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Green and efficient synthesis of azo Schiff bases

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Abstract

Pure azo Schiff bases were readily and conveniently accessible in high yields by mixing of the reagents either as aqueous slurry, or by grinding at room temperature. This method, unlike a classical method, needs neither harsh conditions nor organic solvents. The satisfactory results were obtained with excellent yields, short reaction time, and operational simplicity in the experimental procedure. Comparison of time and yield in this green method with the classical methods is also performed.

Keywords: Azo Schiff bases; imines; solvent-free; green chemistry; grinding

1. Introduction

Azo dyes constitute one of the largest and most varied groups of synthetic organic dyes in use today [1]. Azo compounds are highly important, well-known and widely used substances in the textile, paper, coloring agents for foods and cosmetics industries. Other applications include emerging technologies like liquid crystals, organic photoconductors and non-linear optics [2-3]. Azo compounds serve as important analytical tools by providing a strongly chromophoric label, the concentration of which is easily determined by colorimetric, spectrophotometric or spectrofluorimetric methods. Besides, azo compounds are important analytical aid compounds serving as pH indicators, complexometric indicators and to a lesser extent, pre-concentration reagents [4]. The pharmacological use of azo compounds originates from the discovery of the antibacterial action of Prontosil on streptococcal infections by Dogmagk [5]. Furthermore, azo compounds were reported to show a variety of biological activities including antibacterial [6], antifungal [7], pesticidal [8], antiviral [9] and anti-inflammatory [10] activities.

Recently heterocyclic azo compounds have been used in the Mitsunobu reaction [11]. Usually, azo compounds were synthesized by diazotization of the amine in mineral acid at about 0 °C [12-15].

Schiff bases are used as substrates in the preparation of a large amount of bioactive and industrial compounds [16-20].

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In addition, Schiff bases are well-known to have biological activites such as antibacterial [21-22], antifungal [23-24], antitumor [25-26], antiviral [27-28], anti-HIV-1 [29], antiproliferative [30], herbicidal [31] and anti-influenza A virus [32] activities. It has been suggested that azomethine linkage (C=N) might be responsible for the biological activities of Schiff bases [33]. Also, Schiff base ligands have been recognized as 'privileged ligands' and they are able to coordinate with various metals and stabilize them in various oxidation states, enabling the applications of Schiff base metal complexes in a large variety of useful catalytic transformations [34-36]. Some Schiff bases have been reported as effective corrosion inhibitors for metal alloys in acidic media [37-39].

Perhaps the most common method for preparing Schiff bases is the reaction of aldehydes and ketones with primary amines [40]. The reaction is generally carried out by refluxing the carbonyl compounds and amines in organic solvents by separating the water as formed with an azeotroping agent or by anhydrous Na_2SO4 and $MgSO_4$ [41-45].

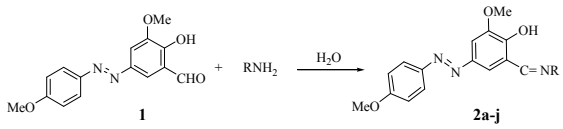
Recent years have witnessed a major drive to increase the efficiency of organic transformations while lowering the amount of waste materials. Many organic solvents are hazardous and can be deleterious to human health. They are volatile and cause an environmental threat by polluting the atmosphere [46-47]. The replacement of volatile organic solvents in organic reaction processes is an important green chemistry goal. The use of water as a biodegradable, nonflammable and readily available resource is attractive [48-50]. Furthermore, the solvent-free reaction or solid-state

reaction are green methods in the organic synthesis which have numerous advantages: reduced pollution, low costs, and simplicity in process and handling [51-52]. Mechanochemistry can be as simple as grinding two reactants in a mortar pestle and mortar or more complex, as with the use of commercially available ball mills [53-55].

Some new azo Schiff bases in organic solvents have been previously reported by the authors [56]. According to the above facts and in embracing the principles of green chemistry, herein we report two clean, simple and versatile routes to mono and bis azo Schiff bases in water or by grinding.

2. Results and discussion

Azoaldehyde **1** was prepared from *p*-anisidine and 2-hydroxy-3-methoxybenzaldehyde (*o*-vanillin) in aqueous medium at 0-5 ^{o}C according to a reported method and was purified by recrystallization from warm 95% ethanol.[56] Then azoaldehyde **1** reacted with amines in a small amount of water at room temperature to produce azo Schiff bases **2a-j** in excellent yields (Scheme 1, Table 1). The crystalline solids formed were collected by filtration, washed with water and dried in a desiccator to give pure products. The structures of the target compounds were well characterized by IR, ^{1}H NMR, ^{13}C NMR and MS Spectra.



Scheme 1. Synthesis of azo Schiff bases **2a-j** in water suspension

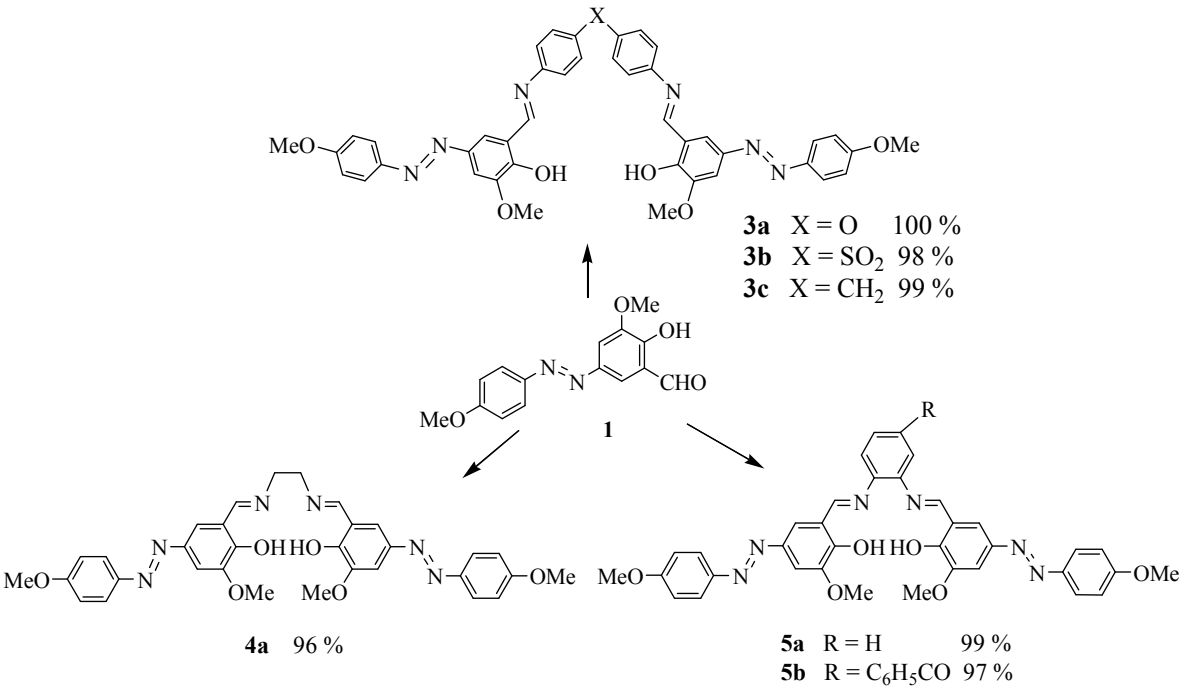
Comparison of this method with the conventional methods (e.g. refluxing in ethanol) showed the priority due to saving time and energy. Because of the low nucleophilicity of 4-chloroaniline and 4-nitroaniline, the yields of **2i-j** were moderate (Entry 9-10). When the mentioned reactions were performed in the presence of K_2CO_3 as a base, the yield increased and the time decreased (Entry 11-12). After these successful results, the bis azo Schiff bases **3a-c, 4a** and **5a-b** were synthesized using azoaldehyde **1** and the corresponding bis amine at room temperature for 1 hour (Scheme 2).

Condensation reaction of aldehydes and *p*-amino azobenzene in a water suspension medium was also found to produce azo Schiff bases **6a-g** quite efficiently. *p*-Amino azobenzene reacted with equimolar of different aldehydes in water suspension at room temperature to give azo Schiff bases **6a-g** in high yields at lower time than refluxing ethanol (Scheme 3, Table 2). All the synthesized products were characterized on the basis of their IR, ^{1}H NMR, ^{13}C NMR and Mass Spectra.

Table 1. Synthesis of azo Schiff bases **2a-j**

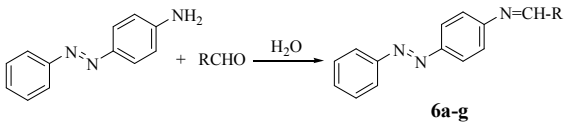
Entry	Product	R	Refluxing ethanol		Aqueous slurry	
			Time/min	Yield %	Time/min	Yield %
1	**2a**	4-$MeOC_6H_4$	120	99	30	100
2	**2b**	3-$MeOC_6H_4$	180	99	30	99
3	**2c**	4-MeC_6H_4	180	99	45	98
4	**2d**	3-MeC_6H_4	180	98	45	99
5	**2e**	C_6H_5	480	99	45	97
6	**2f**	$C_6H_5CH_2$	480	98	45	98
7	**2g**	3-HOC_6H_4	360	98	30	98
8	**2h**	2,4-di$MeOC_6H_3$	120	99	30	100
9	**2i**	4-ClC_6H_4	600	78	120	65
10	**2j**	4-$NO_2C_6H_4$	600	71	120	53
11	**2i**	4-ClC_6H_4	-	-	45	93[a]
12	**2j**	4-$NO_2C_6H_4$	-	-	45	90[a]

[a] The reaction was performed in the presence of K_2CO_3.



Scheme 2. Synthesis of bis azo Schiff bases **3a-c**, **4a** and **5a-b** in water suspension

We next decided to prepare azo Schiff bases by grinding corresponding amines and aldehydes without solvents in a mortar. When different amines and azoaldehyde **1** were ground together at room temperature, the reaction starts immediately, usually with gentle heat production but without melting because azo Schiff bases have high melting points. Indication of softening for some seconds followed by immediate hardening was visually observed only in synthesis with benzyl amine. The mixture was ground together for 1 min and was kept for 90 min.



Scheme 3. Synthesis of azo Schiff bases **6a-g** in water suspension

On the basis of these successful results, synthesis of bis azo Schiff bases **3a-c, 4a**, **5a-b** and azo Schiff bases **6a-g** were also performed by mechanochemical method (grinding of reactants together) at room temperature (Table 3). The water produced in the reaction was removed at 70 ^{o}C under vacuum.

Comparison of this method to the conventional method (refluxing ethanol) showed that the synthesis of azo Schiff bases in solvent-free method is faster and more inexpensive than the conventional method since in the former method, the reactions proceeded at room temperature with high yields. It is noteworthy that azo Schiff bases **2i-j** were obtained in excellent yields by grinding without the need for any base. This method has the following merits: high yield, easy separation and purification, simple instruments, mild condition, and no solvents.

3. Experimental

General: All required chemicals were purchased from Merck, Fluka and Acros chemical companies. IR spectra were run on a Shimadzu FT-IR 8000 spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ using a Bruker Avance DPX instrument (^{1}H NMR 250 MHz, ^{13}C NMR 62.9 MHz). Chemical shifts were reported in ppm (δ) downfield from TMS. All of the coupling constants (*J*) are in Hertz. The mass spectra were recorded on a Shimadzu GC-MS QP 1000 EX instrument. Melting points were determined in open capillaries with Buchi 510 melting point apparatus and are not corrected. Thin-layer chromatography was carried out on silica gel 254 analytical sheets obtained from Fluka. Azoaldehyde **1** (2-hydroxy-3-methoxy-5(4-methoxyphenylazo) benzaldehyde) was synthesized *via* the reported procedures [56]. Spectral data for **2a-b**, **2d-g** and **3a-b** have been previously reported [56].

Table 2. Synthesis of azo Schiff bases **6a-g**

Entry	Product	R	Refluxing ethanol		Aqueous slurry	
			Time/min	Yield %	Time/min	Yield %
1	**6a**	4-$NO_2C_6H_4$	300	96	30	98
2	**6b**	4-ClC_6H_4	300	91	30	98
3	**6c**	2-OHC_6H_4	300	95	45	99
4	**6d**	4-$MeOC_6H_4$	300	89	45	96
5	**6e**	4-MeC_6H_4	300	84	45	91
6	**6f**	C_6H_5	390	83	45	94
7	**6g**	$C_6H_5CH_2$	390	80	45	90

General procedure for the preparation of azo Schiff bases in water

Solid starting materials were finely powdered before use. A mixture of aldehyde (2.5 mmol) and amine (2.5 mmol) was stirred in a small amount of water (5 ml) at room temperature for the mentioned time. In the case of bis azo Schiff bases 5.0 mmol aldehyde was used. The crystalline powder formed was collected by filtration, washed with water and dried in a desiccator to give azo Schiff bases. If the reaction need a base, K_2CO_3 (0.41 g, 3.0 mmol) was added to the reaction mixture. The same procedure was used in the synthesis of bis azo Schiff bases with amine (2.5 mmol) and aldehyde (5.0 mmol).

General procedure for the solvent-free synthesis of azo Schiff bases

All solvent-free reactions were performed by grinding together 5.0 mmol of the pure amine with 5.0 mmol of the pure aldehyde in a mortar for one min and keeping the mixture at room temperature for 1.5 h in order to be formed quantitatively. The water produced in the reaction was removed at 70 ^oC under vacuum. The same procedure was used in the synthesis of bis azo Schiff bases with amine (5.0 mmol) and aldehyde (10.0 mmol).

4-((4-Methoxyphenyl)diazenyl)-2-methoxy-6-((*p*-tolylimino)methyl)phenol (**2c**): Red solid. mp: 139-141 ^oC. IR (KBr) (cm^{-1}): 1417 (N=N), 1612 (C=N), 3211-3637 (OH). ^1H NMR ($CDCl_3$) δ 2.31 (Me, s, 3H), 3.79, 3.82 (2OMe, s, 6H), 6.80-7.83 (ArH, m, 10H), 8.36 (HC=N, s, 1H), 14.29 (OH, br, 1H). ^{13}C NMR ($CDCl_3$) δ 20.5 (Me), 55.3, 55.7 (OMe), 108.4-158.7 (aromatic carbons), 162.2 (HC=N). GC-MS *m/z* = 375 [M^+].

4-((4-Methoxyphenyl)diazenyl)-2-((2,4-dimethoxyphenylimino)methyl)-6-methoxyphenol (**2h**): Dark red solid. mp: 176-178 ^oC. IR (KBr) (cm^{-1}): 1422 (N=N), 1609 (C=N), 3196-3618 (OH). ^1H NMR ($CDCl_3$) δ 3.78, 3.83, 3.85, 3.88 (4OMe, s, 12H), 6.93-7.86 (ArH, m, 9H), 8.42 (HC=N, s, 1H), 14.33 (OH, br, 1H). ^{13}C NMR ($CDCl_3$) δ 55.7, 55.9, 56.2, 56.6 (OMe), 110.4-156.9 (aromatic carbons), 161.5 (HC=N). GC-MS *m/z* = 421 [M^+].

4-((4-Methoxyphenyl)diazenyl)-2-((4-chlorophenylimino)methyl)-6-methoxyphenol (**2i**): Light brick red solid. mp: 126-128 ^oC. IR (KBr) (cm^{-1}): 1414 (N=N), 1615 (C=N), 3219-3642 (OH). ^1H NMR ($CDCl_3$) δ 3.80, 3.83 (2OMe, s, 6H), 6.88-7.93 (ArH, m, 10H), 8.30 (HC=N, s, 1H), 14.38 (OH, br, 1H). ^{13}C NMR ($CDCl_3$) δ 55.1, 55.5 (OMe), 106.3-155.6 (aromatic carbons), 163.4 (HC=N). GC-MS *m/z* = 397 [M^+, ^{37}Cl], 395 [M^+, ^{35}Cl].

4-((4-Methoxyphenyl)diazenyl)-2-methoxy-6-((4-nitrophenylimino)methyl)phenol (**2j**): Crimson solid. mp: 182-184 ^oC. IR (KBr) (cm^{-1}): 1344, 1520 (NO_2), 1419 (N=N), 1610 (C=N), 3203-3635 (OH). ^1H NMR ($CDCl_3$) δ 3.86, 3.90 (2OMe, s, 6H), 6.93-8.11 (ArH, m, 10H), 8.46 (HC=N, s, 1H), 14.29 (OH, br, 1H). ^{13}C NMR ($CDCl_3$) δ 55.5, 55.8 (OMe), 114.0-158.6 (aromatic carbons), 163.9 (HC=N). GC-MS *m/z* = 406 [M^+].

Bis[5-(4-methoxyphenylazo)-2-hydroxy-3-methoxybenzaldehyde]-4,4′-diiminophenyl methane (**3c**): Dark red solid. mp: 217-219 ^oC. IR (KBr) (cm^{-1}): 1422 (N=N), 1617 (HC=N), 3244-

Table 3. Synthesis of azo Schiff bases **2a-j**, **3a-c**, **4a**, **5a-b** and **6a-g** by solvent-free method

Product	Yield %	Product	Yield %	Product	Yield %
2a	100	**2i**	90	**6a**	100
2b	100	**2j**	91	**6b**	100
2c	100	**3a**	100	**6c**	100
2d	98	**3b**	95	**6d**	99
2e	96	**3c**	98	**6e**	100
2f	93	**4a**	98	**6f**	97
2g	98	**5a**	100	**6g**	98
2h	100	**5b**	97	-	-

3666 (OH). ^{1}H NMR ($CDCl_3$) δ 3.82, 3.86 (4OMe, s, 12H), 3.93 (CH_2, s, 2H), 6.84-7.89 (ArH, m, 20H), 8.39 (2HC=N, s, 2H), 14.31 (2 OH, br, 2H). ^{13}C NMR ($CDCl_3$) δ 42.7 (CH_2), 55.8, 56.2 (OMe), 107.1-159.5 (aromatic carbons), 163.6 (HC=N).

6,6'-(Ethane-1,2-diylbis(azan-1-yl-1-ylidene))bis(methan-1-yl-1-ylidene))bis(2-methoxy-4-((4-methoxyphenyl)diazenyl)phenol) (**4a**): Dark orange solid. mp: 191-193 ^{o}C. IR (KBr) (cm^{-1}): 1415 (N=N), 1622 (HC=N), 3217-3653 (OH). ^{1}H NMR ($CDCl_3$) δ 3.77, 3.82 (4OMe, s, 12H), 3.89 (2 CH_2, s, 4H), 6.76-7.62 (ArH, m, 12H), 8.48 (2HC=N, s, 2H), 14.19 (2 OH, br, 2H). ^{13}C NMR ($CDCl_3$) δ 55.4, 55.7 (OMe), 58.9 (CH_2), 113.7-156.5 (aromatic carbons), 165.1 (HC=N).

Bis[5-(4-methoxyphenylazo)-2-hydroxy-3-methoxybenzaldehyde]-1,2-phenylene diimine (5a): (**3c**): Dark red solid. mp: 185-187 ^{o}C. IR (KBr) (cm^{-1}): 1426 (N=N), 1605 (HC=N), 3163-3672 (OH). ^{1}H NMR ($CDCl_3$) δ 3.81, 3.86 (4OMe, s, 12H), 6.97-7.88 (ArH, m, 16H), 8.66 (2HC=N, s, 2H), 13.94 (2 OH, br, 2H). ^{13}C NMR ($CDCl_3$) δ 55.6, 55.9 (OMe), 105.5-156.9 (aromatic carbons), 163.3 (HC=N).

(3,4-Bis{[2-hydroxy-3-methoxy-5-(4-methylphenylazo)benzylidene]-amino}phenyl)phenyl methanone (5b): Red solid. mp: 140-142 ^{o}C. IR (KBr) (cm^{-1}): 1419 (N=N), 1605 (HC=N), 1659 (C=O), 3155-3650 (OH). ^{1}H NMR ($CDCl_3$) δ 3.87, 3.91 (4OMe, s, 12H), 6.91-7.85 (ArH, m, 20H), 8.70 (2HC=N, s, 2H), 13.89 (2 OH, br, 2H). ^{13}C NMR ($CDCl_3$) δ 55.9, 56.4 (OMe), 105.7-154.2 (aromatic carbons), 162.8 (HC=N), 195.6 (C=O).

(4-Nitrobenzylidene)-4-(phenyldiazenyl)aniline (6a): Red solid. mp: 171-173 ^{o}C. IR (KBr) cm^{-1}: 1341, 1534 (NO_2), 1411 (N=N), 1606 (C=N). ^{1}H NMR ($CDCl_3$) δ 6.81-8.14 (ArH, m, 13H), 8.72 (HC=N, s, 1H). ^{13}C NMR ($CDCl_3$) δ 114.6-155.2 (aromatic carbons), 161.3 (HC=N). GC-MS m/z = 330 [M$^+$]

(4-Chlorobenzylidene)-4-(phenyldiazenyl)aniline (6b): Orange solid. mp: 156-158 ^{o}C. IR (KBr) cm^{-1}: 1415 (N=N), 1609 (C=N). ^{1}H NMR ($CDCl_3$) δ 6.89-8.03 (ArH, m, 13H), 8.61 (HC=N, s, 1H). ^{13}C NMR ($CDCl_3$) δ 117.5-153.9 (aromatic carbons), 161.9 (HC=N). GC-MS m/z = 321 [M$^+$, ^{37}Cl], 319 [M$^+$, ^{35}Cl].

2-((4-(Phenyldiazenyl)phenylimino)methyl)phenol (**6c**)**:** Orange solid. mp: 162-164 ^{o}C. IR (KBr) cm^{-1}: 1423 (N=N), 1609 (C=N), 3137-3623 (OH). ^{1}H NMR ($CDCl_3$) δ 6.76-8.04 (ArH, m, 13H), 8.47 (HC=N, s, 1H), 13.75 (OH, br, 2H). ^{13}C NMR ($CDCl_3$) δ 115.8-159.9 (aromatic carbons), 162.4 (HC=N). GC-MS m/z = 301 [M$^+$].

***N*-(4-Methoxybenzylidene)-4-(phenyldiazenyl)aniline (6d):** Red solid. mp: 140-142 ^{o}C. IR (KBr) cm^{-1}: 1416 (N=N), 1614 (C=N). ^{1}H NMR ($CDCl_3$) δ 3.80 (OMe, s, 3H), 6.87-8.02 (ArH, m, 13H), 8.63 (HC=N, s, 1H). ^{13}C NMR ($CDCl_3$) δ 55.5 (OMe), 117.1-158.5 (aromatic carbons), 163.0 (HC=N). GC-MS m/z = 315 [M$^+$].

***N*-(4-Methylbenzylidene)-4-(phenyldiazenyl)aniline** (**6e**)**:** Dark orange solid. mp: 149-151 ^{o}C. IR (KBr) cm^{-1}: 1413 (N=N), 1607 (C=N). ^{1}H NMR ($CDCl_3$) δ 2.27 (Me, s, 3H), 6.92-7.91 (ArH, m, 13H), 8.67 (HC=N, s, 1H). ^{13}C

NMR ($CDCl_3$) δ 21.1 (Me), 112.8-154.3 (aromatic carbons), 161.7 (HC=N). GC-MS m/z = 299 [M^+].

***N*-Benzylidene-4-(phenyldiazenyl)aniline (6f):** Orang solid. mp: 155-157 ^oC. IR (KBr) cm^{-1}: 1414 (N=N), 1619 (C=N). ^1H NMR ($CDCl_3$) δ 6.76-7.88 (ArH, m, 14H), 8.57 (HC=N, s, 1H). ^{13}C NMR ($CDCl_3$) δ 119.4-156.8 (aromatic carbons), 162.5 (HC=N). GC-MS m/z = 285 [M^+].

4-(Phenyldiazenyl)-*N*-(2-phenylethylidene)aniline (6e): Light orange solid. mp: 119-121 ^oC. IR (KBr) cm^{-1}: 1411 (N=N), 1624 (C=N). ^1H NMR ($CDCl_3$) δ 3.26 (CH_2, d, 2H, J = 5.9), 6.93-7.80 (ArH, m, 14H), 8.26 (HC=N, t, 1H, J = 5.9). ^{13}C NMR ($CDCl_3$) δ 33.7 (CH_2), 117.3-154.5 (aromatic carbons), 161.8 (HC=N). GC-MS m/z = 299 [M^+].

4. Conclusions

In conclusion, we have developed convenient, fast and green procedures for the synthesis of azo Schiff bases that requires neither organic solvent nor refluxing condition. The yields were excellent and reactions were fast.

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