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Nano ZnO Catalyzed One-Pot Synthesis of Benzimidazoles from *o*-Phenylenediamine with Aldehydes

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Nano-ZnO was found to be a highly efficient and reusable heterogeneous catalyst for the one-pot synthesis of substituted benzimidazoles from aromatic aldehydes with *o*-phenylenediamine in moderate to good yield. The spent catalyst can be easily recovered and reused for five cycles with consistent activity.

Keywords: Nano-ZnO, Benzimidazole, Heterogeneous catalyst, *o*-Phenylenediamine, Aldehyde.

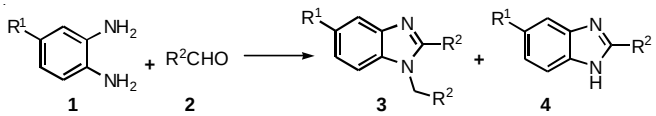
INTRODUCTION

Benzimidazole derivatives are important intermediates in many organic reactions and also exhibit various biological activities such as antiulcers, antihypertensives, antivirals, antifungals, anticancers and antihistamines[1-7]. The most common method reported in the literature for synthesis of these compounds involves the condensation of *o*-phenylenediamines and carboxylic acids or their derivatives, but several drawbacks remain associated with such reactions, including the use of harsh acids and under high temperature conditions[8-10]. Synthesis of benzimidazoles have also been reported using other approaches, including the condensation of *o*-phenylenediamines with aldehydes under oxidative conditions, or using homogeneous catalysts such as Lewis acids, or heterogeneous catalyst[11-16]. In recent years, there has been a significant progress on the use and design of metal nanoparticles as catalysts due to their high catalytic activity, efficient recyclability and facile separation of products. There are a few reports available in the literature for the use of nano crystalline ZnO as a heterogeneous catalyst for various organic reactions[17-19]. Herein, we report an efficient synthesis of benzimidazole derivatives from *o*-phenylenediamines with aldehydes using nano ZnO catalyst.

EXPERIMENTAL

Nano ZnO was purchased from Aladdin Chemistry Co. Ltd. Under otherwise noted, other materials were obtained from commercial suppliers and used without further purification. ^{1}H NMR (500 MHz) spectra were recorded on a Bruker Avance spectrometer in $CDCl_3$ or DMSO-d_6 with Me_4Si as an internal standard.

General procedure for the synthesis of benzimidazoles: To a reactor containing 1,2-phenylenediamine (1 mmol), benzaldehyde (2.2 mmol) and $Cl_2CHCHCl_2$ (2 mL) was added nano ZnO (0.1 mmol). The mixture was then stirred at 80 °C until the reaction was completed as judged by TLC. The mixture was filtered and the recovered nano ZnO catalyst was washed with water and methanol with no further purification before reuse. The filtrate was extracted with ethyl acetate (3 × 10 mL). The organic layer was washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash chromatography to give the pure product (**Scheme-I**).



Scheme-I: Synthesis of benzimidazoles from *o*-phenylenediamine with aryl aldehyde

1-Benzyl-2-phenyl-1H-benzo[d]imidazole (3a): White solid, m.p. 128-130 °C (lit.[20] 129-131 °C), yield: 87 %; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.91 (d, *J* = 7.9 Hz, 1H), 7.76-7.67 (m, 2H), 7.51-7.46 (m, 3H), 7.38-7.31 (m, 4H), 7.27-7.21 (m, 2H), 7.13 (d, *J* = 7.0 Hz, 2H), 5.48 (s, 2H).

2-Phenyl-1H-benzo[d]imidazole (4a): White solid, m.p. 299-301 °C (lit.[21] 290-292 °C), yield: 10 %; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.13-8.01 (m, 2H), 7.67-7.65 (m, 2H), 7.51-7.47 (m, 3H), 7.32-7.28 (m, 2H).

1-(2-Methyl-benzyl)-2-*p*-tolyl-1H-benzo[d]imidazole (3b): Light yellow solid, m.p. 128-130 °C (lit.[22] 129-130 °C), yield: 63 %; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.87 (d, *J* = 8.1 Hz, 1H), 7.60 (d, *J* = 8.1 Hz, 2H), 7.33-7.29 (m, 1H), 7.27-7.26 (m, 2H), 7.25-7.19 (m, 2H), 7.15 (d, *J* = 8.0 Hz, 2H), 7.02 (d, *J* = 8.0 Hz, 2H), 5.43 (s, 2H), 2.42 (s, 3H), 2.35 (s, 3H).

2-*p*-Tolyl-1H-benzo[d]imidazole (4b): Brown solid, m.p. 275-276 °C (lit.[21] 262-264 °C), yield: 33 %; ^{1}H NMR (500 MHz, $CDCl_3$) δ 12.83 (s, 1H), 8.07 (d, *J* = 8.0 Hz, 2H), 7.62-7.54 (m, 2H), 7.37 (d, *J* = 8.0 Hz, 2H), 7.20-7.18 (m, 2H), 2.39 (s, 3H)

1-(4-Methoxybenzyl)-2-(4-methoxyphenyl)-1H-benzo[d]imidazole (3c): White solid, m.p. 129-130 °C (lit.[23] 129-131 °C), yield: 62 %; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.88 (d, *J* = 7.9 Hz, 1H), 7.67 (d, *J* = 8.6 Hz, 2H), 7.33-7.31 (m, 1H), 7.25-7.24 (m, 2H), 7.05 (d, *J* = 8.6 Hz, 2H), 6.99 (d, *J* = 8.6 Hz, 2H), 6.89-6.86 (m, 2H), 5.42 (s, 2H), 3.87 (s, 3H), 3.81 (s, 3H).

2-(4-Methoxyphenyl)-1H-benzo[d]imidazole (4c): White solid, m.p. 236-238 °C (lit.[21] 222-224 °C), yield: 5 %; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.09 (d, *J* = 8.8 Hz, 2H), 7.69-7.67 (m, 2H), 7.31-7.28 (m, 2H), 6.84 (d, *J* = 8.8 Hz, 2H), 3.77 (s, 3H).

1-(2-Methoxybenzyl)-2-(2-methoxyphenyl)-1H-benzo[d]imidazole (3d): Light yellow solid, m.p. 157-158 °C (lit.[22] 150-152 °C), yield: 77 %; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.86 (d, *J* = 8.0 Hz, 1H), 7.55 (dd, *J* = 7.5, 1.6 Hz, 1H), 7.50-7.41 (m, 1H), 7.29-7.27 (m, 1H), 7.24-7.19 (m, 3H), 7.08-7.04 (m, 1H), 6.97 (d, *J* = 8.4 Hz, 1H), 6.85 (d, *J* = 8.4 Hz, 1H), 6.79-6.76 (m, 1H), 6.70 (d, *J* = 6.9 Hz, 1H), 5.25 (s, 2H), 3.80 (s, 3H), 3.60 (s, 3H).

2-(2-Methoxyphenyl)-1H-benzo[d]imidazole (4d): White solid, m.p. 164-166 °C (lit.[21] 156-158 °C), yield: 16 %; ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.11 (s, 1H), 8.33 (dd, *J* = 7.7, 1.7 Hz, 1H), 7.69-7.56 (m, 2H), 7.52-7.46 (m, 1H), 7.25 (d, *J* = 8.3 Hz, 1H), 7.23-7.15 (m, 2H), 7.14-7.10 (m, 1H), 4.04 (s, 3H).

1-(3-Methoxybenzyl)-2-(3-methoxyphenyl)-1H-benzo[d]imidazole (3e)[24]: Colourless oil, yield: 63 %; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.92 (d, *J* = 7.9 Hz, 1H), 7.38-7.31 (m, 2H), 7.28-7.23 (m, 5H), 7.05-7.02 (m, 1H), 6.85-6.82 (m, 1H), 6.71-6.66 (m, 2H), 5.43 (s, 2H), 3.74 (s, 3H), 3.73 (s, 3H).

2-(3-Methoxyphenyl)-1H-benzo[d]imidazole (4e): White solid, m.p. 218-220 °C (lit.[25] 205-206 °C), yield: 36 %; ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.89 (s, 1H), 7.78-7.75 (m, 2H), 7.67 (d, *J* = 7.7 Hz, 1H), 7.54 (d, *J* = 7.4 Hz, 1H), 7.48-7.45 (m, 1H), 7.23-7.119 (m, 2H), 7.08-7.05 (m, 1H), 3.87 (s, 3H).

2-(Benzo[d][1,3]dioxol-5-yl)-1-(benzo[d][1,3]dioxol-5-ylmethyl)-1H-benzo[d]imidazole (3f): White solid, m.p. 176-179 °C (lit.[26] 170-171 °C), yield: 48 %; ^{1}H NMR (500 MHz, CDCl3) δ 7.84 (d, *J* = 8.0 Hz, 1H), 7.32-7.17 (m, 5H), 6.90 (d, *J* = 8.0 Hz, 1H), 6.76 (d, *J* = 8.0 Hz, 1H), 6.59-6.57 (m, 2H), 6.05 (s, 2H), 5.97 (s, 2H), 5.37 (s, 2H).

2-(Benzo[d][1,3]dioxol-5-yl)-1H-benzo[d]imidazole (4f): Light yellow solid, m.p. 266-267 °C (lit.[27] 245-247 °C), yield: 51 %; ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.74 (s, 1H), 7.73 (d, *J* = 8.1 Hz, 1H), 7.69 (s, 1H), 7.62 (d, *J* = 7.4 Hz, 1H), 7.50 (d, *J* = 7.4 Hz, 1H), 7.23-7.13 (m, 2H), 7.11 (d, *J* = 8.1 Hz, 1H), 6.13 (s, 2H).

4-((2-(4-(Dimethylamino)phenyl)-1H-benzo[d]imidazol-1-yl)methyl)-N,N-dimethylbenzenamine (3g): White solid, m.p. 182-185 °C (lit.[28] 182 °C), yield: 79 %; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.83 (d, *J* = 7.9 Hz, 1H), 7.64 (d, *J* = 8.9 Hz, 2H), 7.26-7.25 (m, 1H), 7.24-7.16 (m, 2H), 7.04 (d, *J* = 8.9 Hz, 2H), 6.75 (d, *J* = 8.9 Hz, 2H), 6.70 (d, *J* = 8.9 Hz, 2H), 5.39 (s, 2H), 3.03 (s, 6H), 2.95 (s, 6H).

1-(4-Fluorobenzyl)-2-(4-fluorophenyl)-1H-benzo[d]-imidazole (3h): Brown solid, m.p. 68-70 °C (lit.[23] 82-84 °C), yield: 34 %; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.87 (d, *J* = 8.0 Hz, 1H), 7.87-7.64 (m, 2H), 7.36-7.32 (m, 1H), 7.29-7.26 (m, 1H), 7.23-7.15 (m, 3H), 7.09-7.01 (m, 4H), 5.41 (s, 2H).

2-(4-Fluorophenyl)-1H-benzo[d]imidazole (4h): Light yellow solid, m.p. 266-268 °C (lit.[21] 248-250 °C), yield: 60 %; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.57 (br, 1H), 8.07-8.03 (m, 2H), 7.85-7.70 (m, 1H), 7.65-7.45 (m, 1H), 7.31-7.29 (m, 2H), 7.24-7.19 (m, 2H).

1-(4-Chlorobenzyl)-2-(4-chlorophenyl)-1H-benzo[d]-imidazole (3i): Yellow solid, m.p. 139-140 °C (lit.[22] 136-137 °C), yield: 12 %; ^{1}H NMR (500MHz, $CDCl_3$) δ 7.88 (d, *J* = 8.0 Hz, 1H), 7.60 (d, *J* = 8.5 Hz, 2H), 7.46 (d, *J* = 8.5 Hz, 2H), 7.36-7.28 (m, 4H), 7.1 (d, *J* = 8.0 Hz, 1H), 7.04 (d, *J* = 8.5 Hz, 2H), 5.41 (s, 2H).

2-(4-Chlorophenyl)-1H-benzo[d]imidazole (4i): Brown solid, m.p. 296-298 °C (lit.[21] 284-286 °C), yield: 68 %; ^{1}H NMR (500 MHz, $CDCl_3$) δ 13.01 (s, 1H), 8.19 (d, *J* = 8.4 Hz, 2H), 7.67-7.53 (m, 4H), 7.31-7.15 (m, 2H).

1-(2-Chlorobenzyl)-2-(2-chlorophenyl)-1H-benzo[d]-imidazole (3j): Light yellow solid, m.p. 160-163 °C (lit.[29] 158-159 °C), yield: 57 %; ^{1}H NMR (500MHz, $CDCl_3$) δ 7.91 (d, *J* = 8.0 Hz, 1H), 7.53 (d, *J* = 8.0 Hz, 1H), 7.50-7.41 (m, 2H), 7.38-7.31 (m, 3H), 7.28-7.26 (m, 1H), 7.25-7.15 (m, 2H), 7.07 (t, *J* = 7.5 Hz, 1H), 6.64 (d, *J* = 7.7 Hz, 1H), 5.38 (s, 2H).

2-(2-Chlorophenyl)-1H-benzo[d]imidazole (4j): Light yellow solid, m.p. 216-218 °C (lit.[25] 234-235 °C), yield: 36 %; ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.25 (s, 1H), 8.48 (dd, *J* = 7.7, 1.9 Hz, 1H), 7.90-7.84 (m, 1H), 7.56 (m, 1H), 7.53 (m, 1H), 7.49-7.41 (m, 2H), 7.33 (m, 2H).

1-(3-Chlorobenzyl)-2-(3-chlorophenyl)-1H-benzo[d]-imidazole (3k)[30]: Colourless oil, yield: 16 %; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.90 (d, *J* = 7.9 Hz, 1H), 7.73 (s, 1H), 7.50 (t, *J* = 8.9 Hz, 2H), 7.44-7.34 (m, 2H), 7.31 (t, *J* = 9.3 Hz, 3H), 7.24 (d, *J* = 7.9 Hz, 1H), 7.14 (s, 1H), 6.96 (d, *J* = 6.8 Hz, 1H), 5.43 (s, 2H).

2-(3-Chlorophenyl)-1H-benzo[d]imidazole (4k): Light yellow solid, m.p. 242-244 °C (lit.[25] 236-238 °C), yield: 79 %; ^{1}H NMR (500 MHz, DMSO-d_6) δ 13.05 (s, 1H), 8.23 (t, *J* = 1.6 Hz, 1H), 8.19-8.10 (m, 1H), 7.69 (d, *J* = 7.8 Hz, 1H), 7.62-7.55 (m, 3H), 7.35-7.10 (m, 2H).

1-(4-Bromobenzyl)-2-(4-bromophenyl)-1H-benzo[d]-imidazole (3l): Brown solid, m.p.159-160 °C (lit.[22] 139-141 °C), yield: 19 %; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.88 (d, *J* = 8.0 Hz, 1H), 7.60 (d, *J* = 8.3 Hz, 2H), 7.52 (d, *J* = 8.3 Hz, 2H), 7.48-7.46 (m, 2H), 7.36-7.32 (m, 1H), 7.29-7.25 (m, 1H), 7.19 (d, *J* = 8.0 Hz, 1H), 6.96 (d, *J* = 8.2 Hz, 2H), 5.38 (s, 2H).

2-(4-Bromophenyl)-1H-benzo[d]imidazole (4l): Brown solid, m.p. 301-303 °C (lit.[21] 293-295 °C), yield: 65 %; ^{1}H NMR (500 MHz, $CDCl_3$) δ 13.01 (s, 1H), 8.12 (d, *J* = 8.5 Hz, 2H), 7.78 (d, *J* = 8.5 Hz, 2H), 7.68 (d, *J* = 7.8 Hz, 1H), 7.54 (d, *J* = 7.8 Hz, 1H), 7.35-7.09 (m, 2H).

2-(Pyridin-3-yl)-1H-benzo[d]imidazole (4m): White solid, m.p. 264-266 °C (lit.[31] 246-248 °C), yield: 56 %; ^{1}H NMR (500MHz, DMSO-d_6) δ 13.12 (s, 1H), 9.35 (d, *J* = 1.9 Hz, 1H), 8.70-8.68 (m, 1H), 8.52-8.49 (m, 1H), 7.70 -7.59 (m, 3H), 7.28-7.15 (m, 2H).

1-Benzyl-5-nitro-2-phenyl-1H-benzo[d]imidazole (3n): Red solid, m.p.148-149 °C (lit.[32] 148 °C), yield: 12 %; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.27 (dd, *J* = 8.8, 2.1 Hz, 1H), 8.19 (m, 1H), 7.92 (d, *J* = 8.8 Hz, 1H), 7.76-7.72 (m, 2H), 7.57-7.50 (m, 2H), 7.40-7.35 (m, 4H), 7.11-7.08 (m, 2H), 5.57 (s, 2H).

5-Nitro-2-phenyl-1H-benzo[d]imidazole (4n): Brown solid, m.p. 124-127 °C (lit.[33] 147.1-149.0 °C), yield: 61 %; ^{1}H NMR (500 MHz, DMSO-d_6) δ 13.63 (s, 1H), 8.65-39 (m, 1H), 8.24-8.22 (m, 2H), 8.16-8.14 (m, 1H), 7.90-7.65 (m, 1H), 7.64-7.56 (m, 3H).

RESULTS AND DISCUSSION

Initially, the reaction between *o*-phenylenediamine (1 mmol) and benzaldehyde (2.2 mmol) was selected for the synthesis of benzimidazole as a model reaction for optimizing the reaction conditions. The results are summarized in Table-1. The reactions using 20 mol % nano ZnO with a size of about 30 nm proceeded efficiently to form the 2-phenyl benzimidazole (**3a**) in 87 % isolated yield and a minor amount of 1-benzyl-2-phenyl-1*H*-benzimidazole (**4a**) (10 %) at 80 °C in $Cl_2CHCHCl_2$ (Table-1, entry 1). When the loading catalyst was reduced to 10 mol %, the yield of the product **4a** was increased significantly up to 25 % (Table-1, entry 2). For comparison, it was also observed that reaction temperatures higher or lower than 80 °C resulted in decreased yields of **3a** (Table-1, entries 3 and 4). A number of common solvents were examined, $Cl_2CHCHCl_2$ appeared to be the best one for the synthesis of 1,2-disubstituted benzimidazole **3a** and DMSO resulted in the formation of 1-substituted benzimidazole **4a** as a main product (Table-1, entries 1, 5-11).

With the optimal reaction conditions in hand, the scope of nano ZnO catalyzed synthesis of benzimidazoles was explored. The results are summarized in Table-2. It was observed that the reaction was found to be deeply impacted by the electronic effects of the substituents on the aryl aldehyde and *o*-phenylenediamine. The aromatic aldehyde with an electron-donating group such as Me or MeO groups on the benzene ring all gave a mixture with the 1,2-disubstituted benzimidazoles as the major products and small amounts of the 1-substituted benzimidazoles in good yield. In sharp contrast, with an electron-withdrawing substituent at the *para*- or *meta*-positions on the aromatic ring, the formation of 2-aryl benzimidazoles **4** predominated over 1-arylmethyl-2-aryl benzimidazoles **3**, except for the case of a *ortho*-Cl substituent at aryl aldehyde. Furthermore, 3-pyridinylaldehyde reacted with *o*-phenylenediamine to afford only product **4m** with 56 % yield (Table-2, entry 13). In addition, *o*-phenyldiamine containing *p*-NO_2 group on the benzene ring was tolerated for the reaction, obtaining the corresponding benzimidazoles **3n** and **4n** in 12 % and 61 % yields, respectively (Table-2, entries 4-5).

TABLE-1
OPTIMIZATION OF NANO ZnO CATALYZED SYNTHESIS OF BENZIMIDAZOLES FROM *o*-PHENYLENEDIAMINE AND BENZALDEHYDE[a]

Entry	ZnO (mol %)	Solvent	Temp. (°C)	Yield of **3a** (%)[b]	Yield of **4a** (%)[b]
1	20	$CHCl_2CHCl_2$	80	87	10
2	10	$CHCl_2CHCl_2$	80	74	25
3	10	$CHCl_2CHCl_2$	60	51	45
4	10	$CHCl_2CHCl_2$	120	53	29
5	20	$CHCl_3$	60	74	23
6	20	H_2O	80	67	29
7	20	C_2H_5OH	80	63	35
8	20	1,4-dioxane	80	30	69
9	20	CH_3CN	80	44	55
10	20	THF	80	42	51
11	20	DMSO	80	38	54

[a]The reactions were performed with *o*-phenyldiamine (1.0 mmol), benzaldehyde (2.2 mmol) and nano ZnO in solvent (1 mL) for 1 h.
[b]Isolated yields.

TABLE-2
NANO ZnO CATALYZED SYNTHESIS OF BENZIMIDAZOLES[a]

Entry	R^1	R^2	Time (h)	Yield of **3** (%)	Yield of **4** (%)
1	H	C_6H_5	1	**3a**: 87	**4a**: 10
2	H	4-$CH_3C_6H_5$	5	**3b**: 63	**4b**: 33
3	H	4-$CH_3OC_6H_5$	5	**3c**: 63	**4c**: 5
4	H	2-$CH_3OC_6H_5$	2	**3d**: 77	**4d**: 16
5	H	3-$CH_3OC_6H_5$	5	**3e**: 63	**4e**: 36
6	H	3,4-$CH_2O_2C_6H_3$	3	**3f**: 48	**4f**: 51
7	H	4-$(CH_3)_2NC_6H_5$	4	**3g**: 79	–
8	H	4-FC_6H_5	5	**3h**: 34	**4h**: 60
9	H	4-ClC_6H_5	3	**3i**: 12	**4i**: 68
10	H	2-ClC_6H_5	5	**3j**: 57	**4j**: 36
11	H	3-ClC_6H_5	5	**3k**: 16	**4k**: 79
12	H	4-BrC_6H_5	5	**3l**: 19	**4l**: 65
13	H	3-Pyridinyl	5	–	**4m**: 56
14	NO_2	C_6H_5	14	**3n**: 12	**4n**: 61

[a]The reactions were performed with **1** (1.0 mmol), **2** (2.2 mmol) and nano ZnO (20 mol %) in $Cl_2CHCHCl_2$ (1 mL) at 80 °C.
[b]Isolated yields.

The reusability of nano ZnO catalyst was studied for the reaction of *o*-phenylenediamine with 4-dimethylaminobenzaldehyde in $Cl_2CHCHCl_2$. The results are summarized in Table-3. The catalyst nano ZnO was recovered by a simple filtration and reused with consistent activity even after the fifth cycle (Table-3).

Conclusion

In conclusion, a very efficient procedure for the one-pot synthesis of substituted benzimidazoles from aromatic aldehydes and *o*-phenyldiamine has been developed using easily recyclable heterogeneous nano ZnO catalyst. A wide range of aryl aldehyde can be tolerated, giving the corresponding substituted benzimidazoles in good yields. The ratio of substituted 2-aryl benzimidazoles and substituted 1-arylmethyl-2-aryl benzimidazoles is impacted by the electronic effects of the substituents on aryl aldehydes.

TABLE-3
REUSABILITY OF NANO ZnO FOR THE REACTION *o*-PHENYLENEDIAMINE WITH 4-DIMETHYLAMINOBENZALDEHYDE[a]

Recycle	Time (h)	Yield of **3g** (%)[b]
1	1	79
2	1	77
3	1	74
4	1	58
5	1	58
6	1	60

[a]The reactions were performed with *o*-phenylenediamine (1.0 mmol), 4-dimethylaminobenzaldehyde (2.2 mmol) and nano ZnO (20 mol %) in $Cl_2CHCHCl_2$ (1 mL) at 80 °C for 1 h.
[b]Isolated yields.

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