *m/z*: calcd. for $C_{14}H_{15}N_2O_2$ $[M+H]^+$ 213.1028; found: 213.0997; EI-MS (*m/z*): 212.2 $[M]^+$, 135, 115, 107, 92, 77, 51.

B: EI-MS (*m/z*): 242.2 $[M]^+$, 135, 107, 92, 77, 64.

C: EI-MS (*m/z*): 182.2 $[M]^+$, 152, 105, 77, 51.

Table 4, Entry 5d:[30] EI-MS (*m/z*): 210.5 $[M]^+$, 165, 133, 105, 77, 51.

Table 4, Entry 5e:[31] EI-MS (*m/z*): 210.4 $[M]^+$, 194, 165, 133, 105, 77, 51.

Table 4, Entry 5f:

A: Red solid; ^{1}HNMR (400 MHz, $CDCl_3$): δ = 7.94 (m, 2H), 7.52 (m, 3H), 7.17 (d, J = 8Hz, 2H), 6.63 (t, J = 4Hz, 1H), 3.88 (s, 6H); ^{13}C (126 MHz, $CDCl_3$): δ = 161.1, 154.4, 152.5, 131.1, 129.1, 122.9, 103.9, 100.9, 55.6; HRMS (ESI) *m/z*: calcd. for$C_{14}H_{15}N_2O_2$ $[M+H]^+$ 243.1134; found: 243.1078; EI-MS (*m/z*): 242.4 $[M]^+$, 214, 137, 122, 105, 77, 51;

C: EI-MS (*m/z*): 182.2 $[M]^+$, 152, 105, 77, 51.

Table 4, Entry 5g:[29]

A: Yellow solid; ^{1}HNMR (400 MHz, $CDCl_3$): δ = 7.91 (m, 2H), 7.79 (d, J = 8Hz, 2H), 7.30 (d, J = 8Hz, 2H), 7.01 (m, 2H), 3.89 (s, 3H), 2.43 (s, 3H); ^{13}C (126 MHz, $CDCl_3$): δ = 161.8, 150.8, 147.0, 140.8, 129.7, 124.5, 122.5, 114.1, 55.5, 21.4; HRMS (ESI) *m/z*: calcd. for $C_{14}H_{15}N_2O$ $[M+H]^+$ 227.1184; found: 227.1169; EI-MS (*m/z*): 226.4 $[M]^+$, 214, 135, 107, 91, 77, 64.

B: EI-MS (*m/z*): 242.2 $[M]^+$, 135, 107, 92, 77, 64.

C: EI-MS (*m/z*): 210.0 $[M]^+$, 166, 119, 91, 65.

Table 4, Entry 5h:[32]

A: Yellow solid; ^{1}HNMR (400 MHz, $CDCl_3$): δ = 7.91 (m, 2H), 7.76 (m, 2H), 7.63 (m, 2H), 7.02 (m, 2H), 3.90 (s, 3H); ^{13}C (126 MHz, $CDCl_3$): δ = 162.3, 151.5, 146.8, 132.4, 132.2, 124.9, 124.1, 114.3, 55.6; HRMS (ESI) *m/z*: calcd. for $C_{13}H_{12}N_2OBr$ $[M+H]^+$ 291.0133; found: 291.0099; EI-MS (*m/z*): 290 $[M]^+$, 242, 156, 135, 107, 77.

C: EI-MS (*m/z*): 338 $[M]^+$, 281, 207, 177, 81.

Table 4, Entry 5i:[33]

A: Yellow solid; ^{1}HNMR (400 MHz, $CDCl_3$): δ = 7.91 (m, 2H), 7.83 (m, 2H), 7.47 (m, 2H), 7.02 (m, 2H), 3.90 (s, 3H); ^{13}C (126 MHz, $CDCl_3$): δ = 162.3, 151.1, 146.8, 136.1, 129.2, 124.8, 123.8, 114.2, 55.6; HRMS (ESI) *m/z*: calcd. for $C_{13}H_{12}N_2OCl$ $[M+H]^+$ 247.0638; found: 247.0644. EI-MS (*m/z*): 246.0 $[M]^+$, 207, 135, 107, 75.

B: EI-MS (*m/z*): 242.2 $[M]^+$, 135, 107, 92, 77, 64.

C: EI-MS (*m/z*): 250.0 $[M]^+$, 207, 152, 139, 111, 75.

Table 5, Entry 6a:[34] Off white solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.10 (m, 3H), 7.90 (d, J = 7Hz, 1H), 7.50 (m, 4H), 7.39 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 168.0, 154.2, 135.1, 133.6, 130.9, 129.0, 127.6, 126.3, 125.2, 123.2, 121.6; HRMS (ESI) *m/z*: calcd. for $C_{13}H_9NS$ $[M+H]^+$ 212.0534, found 212.0525.

Table 5, Entry 6b:[34] White solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.06 (m, 3H), 7.90 (d, J = 7Hz, 1H), 7.49 (m, 3H), 7.40 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 166.6, 154.0, 137.0, 135.0, 132.1, 129.3, 128.7, 126.5, 125.4, 123.3, 121.6; HRMS (ESI) *m/z*: calcd. for $C_{13}H_8NSCl$ $[M+H]^+$ 246.0144, found 246.0133.

Table 5, Entry 6c:[21] Pale yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.07 (m, 3H), 7.87 (d, J = 7Hz, 1H), 7.50 (m, 1H), 7.37 (m, 1H), 7.02 (m, 2H), 3.87 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 167.8, 161.9, 154.2, 134.9, 129.1, 126.4, 126.2, 124.8, 122.8, 121.5, 114.3, 55.4; HRMS (ESI) *m/z*: calcd. for $C_{14}NSO$ $[M+H]^+$ 242.0640, found 242.0636.

Table 5, Entry 6d:[35] Pale yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.20(d, J = 7Hz, 2H), 8.11 (d, J = 7Hz, 1H), 7.93 (d, J = 7Hz, 1H), 7.75 (d, J = 7Hz, 2H), 7.53 (t, J = 7Hz, 1H), 7.43 (t, J = 7Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 154.0, 150.8, 140.5, 135.2, 126.8, 126.2, 123.9, 121.8, 121.2; HRMS (ESI) *m/z*: calcd. for $C_{14}H_8F_3NS$ $[M+H]^+$ 280.0408, found 280.0401.

Table 5, Entry 6e:[34] White crystal; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.13 (d, J = 7Hz, 1H), 8.00 (s, 1H), 7.90 (t, J = 7Hz, 2H), 7.53 (m, 1H), 7.40 (t, J = 7Hz, 2H), 7.32 (d, J = 7Hz, 1H), 2.48 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 168.3, 154.2, 138.8, 135.1, 133.5, 131.8, 128.9, 128.0, 126.3, 125.1, 124.9, 123.2, 121.6, 21.4; HRMS (ESI) *m/z*: calcd. for $C_{14}H_{11}NS$ $[M+H]^+$ 226.0690, found 226.0685.

Table 5, Entry 6f:[35] Off white solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.78 (d, J = 7Hz, 2H), 8.14 (d, J = 7Hz, 1H), 7.96 (m, 3H), 7.56 (m, 1H), 7.48 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 165.1, 153.9, 150.7, 140.4, 135.2, 126.8, 126.2, 123.9, 121.9, 121.2; HRMS (ESI): calcd. for $C_{12}H_9N_2S$ $([M+H]^+$ 213.0480, found 213.0480.

Table 5, Entry 6g:[36] Pale yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.55 (s, 1H), 8.20 (m, 1H), 8.14 (m, 1H), 7.90 (m, 4H), 7.53 (m, 3H), 7.39 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 168.1, 154.2, 135.1, 134.6, 133.1, 130.9, 128.3, 128.8, 127.9, 127.6, 127.5, 126.9, 126.4, 125.2, 124.4, 123.2, 121.7; HRMS (ESI) *m/z*: calcd. for $C_{17}H_{11}NS$ $[M+H]^+$ 262.0690, found 262.0685.

Table 6, Entry 7a:[26] White solid; ^{1}HNMR (400 MHz, $CDCl_3$): δ = 7.58 (d, J = 8Hz, 4H), 7.35 (m, 4H), 7.28 (m, 2H); ^{13}C (126 MHz, $CDCl_3$): δ = 137.2, 129.2, 127.7, 127.3; EI-MS (*m/z*): 218.2 $[M]^+$, 185, 154, 109, 65.

Table 6, Entry 7b:[26] White solid; ^{1}HNMR (400 MHz, $CDCl_3$): δ = 7.54 (d, J = 8Hz, 4H), 7.23 (d, J = 8Hz, 4H), 2.45 (s, 6H); ^{13}C (126 MHz, $CDCl_3$): δ = 137.5, 134.1, 130.0, 128.7, 21.2; EI-MS (*m/z*): 246.2 $[M]^+$, 213, 182, 167, 123, 91, 79, 45.

Table 6, Entry 7c:[26] Off white solid; ^{1}HNMR (400 MHz, $CDCl_3$): δ = 7.41 (d, J = 8Hz, 4H), 7.12 (d, J = 8Hz, 4H), 2.34 (s, 6H); ^{13}C (126 MHz, $CDCl_3$): δ = 137.4, 134.0, 129.8, 128.6, 21.0; EI-MS (*m/z*): 278.3 $[M]^+$, 246, 139, 96, 70.

Table 6, Entry 7d:[26] White solid; ^{1}HNMR (400 MHz, $CDCl_3$): δ = 7.40 (m, 10H), 3.71 (s, 4H); ^{13}C (126 MHz, $CDCl_3$): δ = 137.5, 129.6, 128.6, 127.6, 43.4; EI-MS (*m/z*): 246.1 $[M]^+$, 181, 121, 91, 65.

Table 6, Entry 7e:[26] Pale yellow solid; ^{1}HNMR (400 MHz, $CDCl_3$): δ = 7.18 (d, J = 4Hz, 4H), 6.71 (d, J = 8Hz, 2H), 6.60 (s, 2H), 4.34 (s, 4H); ^{13}C (126 MHz, $CDCl_3$): δ = 148.6, 136.8, 131.6, 118.7, 118.2, 115.2; EI-MS (*m/z*): 248.0 $[M]^+$, 207, 124, 71.

Table 6, Entry 7f:[26] Brown solid; ^{1}HNMR (400 MHz, $CDCl_3$): δ = 7.40 (m, 2H), 6.34 (m, 2H), 6.24 (d, J = 4Hz, 2H), 3.70 (s, 4H); ^{13}C (126 MHz, $CDCl_3$): δ = 150.2, 142.5, 110.8, 109.0, 35.6; EI-MS (*m/z*): 226.02$[M]^+$, 161, 81, 53.

Table 6, Entry 7g:[26] White solid; ^{1}HNMR (400 MHz, $CDCl_3$): δ = 2.68-2.71 (m, 2H), 2.03-2.05 (m, 4H), 1.77-1.79 (m, 4H), 1.60-1.63 (m, 2H),

1.25-1.34 (m, 10H); ^{13}C (126 MHz, $CDCl_3$): δ = 49.9, 32.8, 26.1, 25.7; EI-MS (*m/z*): 230.10 $[M]^+$, 148, 83.10.

Table 6, Entry 7h:[26] White solid; ^{1}HNMR (400 MHz, $CDCl_3$): δ = 2.69 (t, *J* = 8Hz, 4H), 1.66 (m, 4H), 1.42 (m, 4H), 0.97 (t, *J* = 7Hz, 6H); ^{13}C (126 MHz, $CDCl_3$): δ = 38.8, 31.3, 21.6, 13.6; EI-MS (*m/z*): 178.00 $[M]^+$, 122, 88, 57.

Table 6, Entry 7i: Off-white solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.75 – 7.36 (m, 4H), 7.18 (dd, *J* = 7.6, 5.3 Hz, 2H), 7.07 – 6.74 (m, 2H), 3.84 (d, *J* = 5.2 Hz, 3H), 2.40 (d, *J* = 4.9 Hz, 3H); EI-MS (*m/z*): 262.10 $[M]^+$, 229.9, 171, 139, 95.

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Key Topic: Oxidation of Amines

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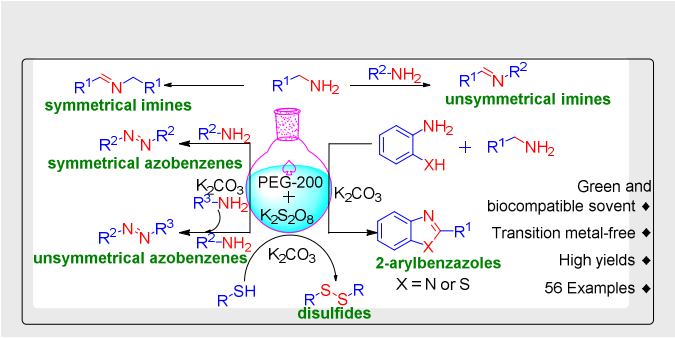
Transition Metal-Free Oxidative Coupling of Primary Amines in Polyethylene Glycol at Room Temperature: Synthesis of Imines, Azobenzenes, Benzothiazoles and Disulfides



A transition metal-free protocol has been developed for the oxidative coupling of primary amines to imines and azobenzenes, thiols to disulfides and 2-aminothiophenols to benzothiazoles offering excellent yields. The advantageous features of the present environmentally benign methodology includes the usage of biocompatable and green reaction conditions like solvent, room temperature reactions, transition metal-free approach and moreover, it offers broader substrate scope.