Manganese(IV) dioxide-catalyzed synthesis of quinoxalines under microwave irradiation

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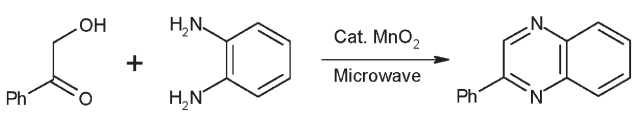
We synthesize quinoxalines, catalyzed by manganese(IV) dioxide, from a variety of α-hydroxyketones followed by trapping with aromatic or aliphatic 1,2-diamines without using a solvent, within one minute under microwave irradiation.

While we have been studying the use of transition metal nanoparticles in catalysis,[1] a recent publication about the preparation of nanoparticles of MnO/Mn_3O_4 attracted our attention.[2] Thus, we decided to study the use of nanoparticles of manganese oxides in catalysis. To begin with, we surveyed the use of manganese dioxide in organic synthesis. Manganese dioxide is widely used as an oxidant in many organic reactions.[3] Among them, the work[4] reported by Taylor's group attracted our attention. Taylor and other researchers used 10 equiv MnO_2 in their oxidation reactions.[4,5] For example, quinoxalines have been prepared by the reaction of α-hydroxyketone (1 equiv) with 1,2-diamine (2 equiv) in the presence of molecular sieves and MnO_2 (10 equiv) in dichloromethane for 90 min.[4a] We noted that the use of a large excess of MnO_2 may result in the production of chemical waste. Recently, we found that quinoxalines could be obtained in high yields within 1 min by using a catalytic amount of MnO_2 under microwave irradiation without using a solvent. Thus, as a result of this study, we have developed an environmentally-friendly process of quinoxaline production.

We first studied a reaction between 1,2-diaminobenzene and 2-hydroxyacetophenone ($PhC(O)CH_2OH$) by screening the reaction conditions, including the amount of MnO_2, the reaction time, the reaction temperature, and the solvent (Scheme 1, Table 1).

First, the use of MnO_2 was cut down to 10 mol% using dichloromethane as a solvent (entry 1). As the table shows, the reaction went to completion without any problems. Moreover, no diazo compounds were formed as byproducts. When MnO was used instead of MnO_2, the yield (86%) was almost the same. Thus, both MnO and MnO_2 are effective catalysts in the tandem oxidative reaction. However, due to economic reasons, we chose commercially available MnO_2. The use of manganese oxide nanoparticles (entry 3) was not helpful for the yield of the reaction. When 1 mol% of MnO_2 was used (entry 4), the yield was still 53%.



Scheme 1

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Recently, microwave-assisted reactions have been highlighted due to their short reaction times compared to those of the conventionally heated reactions.[6,7] Thus, we used microwave as an energy source in our reaction. As expected, the reaction time was shortened to 1 min, but with a poor yield. We used dichloromethane as a solvent in order to compare with the case of the conventional heating, although dichloromethane has been known as a poor solvent under microwave heating. We also screened other solvents such as methanol and water (entries 6 and 7). The use of water as a solvent seemed likely to be unsuitable because of water condensation reactions. In any case, when water was used as a reaction medium, the yield was poor. Thus, the change of the reaction medium did not help the yield of the reaction. However, when the reaction was carried out without a solvent (entry 8), the yield was dramatically improved to 81%. Interestingly, when the reaction was conducted in an open vessel (entry 9), a much lower yield (36%) was obtained. Thus, all other reactions were performed in a pressurized reactor. Moreover, with this technique, when the amount of MnO_2 used was cut down to 0.1 mol% (entry 10), the yield was still 63%. Thus, by using 0.1 mol% of MnO_2 under microwave irradiation without using a solvent, the reaction can be carried out within 1 min.

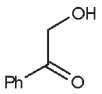
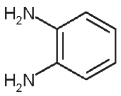
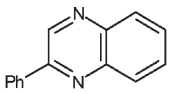
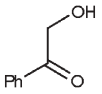
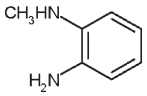
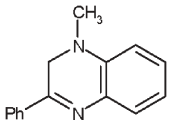
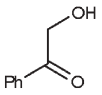
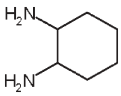
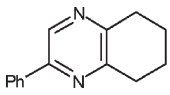
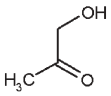
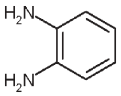
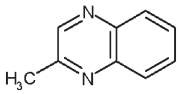
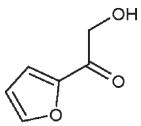
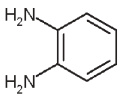
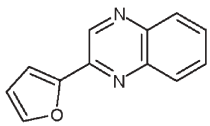
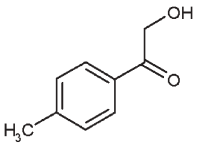
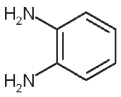
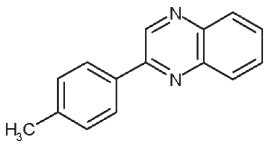
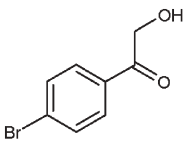
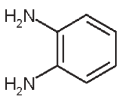
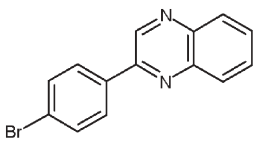
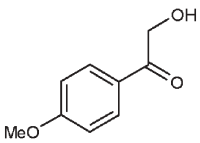
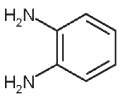
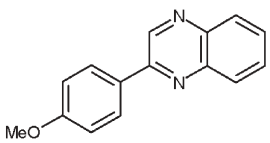
Next we screened other α-hydroxyketones under the same reaction conditions as above (Table 2).[8] Most of the reactions went to completion within 1 min although the yields were highly dependent upon the substrate used. When a methyl group was introduced to one of amines (entry 2), a steric effect of the methyl group might be reflected on the yield, resulting in a moderate yield (48%). An aliphatic diamine (entry 3) was also as a good substrate as aromatic diamines. When hydroxy acetophenone ($CH_3C(O)CH_2OH$) was used instead of $PhC(O)CH_2OH$, the

Table 1 Optimization of the reaction conditions[a]

Entry	Catalyst	Temp/°C	Time	Solvent	Yield (%)[b]
1	10 mol % MnO	100	3 h	CH_2Cl_2	86[c]
2	10 mol % MnO_2	100	3 h	CH_2Cl_2	88[c]
3	10 mol % Mn nanoparticles	100	3 h	CH_2Cl_2	78[c]
4	1 mol % MnO_2	100	3 h	CH_2Cl_2	53[c]
5	1 mol % MnO_2	70	1 min	CH_2Cl_2	17
6	1 mol % MnO_2	70	1 min	MeOH	15
7	1 mol % MnO_2	70	1 min	H_2O	21
8	1 mol % MnO_2	70	1 min	—	81
9	0.1 mol % MnO_2	70	1 min	—	63
10	1 mol % MnO_2	70	1 min	CH_2Cl_2	19[d]
11	1 mol % MnO_2	70	1 min	—	36[d]

[a] Reaction conditions: sealed tube, MW 70 °C. [b] Isolated yield. [c] conventional thermal heating. [d] Open tube.

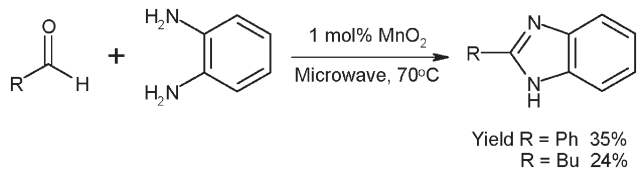
Table 2 MnO_2-catalyzed formation of quinoxalines[a]

Entry	α-Hydroxyketones	1,2-Diamines	Product	Yield (%)[b]
1				81
2				48[c]
3				85
4				47
5				59
6				72
7				46
8				42

[a] All reactions were carried out on a 1 mol% scale. [b] Isolated yield. [c] 1-Methyl-3-phenyl-1,2-dihydro-quinoxaline: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.95–7.92 (m, 2H), 7.48–7.45 (m, 3H), 7.40–7.37 (m, 1H), 7.14 (td, J = 7.97 Hz, 1.53Hz, 1H), 6.81 (td, J = 7.53Hz, 1.22Hz, 1H), 6.69–6.62 (m, 1H), 4.24 (s, 2H), 2.88 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 130.7, 128.9, 128.7, 128.2, 127.2, 126.4, 118.6, 110.5, 50.1, 37.3; HRMS for $C_{15}H_{14}N_2$: calcd. 222.1157, obsd. 222.1161.

change of the phenyl group to the methyl group was manifested in the yield. We envisioned that a furanyl group would be similar to the phenyl group. However, the yield dropped to 59%. Introduction of a functional group such as methyl, bromide, and methoxy to the phenyl group of $PhC(O)CH_2OH$ was not helpful to the yield. A relatively high yield was obtained when a methyl group was introduced.

Next we investigated the extension of our discoveries to other similar reactions. A number of synthetic methods have been developed for the production of 2-substituted benzimidazoles.[9] Recently, Wilfred and Taylor reported[10] a one-pot procedure for the preparation of 2-substituted benzimidazoles from activated alcohols and 1,2-diaminobenzene using an MnO_2 tandem oxidation process. However, no catalytic reactions have been reported



Scheme 2

until now. Thus, we applied our discoveries to the synthesis of benzimidazoles via an MnO_2-catalyzed reaction between aldehydes and 1,2-diaminobenzene (Scheme 2).

The yield was not as high as those in the synthesis of quinoxalines. However, the expected products were obtained in reasonable yields within 1 min of reaction time.

In conclusion, we have developed an environmentally friendly process for the MnO_2-catalyzed synthesis of quinoxalines, from a variety of α-hydroxyketones followed by trapping with aromatic or aliphatic 1,2-diamines without using a solvent, within 1 min under microwave irradiation.

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8 A typical experimental procedure: To a 10 mL glass vial were added 2-hydroxyacetophenone (0.133 g, 0.97 mmol), 1,2-diaminobenzene (0.211 g, 1.95 mmol), 4Å molecular sieves (1.0 g), and activated MnO_2 (Aldrich, product No. 21764-6; 1 mg). The vessel was then heated to 70 °C under microwave irradiation using the Discover Synthesizer (monomode microwave cavity at 2.45 GHz; temperature control by automated adjustment of irradiation power in a range from 0 to 300 W). After 1 min the vial was cooled to r.t. The solution was filtered and concentrated under reduced pressure and purified by flash chromatography on silica eluting with hexane/ether to give 163 mg (81% yield) of 2-phenyl-quinoxaline.

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