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Solid-state radical reactions of 1,3-cyclohexanediones with *in situ* generated imines mediated by manganese(III) acetate under mechanical milling conditions†

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Under solid-state conditions, manganese(III) acetate-mediated radical reactions of 1,3-cyclohexanedione and 5,5-dimethyl-1,3-cyclohexanedione with *in situ* generated imines proceeded efficiently by mechanical milling at room temperature and good to excellent yields were achieved.

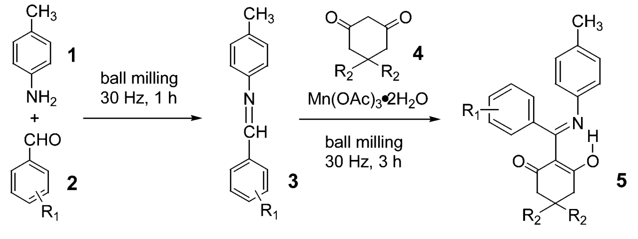
In organic chemistry, manganese(III) acetate ($Mn(OAc)_3$) has been most commonly used in the generation of carbon-centered radicals from various carbonyl compounds and their oxidative addition to alkenes.[1] However, a significant drawback to the use of $Mn(OAc)_3$ is the harsh reaction conditions. As $Mn(OAc)_3$ has poor solubility in organic solvents, acetic acid is almost invariably used, though other organic solvents such as methanol, ethanol, trifluoroethanol, acetonitrile, dichloromethane, monochlorobenzene, and toluene have also been employed in some cases.[2] Under these conditions, the yield is relatively low and the separation procedure at the end of the reaction is rather tedious. In the standard workup procedure, large quantities of water and/or aqueous sodium hydrogen carbonate have to be used to remove the acetic acid and so considerable amounts of aqueous waste would be generated. To circumvent this problem, one of the best methods is to carry out this kind of reaction under solvent-free conditions. The mechanical ball milling technique, which is broadly used to produce alloys, metal oxides and other inorganic materials,[3] has been successfully applied to some organic reactions in recent years and offers the advantages of reduced pollution, low cost, and simplicity in process and handling.[4] On the other hand, although $Mn(OAc)_3$-promoted radical addition to alkenes has for a long time attracted research efforts, a survey of the related literature revealed that the corresponding radical addition to imines has not been reported. Radical addition to the C=N bond has begun to emerge as a useful synthetic process only since the 1980s. Among the various C=N-containing functional groups, the most commonly used radical receptors are oxime ethers and hydrazones. Imines are rarely used due to their proneness to hydrolysis and tautomerization.[5] Furthermore, in contrast to many known intramolecular reactions, there are few reports on intermolecular radical additions to C=N bonds.[5]

With a view to the above reasons and to establishing efficient and milder reaction conditions in this field, we have investigated the novel manganese(III) acetate dihydrate ($Mn(OAc)_3·2H_2O$)-mediated intermolecular radical additions of 1,3-cyclohexanediones to *in situ* generated imines promoted by the mechanical ball milling technique (Scheme 1).

In our present protocol all the reactions were carried out under solid-state conditions. The first-step reactions of 4-methylaniline **1** with aldehydes **2** could afford quantitatively imines **3**, which were directly used as radical receptors in the following process without further separation.[6] The detailed results for the radical reactions of 1,3-cyclohexanediones with various *in situ* generated imines are summarized in Table 1.

According to the results shown in Table 1, it can be seen that good to excellent yields have been achieved even though these reactions were performed under solvent-free and one-pot conditions. However, traditional $Mn(OAc)_3$-mediated radical reactions in organic solvents usually gave yields less than 70%. Our present method could be extended to liquid starting materials as well. For example, when aniline was employed instead of **1**, a similar result was achieved. However, an accurate yield could not be obtained because the jar of the ball-milling apparatus was not airtight and thus leakage occurred during the imine formation in the first step.

The efficiency of the current solid-state procedure may be ascribed to an enhanced reaction rate resulting from ultimately high concentrations of reactants with no use of solvent, and the high mechanical energy that can greatly enforce the reaction.[4e] Furthermore, the high reactivity of the substrates also contributes to this efficiency to a great extent. This point may be understood from the reaction mechanism. Based on the related literature[1,7] and the fact that two molar equivalents of $Mn(OAc)_3$ are required for the completion of the reaction, a tentative mechanism for the reaction may be formulated as shown in Scheme 2. The addition of the Mn(III) enolate **6** to the imine **3** gives the nitrogen-centered radical **7**, followed by oxidation with $Mn(OAc)_3$ to form non-reductive adduct **8** and subsequent enolization to afford product **5**. For 1,3-cyclohexanedione and dimedone, enolization occurs readily and thus the formation of **6** is easy and fast. For imines, the C=N



Scheme 1

Table 1 Solid-state radical reactions of 1,3-cyclohexanedione and dimedone with *in situ* generated imines

Product $\mathbf{5}$[a]			
	R_1	R_2	Yield (%)[b]
5a	4-NO_2	CH_3	84
5b	3-NO_2	CH_3	81
5c	4-CN	CH_3	94
5d	4-Cl	CH_3	89
5e	4-Br	CH_3	93
5f	3,4-Cl	CH_3	91
5g	3,4-OCH_2O	CH_3	84
5h	4-NO_2	H	76
5i	3-NO_2	H	73
5j	4-CN	H	78
5k	4-Cl	H	71
5l	4-Br	H	71
5m	3,4-Cl	H	74
5n	3,4-OCH_2O	H	58

[a] Properly characterized by mp, IR, ^1H NMR, ^{13}C NMR and HRMS spectral data (see ESI). [b] Isolated yield.

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† Electronic supplementary information (ESI) available: detailed experimental procedure for the synthesis and mp, IR, ^1H NMR, ^{13}C NMR and HRMS spectral data of compounds **5a–5n**. See http://www.rsc.org/suppdata/cc/b4/b406402j/

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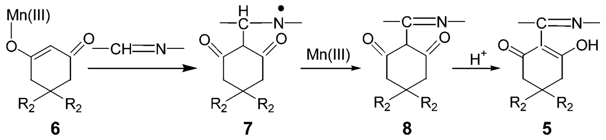
group may exhibit a higher radical addition rate relative to analogous alkene acceptors.[5]

Some of the above reactions have also been tentatively carried out in organic solvents. But the result is much poorer than that of the current mechanical milling procedure. In fact, it is very difficult to obtain the imines quantitatively in the presence of organic solvents. For example, when the reaction of 4-chlorobenzaldehyde with one equivalent of 4-methylaniline was carried out in CH_3CN at room temperature, it was hard to achieve completion, even overnight. Isolation of imine **3d** was attempted in the second step in CH_3CN at room temperature for 6 h, but this condition led to the hydrolysis of the imine and thus a very complicated reaction mixture, which mainly contained the following organic compounds: unreacted imine and dimedone, 4-chlorobenzaldehyde and 4-methylaniline from the hydrolysis of imine **3d**, condensation product from 4-chlorobenzaldehyde with dimedone and a trace of desired product **5d**.[8] To further investigate this reaction, we have examined some other metal salts like those of Ce(IV) and Cu(II), which have also been extensively studied and proved to be efficient catalysts for the generation of carbon-centered radicals. As an example, under these solid-state conditions, compound **5e** was obtained in only 36% yield when catalyzed by Ce(IV) ammonium nitrate (CAN). In the presence of $Cu(OAc)_2$, compound **5e** could not be generated at all.

Among several modes of radical addition to the C=N bond, the most common one is the reductive addition to obtain amines.[5,9] Non-reductive additions had been realized to a much lesser extent.[5,10] But considered from the synthetic perspective, they were greatly neglected and underdeveloped. Herein, the imines act as radical acceptors for the radical addition followed by oxidation with $Mn(OAc)_3$, thus the original C=N bond was reinstalled, which can be reasonably anticipated as a new route to subsequent synthesis of unsymmetrical ketones and employed for further other functionalizations. Interestingly, all the products were obtained exclusively in an enol form under this condition. The identification of these enols is unequivocally ascertained by ^1H NMR, ^{13}C NMR, HRMS, and FT-IR spectra.[6] The singlet at about 14.7 ppm in the ^1H NMR spectra, the signal at about 195–200 ppm in the ^{13}C NMR spectra and the strong absorption at about 3440 cm^{-1} in the IR spectra all strongly support their molecular structures. It can be easily understood that the main contribution to the remarkably high stability of the enols is the high conjugation and thus the high delocalization of the π electron cloud. Furthermore, the intramolecular hydrogen bond between the nitrogen atom in the C=N group and the hydrogen atom in the hydroxyl group may also contribute to stabilize this structure.

In summary, we have developed a novel radical addition to imines mediated by $Mn(OAc)_3{\cdot}2H_2O$ under solid-state mechanochemical conditions for the first time. The high efficiency and good to excellent yield, no separation of the *in situ* generated imines, no use of any solvents in carrying out the reactions and thus the facile additional treatment make this method a potential alternative to the traditional synthetic process. Furthermore, the non-reductive radical addition mode and the corresponding structure of the products are intriguing, which impels us to explore other 1,3-dicarbonyl compounds and subsequent synthetic exploitation on the useful functional groups that remain available in the products. Work in this direction is under investigation.



Scheme 2

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6 Typical procedure is as follows: a mixture of aldehyde (0.2 mmol) and 4-methylaniline (0.2 mmol) was introduced, together with a stainless steel ball of 7.0 mm diameter, into a stainless steel jar (5 mL). The same mixture was introduced into another parallel jar. The two reaction vessels were closed and fixed on the vibration arms of a ball-milling apparatus (Retsch MM200 mixer mill, Retsch GmbH, Haan, Germany), and were milled vigorously at a rate of 1800 rpm at room temperature for 1 h. To the *in situ* generated imines in the two jars were added 0.2 mmol of 1,3-cyclohexanedione and 0.4 mmol of $Mn(OAc)_3{\cdot}2H_2O$, respectively. Then the reaction vessels were allowed to continue to vibrate for 3 h. The resulting mixtures were kept overnight and extracted with ethyl acetate and the desired product was separated by flash column chromatography over silica gel. The spectral data for representative compound **5a**: IR (KBr) ν_{max} 3434, 2952, 1652, 1598, 1548, 1517, 1447, 1350 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 14.68 (bs, 1H, OH), 8.13 (d, J = 8.67 Hz, 2H, Ar), 7.27 (d, J = 8.67 Hz, 2H, Ar), 6.94 (d, J = 8.31 Hz, 2H, Ar), 6.67 (d, J = 8.31 Hz, 2H, Ar), 2.58 (s, 2H, CH_2), 2.31 (s, 2H, CH_2), 2.23 (s, 3H, CH_3), 1.11 (s, 6H, $CH_3 \times 2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.78, 195.42, 167.29, 147.73, 141.20, 137.49, 133.83, 129.87 (2C), 128.91 (2C), 125.43 (2C), 123.61 (2C), 108.09, 53.20, 52.53, 30.56, 28.57 (2C), 21.06; HR-MS (EI-TOF, *m/z* [M^+]) Calc. for $C_{22}H_{22}N_2O_4$ 378.1580, Found 378.1581.

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