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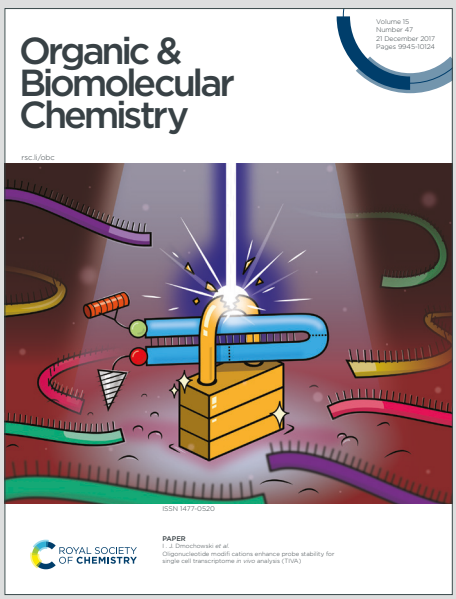

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COMMUNICATION

TEMPO Catalyzed Oxidative Dehydrogenation of Hydrazobenzenes to Azobenzenes

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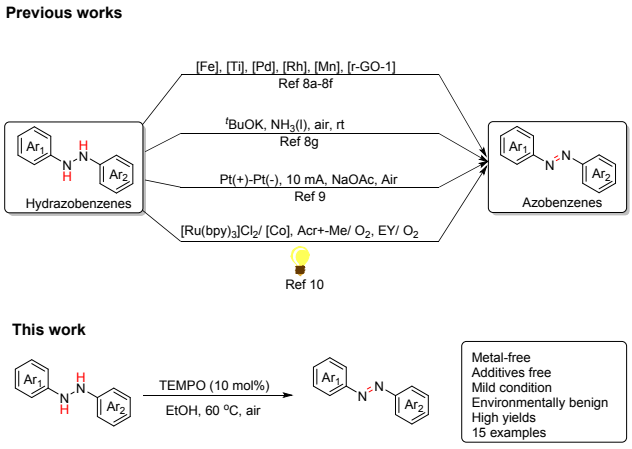
A metal-free direct oxidative dehydrogenation approach for the synthesis of azobenzenes from hydrazobenzenes has been developed by using TEMPO as organocatalyst for the first time. The reaction proceeded in open air under a mild reaction condition. A wide range of hydrazobenzenes readily undergo the dehydrogenation to give the corresponding azobenzenes in excellent yields.

Compounds having N=N double bond are of great interest in various fields. For instance, azobenzenes have profound applications in agrochemical, chemical and pharmaceutical industries as dyes and pigments, indicators, food additives, radical reaction initiators and therapeutic agents.[1] Also, azobenzenes have potential applications in areas of nonlinear optics, optical storage media, chemosensors, liquid crystals, molecular shuttles, nanotubes, and in the manufacture of protective eye glasses and filters.[2] Numerous methods have been reported for the preparation of azobenzenes such as oxidative coupling of anilines,[3] reductive coupling of aromatic nitro compounds,[4] azo coupling reaction,[5] Mills reaction,[6] the Wallach reaction.[7] Direct dehydrogenation of hydrazobenzenes is also one of the indispensable methods for the preparation of azobenzenes. These dehydrogenations can be achieved homogenously by using transition metal salts[8a-d] and heterogeneously by using rGO-1, RhNPS, Meso-Mn_2O_3.[8e-g] Wang and co-workers reported the dehydrogenation of hydrazobenzenes using potassium *tert*-butoxide in liquid ammonia under air at room temperature (rt).[8h] Although the reaction provided efficient methodology, the use of liquid ammonia as a medium limited the reaction applicability. Huang and co-workers recently reported the electrochemical strategy for the dehydrogenation of hydrazobenzenes to generate azobenzenes.[9] Balaraman and co-workers reported the dehydrogenation of hydrazobenzenes utilizing $[Ru(bpy)_3]Cl_2$ as photocatalyst and $Co(dmgH)_2(py)Cl$ as the proton-reduction catalyst.[10a] Recently, our group also reported the dehydrogenation of hydrazobenzenes harnessing the visible light using the organic photocatalyst Acr^+-Me at ambient temperature.[10b] Shortly after we reported, Wu and co-worker also developed visible-light-promoted oxidative dehydrogenation of hydrazobenzenes utilizing Eosin Y as a photocatalyst.[10c]



Scheme 1 Oxidative dehydrogenation of hydrazobenzenes

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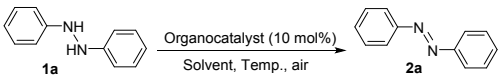
Electronic Supplementary Information (ESI) available: [details of any supplementary

TEMPO ((2,2,6,6-Tetramethylpiperidin-1-yl)oxyl) is stable, low weight radical that shows valuable redox behaviour.[11] It has been extensively used as a catalyst in the area of polymer science, trapping radical processes, oxidation of alcohols to carbonyl compounds, dehydrogenation of N-heterocycles, cyclization reaction.[12,13] However, to the best of our knowledge, there has been no reports on the application of TEMPO as catalyst for the direct oxidative dehydrogenation of NH-NH. These facts about TEMPO inspired us to explore new methods for the preparation of azobenzenes through oxidative dehydrogenation of hydrazobenzenes using TEMPO as catalyst in open air. Herein, we describe a mild and efficient direct oxidative dehydrogenation of hydrazobenzenes for the first time utilizing the commercially available, and easy to handle TEMPO as the catalyst.

A preliminary investigative study was carried out using hydrazobenzene **1a** as the model substrate under aerobic condition (Table 1). Pleasingly, our plan to dehydrogenate hydrazobenzene without metal was achieved by using 10 mol% of TEMPO in acetonitrile (MeCN) at 40 °C affording the desired product **2a** in 95% yield (entry 1). In order to maximize the yield of the reaction, we screened different other organocatalysts such as 4-Hydroxy-TEMPO, 4-Amino- TEMPO, 4-Oxo-TEMPO, Pyridine-N-oxide but there was no improvement in the yield of the desired product (entries 2-5). Next, we investigated the effect of different polar and non-polar solvents on the reactivity of the reaction (entries 6-11). Among them ethanol was found as the best solvent giving the desired product in 97% yield in 30 h (entry 10). No improvement in the yield was observed when the reaction

Table 1. Optimization of the reaction conditions for the oxidative dehydrogenation of hydrazobenzene[a)]



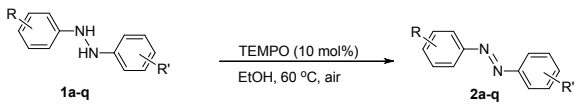
Entry	Organocatalyst	Solvent	Temp (°C)	Time (h)	Yield (%)[b)]
1	TEMPO	MeCN	40	30	95
2	4-Hydroxy-TEMPO	MeCN	40	48	94
3	4-Amino-TEMPO	MeCN	40	30	88
4	4-Oxo-TEMPO	MeCN	40	60	89
5	Pyridine-N-oxide	MeCN	40	72	42
6	TEMPO	DCE	40	24	92
7	TEMPO	Toluene	40	24	91
8	TEMPO	EtOAc	40	24	96
9	TEMPO	1,4-dioxane	40	48	94
10	TEMPO	EtOH	40	30	97
11	TEMPO	THF	40	36	92
12	TEMPO	EtOH	20	64	97
13	**TEMPO**	**EtOH**	**60**	**12**	**99**
14[c)]	TEMPO	EtOH	60	36	92
15[d)]	TEMPO	EtOH	60	8	98
16[e)]	TEMPO	EtOH	60	4	92

a) Reaction conditions: **1a** (0.3 mmol), organocatalyst (10 mol%), solvent (2 mL), Air. b) Isolated yield. c) Organocatalyst loading 5%. d) Organocatalyst loading 20% . e) Under O_2.

temperature was lowered to 20 °C (entry 12). Gratifyingly, the highest reaction yield (99%) was obtained when the reaction temperature was increased to 60 °C (entry 13). Lowering the catalytic loading lowered the yield of reaction as well as slower the reaction while increasing the catalytic loading to 20% has no appreciable effect on the yield of the reaction (entries 14 and 15). Thus, we optimized the reaction at 10%. The reaction proceeded smoothly under oxygen atmosphere in 4 h and obtained the product in 92% yield (entry 16). This study indicates that the most optimal condition for dehydrogenation of hydrazobenzene is by using TEMPO as organocatalyst in EtOH under aerobic condition.

With the established optimal conditions, we sought to evaluate the scope and the generality of the oxidative dehydrogenation by subjecting a series of hydrazobenzenes (Table 2). Various functional groups on the aromatic rings exerted little influence and were well-tolerated in this TEMPO promoted direct oxidative dehydrogenation. The reaction proceeded in excellent yields with both electron activating and electron deactivating substituted substrates. Position of the substituents also has not much effect on the reactivity of the reaction. Unsymmetrical hydrazobenzenes with electron-donating substituents such as 4-CH_3O, 4-NH_2, 4-CH_3, 4-^{t}Bu, 2-CH_3, and 3-CH_3 were well-tolerated giving the desired products in excellent yields (**2b**-**2g**). Electron-withdrawing halogen substituents such as Cl, Br and I either at 2, 3 or 4-positions as well as 4-CF_3 or 4-CO_2Me group on the phenyl ring were smoothly converted to the desired products in excellent yields (**2g**-**2n**). The symmetrical hydrazobenzenes with different substituents such as CH_3, CF_3 in the 4-position of the phenyl rings were well tolerated giving the corresponding products in excellent yields

Table 2. Scope of the TEMPO catalyzed oxidative dehydrogenation of hydrazobenzenes[a)]



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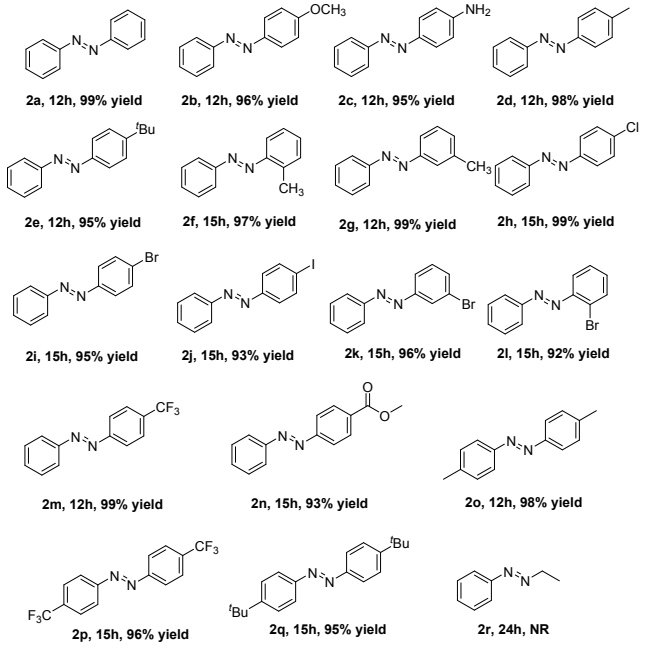
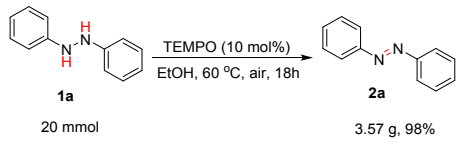


a) Reaction conditions: **1** (0.3 mmol), TEMPO (10 mol%), Air, EtOH (2 mL), 60 °C, Isolated yields.

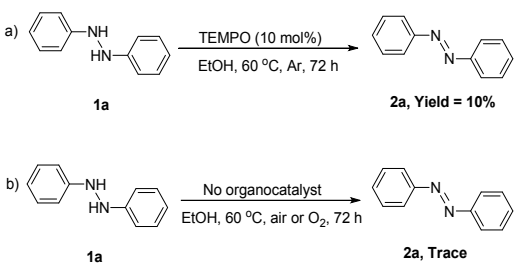
(**2o** and **2p**). Notably, the introduction of bulkier ^{t}Bu-group at the 4-position was equally efficient, giving the desired product in excellent yield 96% (**2q**). However, the hydrazine derivatives with aliphatic substituent may not applicable, as no reaction took place by using **2r**.

To further extend the utility of the methodology, we carried out the scale-up reaction as shown in Scheme 2. This method can be easily scaled up to 3.68 g of the substrate giving the desired product in excellent yield.



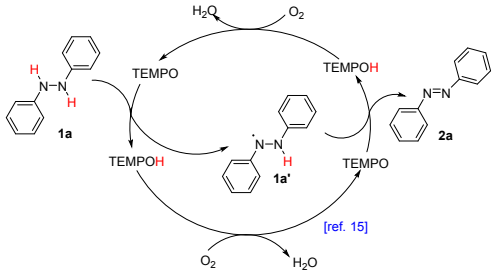
Scheme 2. Scalable synthesis of **2a.**

As control experiments, we carried out the reaction in Argon atmosphere but unfortunately the yield of the desired product was very low (10%) even after 72 h of reaction (Scheme 3a). Next, the reaction was carried out in absence of TEMPO. However, both of the reactions in the air or oxygen were incomplete and the desired product was furnished only in trace after 72 h (Scheme 3b). Thus, suggested that both the components were necessary for the transformation.



Scheme 3. Control Experiments

Based on the literature[14] and experimental results, we proposed a mechanism for the oxidative dehydrogenation of hydrazobenzenes (Scheme 4). The reaction was initiated by the abstraction of a hydrogen atom from hydrazobenzene **1a** by the TEMPO with the generation of intermediate **1a'** and TEMPOH. The generation of TEMPOH was confirmed by GCMS study (see ESI). The TEMPOH is readily oxidized by air to regenerate TEMPO which subsequently abstracts another hydrogen atom from the intermediate **1a'** to give the final product **2a**.



Scheme 4. Plausible mechanism for the dehydrogenation of hydrazobenzene.

In summary, we have developed an efficient, metal-free direct oxidative dehydrogenation for the preparation of azobenzenes from hydrazobenzenes using TEMPO as organocatalyst in open air for the first time. This methodology provides a mild, simple, and environmentally benign approach for the preparation of various azobenzenes. Furthermore, the utility of the reaction on a gram scale is also demonstrated.

Conflicts of interest

There are no conflicts to declare.

Author Contributions

§ These authors contributed equally.

Acknowledgements

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Graphical Abstract: