Synthesis of 4-Acetoxyindoles and Related Derivatives by Means of Air Oxidation of 4-Oxo-4,5,6,7-tetrahydroindoles Obtained from Nitroalkenes and Cyclohexane-1,3-diones

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Abstract: A novel method for synthesizing 4-hydroxyindole derivatives from cyclohexane-1,3-diones and nitroalkenes have been developed in which a newly developed air oxidation of 4-oxo-4,5,6,7-tetrahydroindoles is playing a crucial role.

Key words: indoles, cyclohexane-1,3-diones, nitroalkenes, Michael additions, oxidations

Indoles and their analogues are a very important class of heterocyclic compounds and exhibit interesting biological properties. Among them, 4-hydroxyindoles such as psilocybin (**I**) and psilocin (**II**) exert the potent physiological activity as a serotonin receptor agonist in the central nervous system and have been considered to be responsible for powerful psychotomimetic effects.[1] Thus, there have been considerable studies of the effects of substituents on the 4-hydroxytryptamine scaffolds.[1c] Superior colchicine-like antimitotic activities of 4-hydroxyindole derivatives such as **III**[2] (Figure 1) have recently been introduced, and considerable efforts are being made to develop new anticancer drugs. In order to gain more insight into the structure–activity relationship of compounds of this class, general and effective methods for synthesizing 4-hydroxyindole frameworks are highly requested.

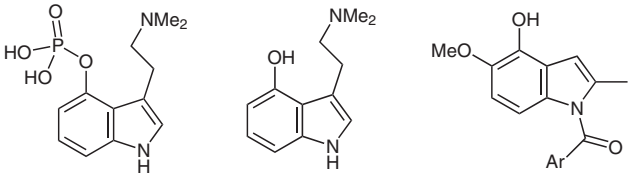

Figure 1 Typical biologically potent 4-hydroxyindoles

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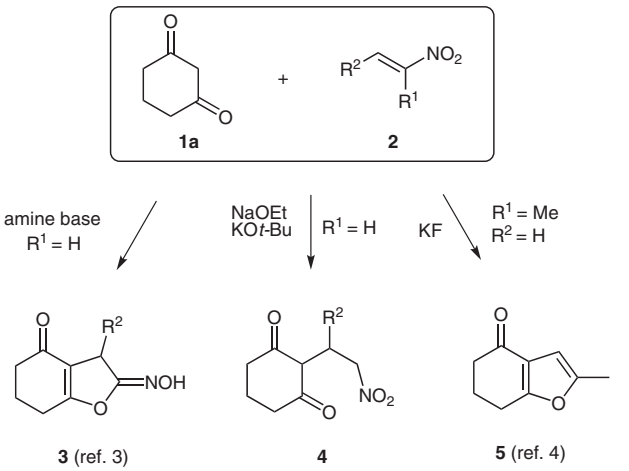
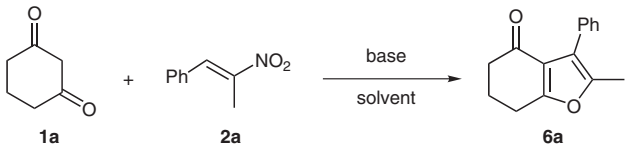


Scheme 1 Three representative reaction pathways for the reactions of cyclohexane-1,3-diones and nitroalkenes

Cyclohexane-1,3-diones have been playing a unique role in synthetic organic chemistry. The C- and O-centered ambident nucleophilicity stemmed from highly enolizable property of this function is very useful for the synthesis of various heterocycles.[3–6] Our continuing efforts to develop cyclohexane-1,3-dione-based cascade reactions,[3] coupled with the previous reports,[4,5] draw our attention to the base-

Table 1 Synthesis of Hydrobenzofuran Framework

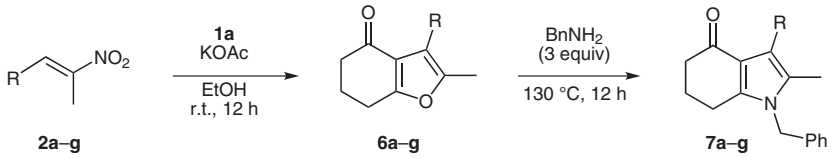


Entry	Base (equiv)	Solvent	Temp (°C)	Time (h)	Yield (%)
1	KF (0.2)	toluene	110	20	0
2	DABCO (0.2)	THF	r.t.	23	30
3	KO*t*-Bu (1.2)	THF	r.t.	30	19
4	KOAc (1.5)	THF	r.t.	19	35
5	KOAc (1.5)	THF	50	16	41
6	KOAc (2)	EtOH	r.t.	21	63
7	KOAc (2)	EtOH–H_2O	r.t.	25	37

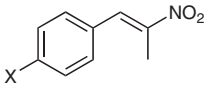
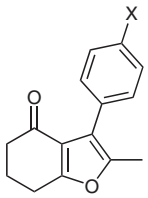
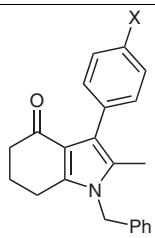
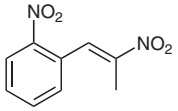
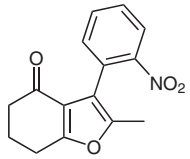
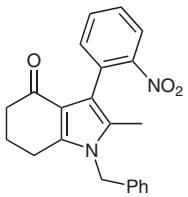
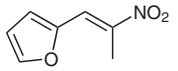
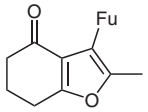
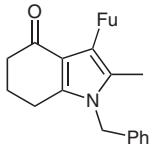
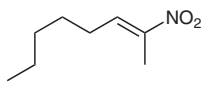
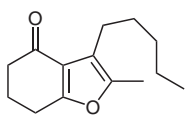
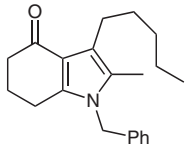
dependent unique chemoselectivity of their conjugate addition reactions to substituted nitroethylenes, which is summarized in Scheme 1. For instance, reaction of dione **1a** with β-substituted nitroethylenes in the presence of amine base selectively afforded bicyclic oximes **3**.[3b,4] On the other hands, alkoxide bases, such as sodium ethoxide or potassium *tert*-butoxide, catalyzed reactions of **1a** and β-substituted nitroethylenes to result in the formations of Michael adducts **4**. In addition, Yoshikoshi et al. reported KF-mediated hydrobenzofuran formation from **1a** and α-methylnitroethylene.[5] Taking these previous interesting results into account, we have envisioned the development of novel indole synthesis utilizing such two-component coupling reactions and further selective transformations of functionality involved in thus-obtained products.

We initially examined the reaction of **1a** and α,β-disubstituted nitroethylene **2a** (Table 1). In this case, however, the reported KF-mediated conditions[5] did not give 3-aryl-4-oxohydrobenzofuran **6a** (entry 1) at all. After extensive efforts to survey bases, we found that potassium acetate is a better reagent for realization of coupling reaction, by which **6a** was obtained in an acceptable yield. We also found that treatment of **6a** with excessive benzylamine at 130 °C without solvent afforded 4-oxo-4,5,6,7-tetrahydroindole **7a** in good yield (Table 2, entry 1). Results for the reactions of dione **1a** and various α,β-disubstituted nitroethylenes **2** leading to 4-oxohydrobenzofurans **6** and 4-oxohydroindoles **7** are summarized in Table 2. In any cases **6** and **7** were obtained under the newly developed conditions, indicating the generality of the two-step process. Desired aromatic or aliphatic substituents can be in-

Table 2 Synthesis of 4-Oxotetrahydroindoles **7**

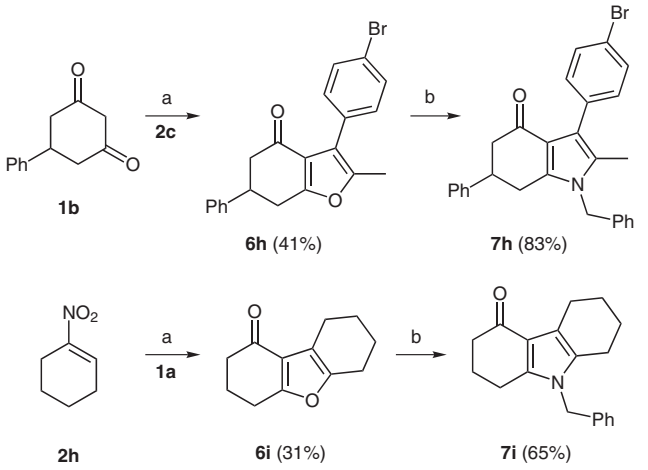


2a–g **6a–g** **7a–g**

Entry	Nitroalkene **2**	Furan **6** (yield, %)	Hydroindole **7** (yield, %)
			
1	**2a** X = H	**6a** X = H (63)	**7a** X = H (85)
2	**2b** X = Me	**6b** X = Me (51)	**7b** X = Me (86)
3	**2c** X = Br	**6c** X = Br (43)	**7c** X = Br (86)
4	**2d** X = OMe	**6d** X = OMe (52)	**7d** X = OMe (85)
5	 **2e**	 **6e** (41)	 **7e** (36)
6	 **2f**	 **6f** (43)	 **7f** (81)
7	 **2g**	 **6g** (37)	 **7g** (53)

troduced to 3-position of **6** or **7** through this sequence of reactions.

When the above sequence of reactions was applied to 5-substituted dione such as **1b**, 6-substituted oxohydroindole **7h** was obtained likewise. Cyclic nitroalkene such as **6i** could also tolerate the same reaction conditions as above to lead to hydrocarbazole **7i** although the yield was somewhat lower as indicated in Scheme 2.



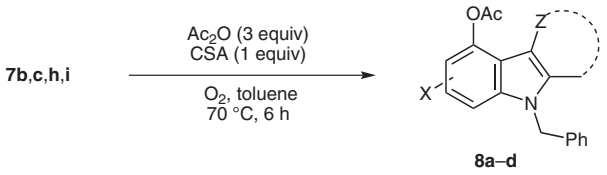
Scheme 2 Two additional examples. *Reagents and conditions*: (a) KOAc (2 equiv), EtOH, r.t., 12 h; (b) benzylamine (3 equiv), 130 °C, 12 h.

We had the idea that a remaining task of converting **7** into 4-hydroxyindoles should be uneventful by relying on venerable traditional ways. However, by contraries, it soon turned out that such aromatization processes were troublesome: widely used palladium-catalyzed dehydrogenation,[7] direct oxidations using DDQ[7] or halogenation–elimination process[9b] totally resulted in almost no reaction. Eventually, we have overcome this difficulty by air-oxidation conditions[8] involving oxygen, acetic anhydride, and camphorsulfonic acid in toluene (70 °C) to obtain 2,3-disubstituted 4-acetoxyindoles **8** in acceptable yields. Pertinent results are summarized in Table 3.[9]

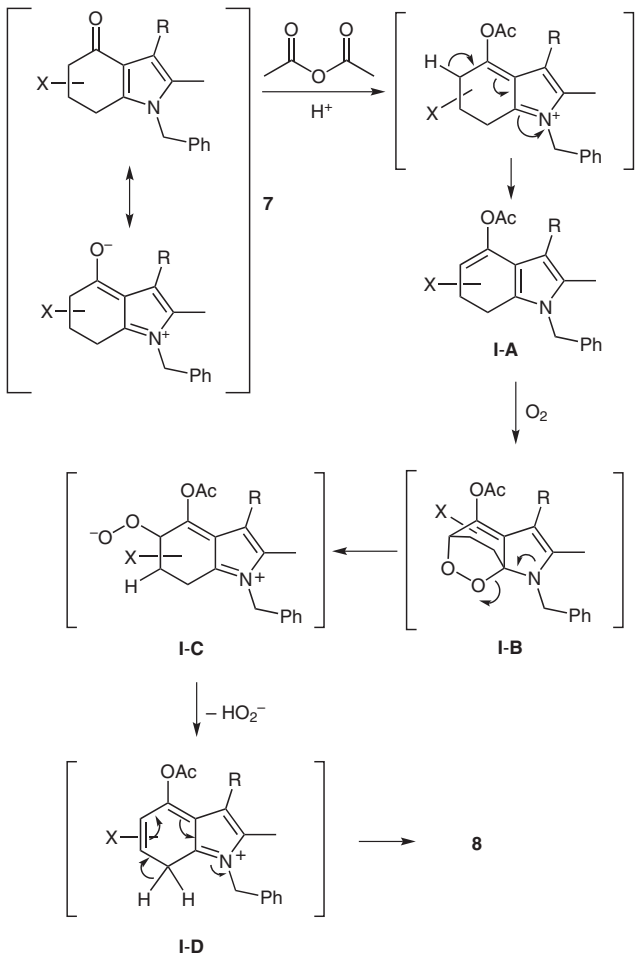
Possible reaction mechanism for the present air oxidation is proposed in Scheme 3. Formation of enol acetate intermediates **I-A** under the reaction conditions could be followed by 1,4-addition of oxygen molecule to the 1-amino-1,3-butadiene part of **I-A** to eventually result in the formation of adduct **I-B**.[10] This adduct undergoes possible fragmentation reaction to give a betaine-type intermediate **I-C** involving a peroxy anion and an iminium ion part. Probably, β-elimination of **I-C** could take place to produce an immediate precursor **I-D** for 4-hydroxyindoles **8** through deprotonation.

Thus, we have established the three-step sequences leading to polysubstituted 4-hydroxyindole derivatives from diones **1**, though yields were not necessarily optimized, featuring experimental simplicity applicable to large-scale preparative work.

Table 3 Synthesis of 2,3-Disubstituted 4-Hydroxyindoles via Air Oxidation



Entry	Hydroindoles **7**	Indoles **8** and **9** (yield, %)
1	**7b**	**8b**: X = H, Y = Me (71)
2	**7c**	**8c**: X = H, Y = Br (67)
3	**7h**	**8h**: X = Ph, Y = Br (62)
4	**7i**	**8i** (18); **9** (44)



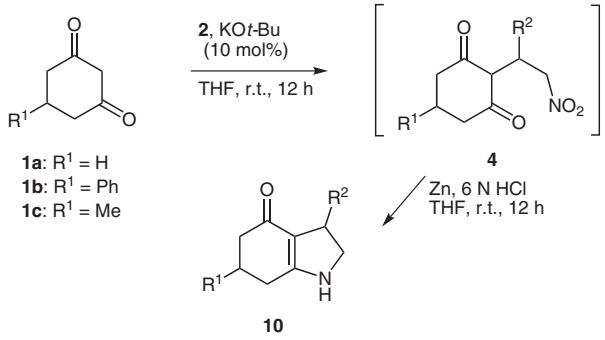
Scheme 3 Possible reaction mechanism of aromatization

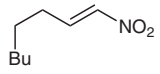
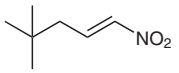
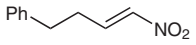
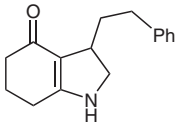
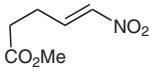
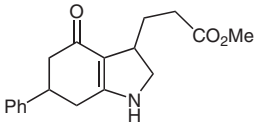
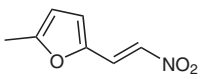
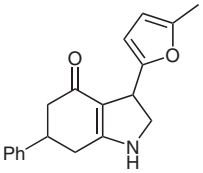
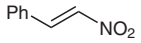
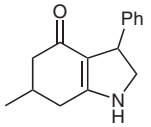
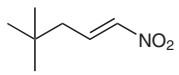
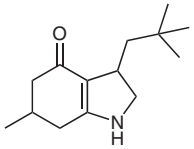
As mentioned in Scheme 1, metal alkoxide catalyzed reactions of **1a** with β-substituted nitroethylenes resulted in the formations of Michael adducts **4**. This intermediate **4**, without isolation, could be converted into 4-oxo-4,5,6,7-tetrahydroindoline frameworks **10** through a series of reactions involving reduction of a nitro group of **4** to the corresponding amine and the following intramolecular nucleophilic attack of the thus-produced amino group. In the event, treatment of β-substituted nitroethylenes and **1** with catalytic amount of KO*t*-Bu followed by the addition of zinc and hydrochloric acid afforded **10** in acceptable yields. These results are summarized in Table 4. Thus, we have developed efficient one-pot synthesis of 4-oxotetrahydroindoline **10** from cyclohexane-1,3-diones **1a–c** (Table 3).When **10** were subjected to the same air-oxidation conditions as those used for the conversion of **7** into indoles **8**, the desired 4-acetoxyindolines **11** were obtained as expected though the improvement of chemical yields for some products may need further investigation as shown in Table 5. Nevertheless, the present synthetic routine is a highly simple and effective chemical process because the complex 4-acetoxyindolines **11** were obtained from diones **1** in two steps.

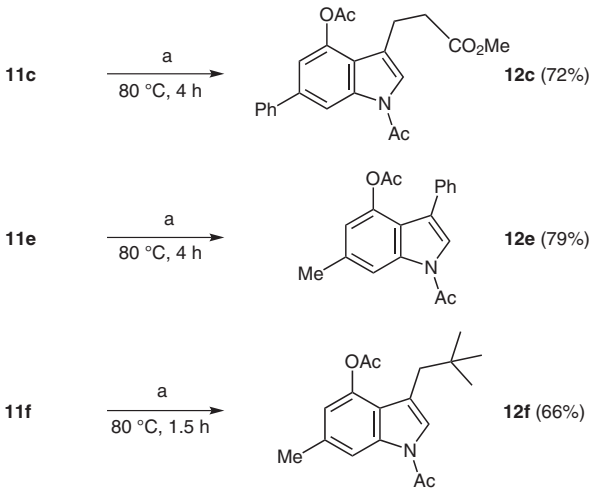
It turned out that DDQ oxidation is applicable to indolines **11c**,**e**,**f** to afford **12c**,**e**,**f** in acceptable yields as illustrated in Scheme 4. Thus, 2-nonsubstituted 4-acetoxyindoles have also become available in a conventional manner.

In conclusion, we have developed novel chemical processes for the synthesis of 4-hydroxyindole derivatives from cyclohexane-1,3-diones and nitroalkenes. In terms of diversity-oriented synthesis[11] of indoles, the present methods deserve consideration because of the diversity of

Table 4 Synthesis of 3-Substituted 4-Oxohexahydroindoles



Entry	Nitroolefin **2**	Dione **1**	Dihydropyrole **10** (yield, %)
1	 **2i**	**1c**	 **10a** (64)
2	 **2j**	**1a**	 **10b** (51)
3	 **2k**	**1c**	 **10c** (41)
4	 **2l**	**1b**	 **10d** (47)
5	 **2m**	**1a**	 **10e** (45)
6	 **2n**	**1b**	 **10f** (25)



Scheme 4 DDQ oxidation of indolines **11**. *Reagents and conditions*: (a) DDQ (2 equiv), dioxane.

available starting diones[12] as well as the convergent nature of the two-component coupling reactions. Explorations of these processes to the synthesis of biologically interesting indoles or natural indole alkaloids are one of our major concerns.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

References and Notes

(1) For recent syntheses for 4-hydroxyindoles, see: (a) Gathergood, N.; Scammells, P. J. *Org. Lett.* **2003**, *5*, 921. (b) Shirota, O.; Hakamata, W.; Goda, Y. *J. Nat. Prod.* **2003**, *66*, 885; and references cited therein. (c) For the structure–activity relationship study of **II**, see: Repke, D. B.; Grotjahn, D. B.; Shulgin, A. T. *J. Med. Chem.* **1985**, *28*, 892.

(2) Liou, J.-P.; Wu, Z.-Y.; Kuo, C.-C.; Chang, C.-Y.; Lu, P.-Y.; Chen, C.-M.; Hsieh, H.-P.; Chang, J.-Y. *J. Med. Chem.* **2008**, *51*, 4351.

(3) (a) Ishikawa, T.; Kadoya, R.; Arai, M.; Takahashi, H.; Kaisi, Y.; Mizuta, T.; Yoshikai, K.; Saito, S. *J. Org. Chem.* **2001**, *66*, 8000. (b) Ishikawa, T.; Miyahara, T.; Asakura, M.; Higuchi, S.; Miyauchi, Y.; Saito, S. *Org. Lett.* **2005**, *7*, 1211.

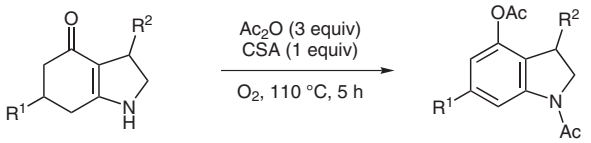
(4) For KF-catalyzed synthesis of 2-hydroxyiminodihydrofurans, see: Miyashita, M.; Kumazawa, T.; Yoshikoshi, A. *J. Org. Chem.* **1980**, *45*, 2945.

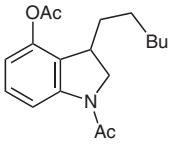
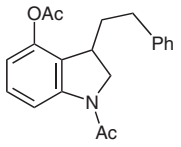
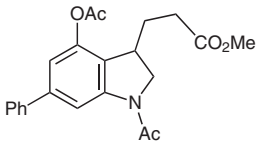
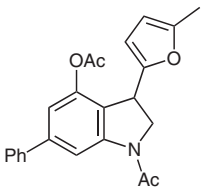
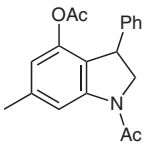
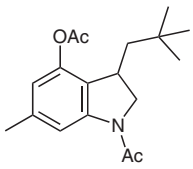
(5) Yanami, T.; Ballatore, A.; Miyashita, M.; Kato, M.; Yoshikoshi, A. *J. Chem. Soc., Perkin Trans. 1* **1978**, 1144.

(6) For the synthesis of 4-oxo-4,5,6,7-tetrahydroindoles, see: (a) Leonarda, P.; Chiara, G.; Giacomo, M.; Maurizio, T. *Tetrahedron Lett.* **2008**, *49*, 459. (b) Kathriarachchi, K. K. A. D. S.; Siriwardana, A. I.; Nakamura, I.; Yamamoto, Y. *Tetrahedron Lett.* **2007**, *48*, 2267. (c) Nayyar, N. K.; Hutchison, D. R.; Martinelli, M. J. *J. Org. Chem.* **1997**, *62*, 982. (d) Matsumoto, M.; Watanabe, N. *Heterocycles* **1984**, *22*, 2313. (e) Bobbitt, J. M.; Kulkarni, C. L.; Dutta, C. P.; Kofod, H.; Chiong, K. N. *J. Org. Chem.* **1978**, *43*, 3541.

(7) 4-Oxo-4,5,6,7-tetrahydroindoles with no substituent at C(3) can be converted into 4-hydroxyindoles by Pd-catalyzed dehydrogenation or DDQ oxidation though in low yields, see: Remers, W. A.; Roth, R. H.; Gibs, G. J.; Weis, M. J. *J. Org. Chem.* **1971**, *36*, 1232.

Table 5 Synthesis of 3-Substituted 4-Acetoxyindolines via Air Oxidation



Entry	Hydroindoles **10**	Indoline **11** (yield, %)
1	**10a** 	**11a** (59)
2	**10b** 	**11b** (63)
3	**10c** 	**11c** (28)
4	**10d** 	**11d** (33)
5	**10e** 	**11e** (54)
6	**10f** 	**11f** (42)

(8) For aromatization of six-membered carbocycles by air oxidation, see: (a) Kawashita, Y.; Nakamichi, N.; Kawabata, H.; Hayashi, M. *Org. Lett.* **2003**, *5*, 3713. (b) Ishikawa, T.; Hino, K.; Yoneda, T.; Murota, M.; Yamaguchi, K.; Watanabe, T. *J. Org. Chem.* **1999**, *64*, 5691.

(9) For the synthesis of 4-hydroxyindoles, see: (a) Somei, M.; Yamada, F. *Heterocycles* **2000**, *53*, 1573. (b) Matsumoto, M.; Ishoda, Y.; Watanabe, N. *Heterocycles* **1986**, *24*, 165. (c) Hegedus, L. S.; Mulhern, T. A.; Mori, A. *J. Org. Chem.* **1985**, *50*, 4282. (d) Remers, W. A.; Weiss, M. J. *J. Am. Chem. Soc.* **1965**, *87*, 5262.

(10) We are considering that transformation of **I-A** to **I-C** may involve an intermediary adduct **I-B** although nucleophilic attack of electron-rich dienamine function in **I-A** toward oxygen molecule, if any, might directly give **I-C** from **I-A** and could not be ruled out.

(11) Schreiber, S. L. *Science* **2000**, *287*, 1964.

(12) For general synthesis of cyclohexane-1,3-diones, see ref. 3a.