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Solvent-free mechanochemical synthesis of azo dyes†

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An efficient diazotization of phenolic compounds with aryltriazenes is herein demonstrated by employing ball milling under catalyst-, promoter- and solvent-free conditions. The present protocol offers several advantages including mild conditions, good selectivity and high yields, simple operation and practical gram-scale synthesis. Overall, this novel strategy significantly improves the reaction efficiency, simplifies purification procedures of the diazotization reaction and provides potential for the industrial preparation of azo dyes.

Introduction

Mechanochemistry with solvent-free and environmentally friendly characteristics is one of the most promising alternatives to traditional liquid-phase-based reactions, demonstrating epoch-making significance in the realization of different types of chemistry.[1] Most organic reactions are carried out in volatile organic solvents, which caused a great proportion of waste generation in a laboratory or industry.[2] However, poor solubility of the reactants in organic solvents also affects the efficiency of the reaction.[2] In addition, solvents may be involved in the reaction to generate byproducts which decrease the efficiency and selectivity of the reaction.[3–5] Therefore, the development of environmentally friendly or solvent-free reactions is of great interest. In recent years, ball milling has been widely used in organic synthesis,[6] such as Suzuki–Miyaura cross-coupling,[7,8] Aza-Morita-Baylis–Hillman reaction,[9] azoxy- and azo-arenes synthesis[10,11] and so on.

Azo dyes are organic compounds that contain –N=N– groups,[12] which were the most common dyes (more than 3000 different varieties) used in the textile industry compared to natural dyes due to their low cost, versatility and colouring ability.[13] They account for approximately 70% of the total amount of dyes, and besides the textile industry, azo dyes are also intensively u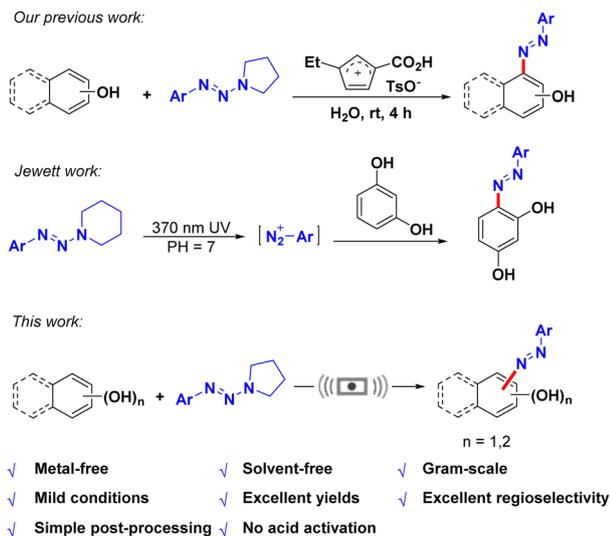sed in the cosmetics, leather, paper, food and pharmaceutical industries.[14] Consequently, various methods were developed for synthesis of azo dyes. Typically, most of these compounds were prepared from aromatic primary amine *via* the diazotization reaction with nitrite to produce aryl diazonium salts, followed by coupling with nucleophiles.[14–19] In particular, environmentally friendly protocols for the synthesis of azo dyes *via* the diazotization and coupling of diazonium salts with phenols or aromatic amines have attracted much attention in recent years, such as: (a) the coupling reaction of resin supported diazonium salts with nucleophiles;[20] (b) gas–solid diazotization of 3-aminopyrazolo[3,4-*b*]pyridine/solid–solid cascade coupling with nucleophiles;[21] (c) *in situ* diazotization of *p*-nitroaniline with sodium nitrite and coupled with *N,N*-diethylaniline in supercritical carbon dioxide under mineral acid-free conditions;[22] (d) one pot diazo coupling under microwave irradiation;[23] (e) the sonochemical method of diazotization and coupling;[24] (f) continuous flow diazotization and coupling in a microreactor system,[25] *etc.* However, all of the above methods have one or more disadvantages, such as the use of solvents in the reaction. The solvent becomes liquid waste after the reaction, resulting in environmental pollution. In addition, some products formed are poorly soluble in the solvent, thus making the reaction and post-treatment process even more complicated. Nowadays, green chemistry and sustainable approaches for organic synthesis have gained tremendous importance due to environmental and ecosystem based concerns. Mechanochemistry assisted organic reactions are proven to be energy efficient, green,[26] fast, solvent-free, and reproducible, show good selectivity, and lead to higher yields.[27,28] Although diazonium salts are common reagents for the synthesis of azo dyes, however, their potentially explosive hazards and unstable nature highly restricted their application, especially for the large scale synthesis of azo dyes. Therefore, developing stable and mild alternative reagents to replace aryl

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Scheme 1   General synthetic pathway for azo dyes.

Table 1   Optimization of reaction conditions[a]

Entry	Variation from the "standard conditions"	Yield[b] (%)
1	None	92
2	100 μL MeCN as an auxiliary grinding agent	90
3	100 μL MeOH as an auxiliary grinding agent	89
4	100 μL H_2O as an auxiliary grinding agent	91
5	1.1 mmol 2a	89
6	5 mm (6 balls) instead of 5 mm (20 balls)	40
7	5 mm (12 balls) instead of 5 mm (20 balls)	77
8	8 mm (1 balls) instead of 5 mm (20 balls)	47
9	8 mm (3 balls) instead of 5 mm (20 balls)	90
10	8 mm (6 balls) instead of 5 mm (20 balls)	68
11	8 mm (10 balls) instead of 5 mm (20 balls)	63
12	2 hours instead of 3 hours	47
13	4 hours instead of 3 hours	93
14	200 rpm instead of 300 rpm	Trace
15	400 rpm instead of 300 rpm	Trace
16	Zirconia balls instead of stainless steel balls	90
17	Mixing without rotational speed	n.r.
18[c]	Solution reaction	Trace

[a] Reactions condition: 1a (1.0 mmol), 2a (1.2 mmol), and 5 mm stainless steel balls were added to a 50 mL stainless steel tank, 300 r for 3 h. [b] Isolated yield. [c] 1a (1.0 mmol), 2a (1.2 mmol) and MeCN (1 mL) stirred in a 10 mL glass tube for 3 h at room temperature.

diazonium salts is highly desirable. Recently, as the masked surrogates of corresponding diazonium salts, aryltriazenes have been widely applied in a variety of synthetic transformations due to their good stability, multiple reactive sites, and mild reaction conditions.[29–31] In particular, they were also used for the efficient synthesis of azo dyes *via* diazotization of phenolic compounds. In 2018, our group developed an ionic liquid promoted diazotization of naphthols with aryltriazenes for the synthesis of azo dyes.[19] In 2021, Jewett's group reported a UV light induced diazotization of phenol with aryltriazenes for protein modification.[32] Herein, we developed a novel metal-, promoter-, catalyst- and solvent-free method for the synthesis of various azo dyes in excellent yields and regioselectivity using ball milling with aryltriazenes as diazotization reagents (Scheme 1).

Results and discussion

As shown in Table 1, at the outset of the investigation, β-naphthol (1a) (1.0 mmol) and *p*-methylphenyltriazene (2a) (1.2 mmol) were employed as model substrates, with stainless steel balls (5.0 mm in diameter, 20 balls) in a stainless steel jar (50 mL) to optimize the reaction. To our delight, the desired product was obtained in 92% yield when the reaction was milled at room temperature at 300 rpm for 3 hours (Table 1, entry 1). We then tried to add a small amount of solvents as auxiliary grinding agents, such as acetonitrile, methanol and water, and the results showed that the solvents had almost no effect on the reaction (Table 1, entries 2–4). Then, the influence of the reactant ratio was further studied. A slightly lower yield was afforded when the dosage of *p*-methylphenyltriazine (2a) was reduced to 1.1 mmol (Table 1, entry 5). The size and number of grinding balls were then investigated; when the number of grinding balls was reduced to 6 and 12, the yield of azo dye was significantly reduced to 40% and 77%, respectively (Table 1, entries 6 and 7). The number of grinding balls with larger size was also
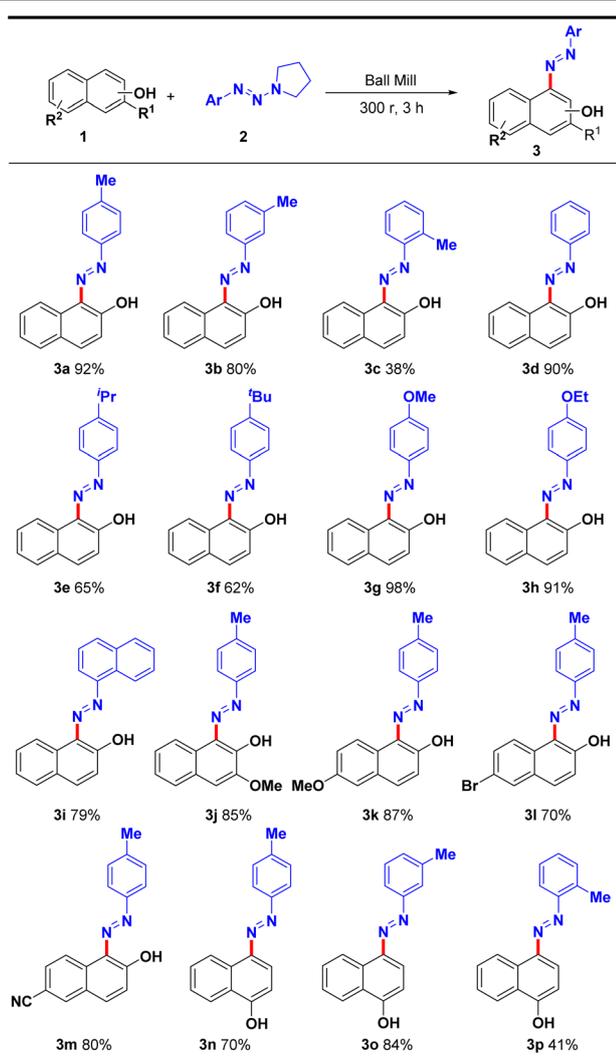
examined, such as 1, 3, 6 and 10 large balls which were used to replace 20 small balls in the reaction, and the results showed that 3 large balls with a diameter of 8 mm gave better yields up to 90%, while the others only afforded moderate yields (47–68%) (Table 1, entries 8–11). In the study of the reaction time, decreasing the reaction time resulted in a lower product yield (Table 1, entry 12); however, prolonging the reaction time did not significantly improve yield (Table 1, entry 13). Subsequently, the effect of speed was also studied. Unfortunately, 200 rpm and 400 rpm only afforded a trace amount of the product (Table 1, entries 14 and 15), because low speeds do not provide enough energy to activate the substrate and high speed splashes the substrates onto the lid and walls of the jar. In addition, on replacing stainless steel balls with zirconia balls, 90% of 3a was obtained, which confirmed that the metal was not involved in this transformation (Table 1, entry 16). In order to verify that the ball milling provided the energy, rather than simply mixing the feedstock, we mixed the reactants without providing a rotational speed and found that there was no product formed (Table 1, entry 17). Furthermore, the superiority of the mechanochemical synthesis was demonstrated by comparing it with the reaction in the liquid phase, and only trace 3a was observed when the reaction was conducted in solution, which confirmed that ball milling played an important role in this

transformation (Table 1, entry 18). Finally, the optimal reaction conditions are therefore as follows: β-naphthol (**1a**) (1.0 mmol) and *p*-methylphenyltriazene (**2a**) (1.2 mmol) together with stainless steel balls (5 mm in diameter, 20 balls) were introduced into a stainless steel jar (50 mL) and milled in the absence of solvent at 300 rpm in air for 3 h.

Once the reaction conditions were optimized, we performed substrate generalization studies by using β-naphthol, α-naphthol and resorcinol derivatives with aryltriazenes, respectively. First, the substrate range of β-naphthol with aryltriazenes was examined (Table 2, **3a–3i**). The reaction was generally effective for electron-donating substituents, most of which can afford moderate to good yields. Both *para-* and *meta*-methyl substituted aryltriazenes are compatible with the reaction, and the desired products can be obtained in 92% and 80% yields (**3a** and **3b**), respectively. However, the *ortho*-substituted substrate reacted less effectively, with a yield of only 38% (**3c**), which is

possibly due to the steric hindrance effect. To our delight, non-substituted phenyltriazene (**2d**), 4-*i*Pr (**2e**) and 4-*t*Bu (**2f**) substituted aryltriazenes delivered good to excellent yields. Furthermore, excellent yields of up to 98% and 91% were obtained when 4-OMe and 4-OEt substituted aryltriazenes were subjected to the reaction (**3g** and **3h**). Notably, the polycyclic aryltriazene also showed good compatibility, and the target product **3i** can be obtained in 79% yield. Then, we examine the universality of substituted β-naphthols, such as 3-methoxy-2-naphthol (**1j**) and 6-methoxy-2-naphthol (**1k**), which smoothly reacted and obtained the corresponding products in 85% and 87% yields, respectively. Fortunately, 2-naphthols bearing electron-withdrawing substituents (bromo & cyano) were also tolerated, and target products **3l** and **3m** can be afforded in good yield. Finally, the reactivity of α-naphthol towards substituted aryltriazenes was investigated, such as *p*-Me (**2n**), *m*-Me (**2o**) and *o*-Me (**2p**) substituted phenyltriazenes, which were also tolerated, and the corresponding products **3n–3p** were generated in 41% to 84% yield.

The substrate scope of various aryltriazenes with resorcinol under the established optimal conditions was next evaluated (Table 3). The results showed that various aryltriazenes bearing electron-donating groups (4-Me, 4-*i*Pr, 4-*t*Bu, 4-OMe and 4-OEt) on the benzene ring and non-substituted substrates all reacted smoothly with resorcinol **4a**. Besides sterically hindered *ortho*-methyl substituted triazene (**5c**) that afforded 35% yield, the desired products **5a–5h** were obtained in moderate to good

Table 2 The scope of substituted aryltriazenes and naphthols[a,b]

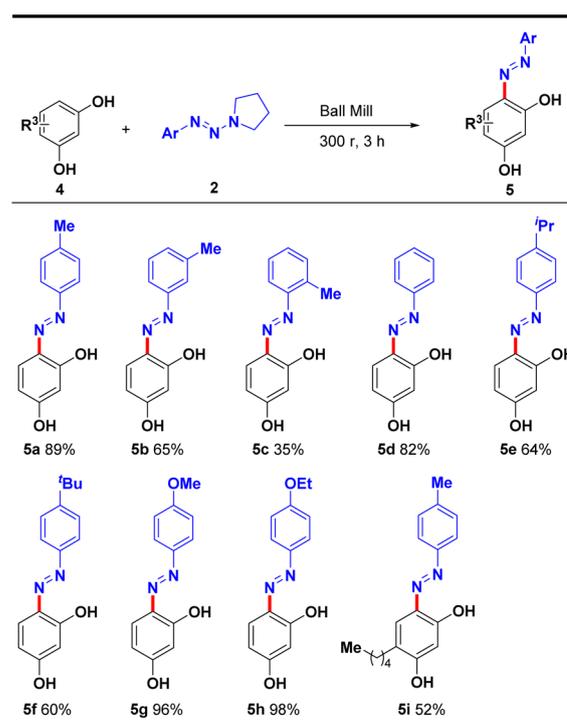**Table 3** The scope of substituted aryltriazenes with resorcinol[a,b]

[a] Reaction conditions: **1** (1.0 mmol), **2** (1.2 mmol), and 5 mm stainless steel balls were added to a 50 mL stainless steel tank and reacted at 300 rpm for 3 h. [b] Isolated yield.

[a] Reaction conditions: **4a** (1.0 mmol), **2** (1.2 mmol), and 5 mm stainless steel balls were added to a 50 mL stainless steel tank and milled at 300 rpm for 3 h. [b] Isolated yield.

yields (60–98%). In addition, substituted resorcinol compounds such as (E)-4-pentyl-6-(p-tolyldiazenyl)benzene-1,3-diol (**4i**) also achieved moderate yields. Notably, due to the poor solubility of resorcinol products in low polar solvents such as petroleum ether or hexane, they can be easily isolated and purified by simple filtering and washing with hexane after the reaction.

To demonstrate the practical utility of this mechanochemical synthesis method, the reaction of resorcinol **4a** and *p*-methylphenyltriazene **2a** was performed at the 20 mmol scale (Scheme 2). The results showed that this protocol could be successfully performed on a gram scale, and the desired product **5a** was obtained smoothly in 91% yield at room temperature in 6 hours of ball milling under solvent-free conditions. It is worth mentioning that the target product (E)-4-(p-tolyldiazen-yl)benzene-1,3-diol (**5a**) was almost insoluble in petroleum ether (PE) and ethyl acetate (EA), while the unreacted resorcinol **4a** and *p*-methylphenyltriazene **2a** are soluble in the above organic solvents. Therefore, as shown in Fig. 1, after the completion of the reaction, the product can be easily isolated from the reaction mixture *via* washing with petroleum ether (PE) (3 × 15 mL) and water (3 × 15 mL), respectively.

To gain insight into the reaction mechanism, a control experiment was carried out (Scheme 3). Under standard conditions, 2-methoxynaphthalene **6a** was used to replace β-naphthol **1a** to react with *p*-methylphenyltriazene **2a**. As expected, no corresponding product **7a** was obtained, suggesting that the weak acidity of the hydroxyl group of β-naphthol **1a**

Scheme 2 Large scale synthesis of **5a**.

Fig. 1 Ball milling setup and process.
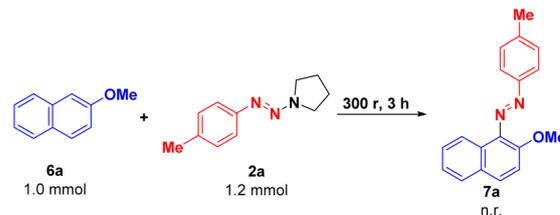
Scheme 3 Mechanism validation experiments.
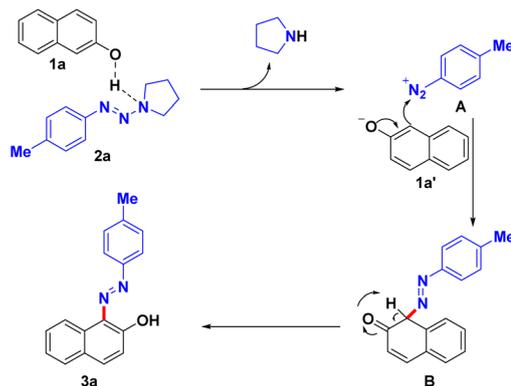
Scheme 4 Proposed reaction mechanism.

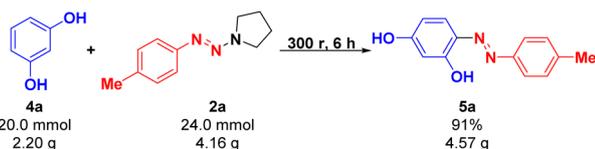plays a role in activating the aryltriazene to provide an aryldiazonium cation for further diazotization.

Based on literature reports[23,29] and mechanism validation experiments, a plausible reaction mechanism is presented in Scheme 4. First, aryltriazene **2a** undergoes N2–N3 cleavage *via* hydrogen bond activation in the presence of weak acid β-naphthol to form an electron donor–acceptor (EDA) complex of aryl diazonium cation and naphthalen-2-olate. Subsequently, the dearomatized intermediate **B** was obtained through electrophilic addition of the aryldiazonium cation to naphthalen-2-olate. Finally, product **3a** was produced through 1,3-proton transfer and restores aromaticity.

Conclusions

In conclusion, the ball milling method for the synthesis of azo dyes was developed, which avoids heating and the use of any solvents and metal catalysts. The reactions were carried out with aryltriazenes that served as reactive, stable diazotization reagents and phenolic compounds as both nucleophiles and as Brønsted acids to activate aryltriazenes for the release of diazonium cation. The present method is simple, easy to scale up, and environmentally friendly and does not require any solvents. The present strategy provides a new insight into the industrial preparation of azo dyes under mild conditions.

Data availability

All experimental and characterization data and detailed experimental procedures are available in the published article and ESI.†

Author contributions

Conflicts of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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