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Formation of cyclopropa[*c*]indole system in the Mn-mediated radical addition of cyclohexane-1,3-diones to N-substituted acrylamides

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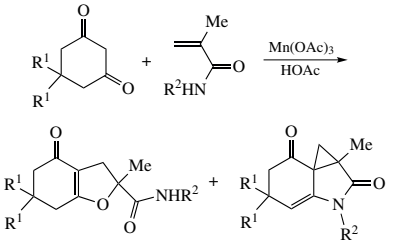
Manganese(III) acetate-mediated radical cyclization of N-substituted acrylamides with cyclohexane-1,3-diones gives 4-oxo-2,3,4,5,6,7-hexahydrobenzofuran-2-carboxamides and unexpected tricyclic 1,1a,5,6-tetrahydro-2*H*-cyclopropa[*c*]-indole-2,7(3*H*)-diones. The structure of one representative tricyclic compound was confirmed by X-ray analysis. The reaction mechanism was examined employing some structural analogues of the reactants.

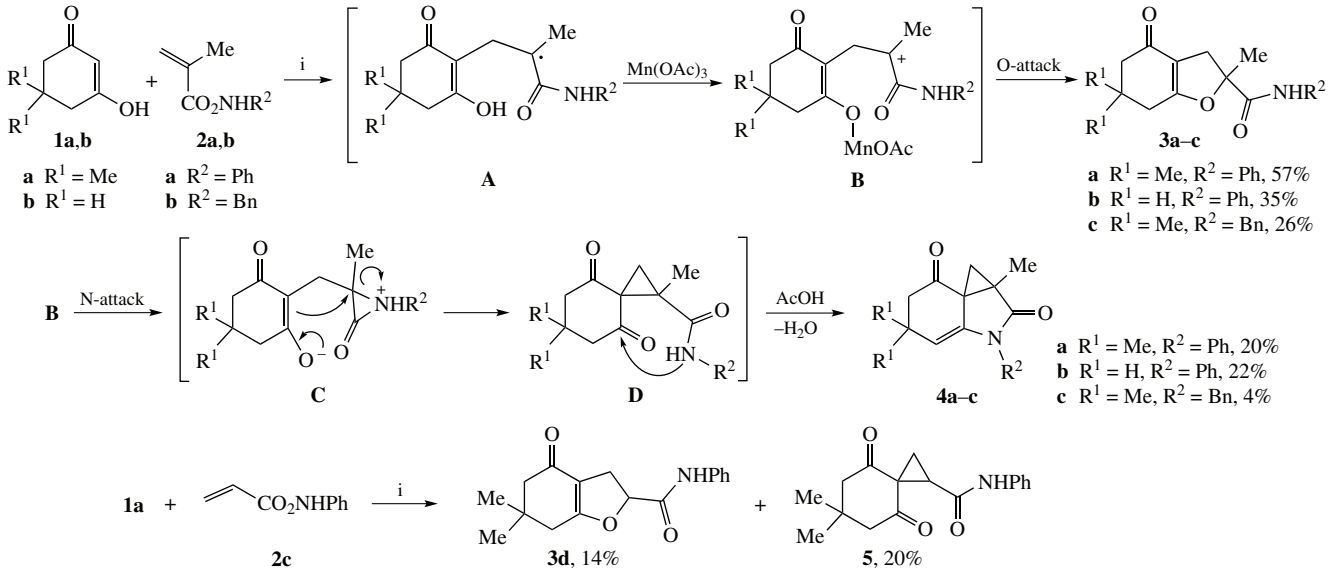


Keywords: manganese(III) acetate, radical addition, dihydrofurans, benzofuran-2-carboxamides, cyclopropa[*c*]indoles, carboxamides.

Transition metal salts (Mn^{3+}, Ce^{4+}, Ag^{+}) capable of gaining single electron are widely used in the synthesis of dihydrofurans, lactones, and natural products for generating C–C bonds[1] mostly from alkenes and active methylene compounds.[2–4] Dihydrofuran derivatives were also synthesized by iodocyclization of allyl-1,3-dicarbonyls.[5] Our research group has focused on the synthesis of dihydrofurans based on $Mn(OAc)_3$-mediated radical reactions of 1,3-dicarbonyls,[6] 3-oxopropanenitriles,[7] fluorinated 1,3-dicarbonyls,[8] 2-hydroxynaphthaquinone,[9] 4-hydroxycoumarin[10] and hydroxy thiazolopyrimidinones[11] with unsaturated systems such as alkynes, alkenes and dienes. Previously, we described the synthesis of dihydrofuran carboxamides from 1,3-dicarbonyl compounds and (meth)acrylamides[12] as well as related reactions leading to *trans*-2,3-dihydrofuran-3-carboxamides.[13,14]

In our previous work,[12] we reported that the reactions of cyclohexane-1,3-diones of type **1** (Scheme 1) with acrylamides gave only dihydrofuran carboxamides of type **3**. However, in this study we found that similar reaction with N-substituted methacrylamides **2a**,**b** afforded, along with required dihydrofurans, unexpected tricyclic products **4** of 1,1a,5,6-tetrahydro-2*H*-cyclopropa[*c*]indole-2,7(3*H*)-dione series (see Scheme 1). Structure of this type is found in natural cycloclavine and was synthetically accessed[15] by some other transformations.

The representative tricyclic product **4a** was obtained in 20% yield alongside dihydrofuran **3a**[16] (57%) from dimedone **1a** and *N*-phenylmethacrylamide **2a**. ^{1}H NMR spectrum of compound **3a** showed that H-2 geminal protons resonated at 2.98 and 3.46 ppm as doublets (J = 15.6 Hz). However, H-1 geminal cyclopropane protons of **4a** were strongly shifted upfield and resonated at 1.47 and 2.07 ppm as doublets (J = 3.6 Hz). Olefin proton of **4a** was observed as a singlet at 5.05 ppm. The structure of **4a** being 1a,5,5-trimethyl-3-phenyl-1,1a,5,6-tetrahydro-2*H*-



Scheme 1 *Reagents and conditions*: i, $Mn(OAc)_3$, AcOH, 80 °C, 30–60 min.

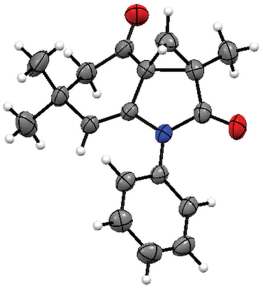
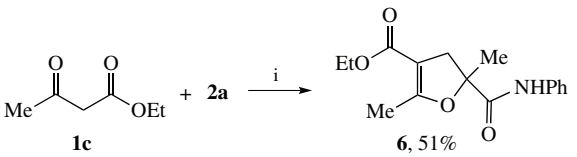


Figure 1 ORTEP diagram of compound **4a**.

cyclopropa[*c*]indole-2,7(3*H*)-dione was ultimately established by X-ray analysis (Figure 1).† Similarly, the reaction of cyclohexane-1,3-dione **1b** and **2a** gave analogous tricyclic product **4b** (22%) along with dihydrofuran **3b** (35%). ^{1}H NMR spectrum of **4b** contained doublets (J = 3.6 Hz) of cyclopropane geminal protons at 1.46 and 2.04 ppm and signal for the alkene proton at 5.16 ppm (dd, J = 7.2 and 2.0 Hz).

To better rationalize whether the *N*-phenyl group has any effect on the formation of tricyclic group, the reaction of *N*-benzylmethacrylamide **2b** with dimedone **1a** was investigated. As a result, dihydrofuran **3c** (26%) and tricyclic product **4c** (4%) were isolated. However, the reaction of *N*-phenylacrylamide **2c** with dimedone **1a** afforded expected dihydrofuran **3d** (14%) and spirocyclic product **5** (20%) instead of a tricyclic compound (see Scheme 1). We suppose that in this case the amide nitrogen in structure **D** is not located close to the carbonyl group, which prevents further cyclization of this spiro intermediate. Interestingly, the reaction of ethyl 3-oxobutanoate **1c** with *N*-phenylacrylamide **2a** produces only 'normal' dihydrofuran derivative **6**[16] (51%) (Scheme 2). The absence of other cyclization products can be explained by the fact that reactant **1c** is linear and its amide nitrogen is not close to the carbonyl group. No product was isolated from the reaction of acetylacetone with acrylamide **2a**.

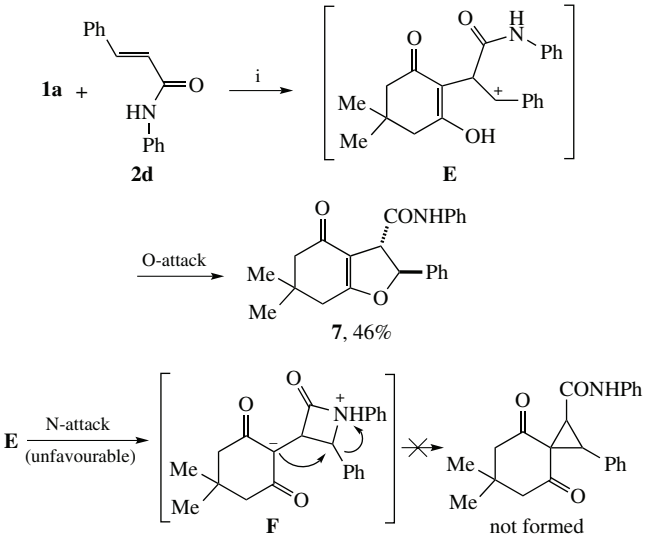
The proposed mechanism for the formation of 'normal' dihydrofurans **3a–d**, **5**, **6** and 'abnormal' tricyclic products **4a–c** is given in Scheme 1. Initially, the reaction of 1,3-dicarbonyls with acrylamides mediated by $Mn(OAc)_3$ forms radical intermediate **A**. Afterwards, carbocation **B** is formed upon oxidation of **A** with $Mn(OAc)_3$. The intramolecular cyclization (O-attack) of **B** produces furans **3a–d**. On the other hand, the intramolecular cyclization (N-attack) of **B** gives aziridine intermediate **C** and intramolecular carbanion attack to the aziridine ring forms spiro-cyclopropane product **D**. Then, tricyclic compounds **4a–c** are formed through N-attack to carbonyl group followed by elimination of water molecule (see Scheme 1).



Scheme 2 *Reagents and conditions*: i, $Mn(OAc)_3$, AcOH, 80 °C, 45 min.

† *Crystal data for* **4a**. $C_{18}H_{19}NO_2$, 281.34 g mol^{-1}, colourless crystal, monoclinic, space group $P1\,21/n\,1$, 296(2) K, 0.71073 Å, a = 10.4868(11), b = 8.0500(8) and c = 18.2365(16) Å, β = 101.892(6)°, crystal size (mm): 0.274×0.339×0.375, V = 1506.5(3) Å^3, Z = 4, d_{calc} = 1.240 g cm^{-3}, μ = 0.081 mm^{-1}; $F(000)$ = 600; θ from 2.08 to 25.00°; $-12 \leqslant h \leqslant 12$, $-8 \leqslant k \leqslant 9$, $-21 \leqslant l \leqslant 20$; R = 11513; T_{min} and T_{max}, 0.9780 and 0.9700; wR_2 = 0.1031.

CCDC 1549687 contains the supplementary crystallographic data (excluding structure data factors) for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* http://www.ccdc.cam.ac.uk.



Scheme 3 *Reagents and conditions*: i, $Mn(OAc)_3$, AcOH, 80 °C, 60 min.

The reaction of dimedone **1a** with cinnamide **2d** generates intermediate benzyl carbocation **E** unlike methacrylamide derivatives **2a**,**b** (Scheme 3). The intramolecular cyclization (O-attack) of **E** gives dihydrofuran **7** (46%). The intermediate azetidine derivative (**F**) can be formed by intramolecular cyclization (N-attack) of **E**. However, since any spiro-cyclopropane compound was not isolated, we think that the mechanism did not proceed through intermediate **F**.

In summary, the $Mn(OAc)_3$-mediated reactions of variously substituted acrylamides with 1,3-dicarbonyl compounds afforded 'normal' dihydrofuran products as well as 'abnormal' cyclopropane ones of cyclopropa[*c*]indole or spiro[2.5]octane series. The study of radical cyclization of some other acrylamides with 1,3-dicarbonyl compounds is an ongoing work of our group.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2020.11.032.

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