A Practical and User-Friendly Method for the Selenium-Free One-Step Preparation of 1,2-Diketones and their Monoxime Analogs

Georg Rüedi,*[a] Matthias A. Oberli,[a] Matthias Nagel,[b] Christophe Weymuth,[a] Hans-Jürgen Hansen[a]

[a] Organisch-chemisches Institut, Universität Zürich, Winterthurerstrasse190, 8057 Zürich, Switzerland
Fax +41(1)6356853; E-mail: georg@access.unizh.ch

[b] Swiss Federal Laboratories for Materials Testing and Research (EMPA), Überlandstrasse 138, 8600 Dübendorf, Switzerland

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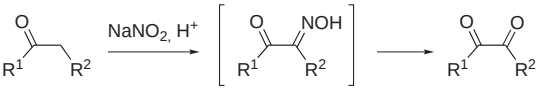
Abstract: Treatment of α-methylene ketones with excess sodium nitrite and aqueous HCl in THF at reduced temperatures provides an effective tool for the preparation of a variety of 1,2-diketones. The diastereoselective synthesis of the corresponding (*Z*)-1,2-dione monoximes could be accomplished under similar conditions, but by using only one equivalent of nitrosating reagent.

Key words: 1,2-diketones, 1,2-dione monoximes, nitrosation, α-oximation, oxidations

1,2-Diketones serve as useful intermediates in organic synthesis and they are frequently present as important substructures of medicinally active compounds.[1,2] Usually, the employment of selenium dioxide is the almost automatic choice for 1,2-diketone formation. However, the concomitantly generated selenium is notoriously difficult to remove from desired end products. In addition, its toxicity makes techniques using selenium compounds inappropriate for syntheses of drugs and medicines. Thus, the development of an efficient synthetic route to 1,2-diketones from simple starting materials continues to be an attractive task for organic chemists. Representative methodologies that have recently been exploited include the rearrangement of α,β-epoxyketones,[3] the oxidation of α-functionalized ketones,[4] 1,2-diols,[5] acetylenes,[6] and epoxides[7] as well as intramolecular reductive coupling reactions of carboxylate precursors.[8,9] However, while the latter is restricted to the preparation of dimers other methods are limited somewhat by the complexity and expensiveness of appropriate starting materials and reagents, unsatisfying yields provided, or their incompatibility with large scale applications.

On the other hand, Fileti and Ponzio reported more than a century ago that 1,2-diketones can be prepared by treating α-methylene ketones with sodium nitrite in aqueous HCl.[10] However, this procedure has been limited to a few applications of water-soluble substrates. Although a range of alkyl nitrites has been applied in order to run the reaction in organic solvents, the desired 1,2-diketones could only be obtained via additional hydrolysis of the isolated monoxime precursors. Herein, we describe a surprisingly simple, but highly effective and practical method that allows for the formation of water-insoluble 1,2-diketones from α-methylene ketones by modifying the procedure described by Fileti and Ponzio. In addition, we demonstrate that this methodology is also applicable to the synthesis of the initially formed 1,2-dione monoximes by only marginally changing the reaction conditions. The latter represent versatile starting compounds for the synthesis of a variety of pharmaceutically active heterocycles and α-amino acid derivatives (Scheme 1).[11]



Scheme 1 Direct route to 1,2-diketones via monoxime intermediates.

We started our investigations with the readily available water-insoluble cyclododecanone (**1**, Table 1). When a suspension of **1** and a one molar equivalent of sodium nitrite in THF was treated with excess concentrated HCl at room temperature for six hours, we obtained solely cyclododecane-1,2-dione monoxime **2** possessing a *Z*-double bond in 75% yield (entry 1).[12] Apparently, the dilute mineral acid medium is unable to mediate subsequent hydrolysis to the corresponding diketone **3**. On the other hand, using a threefold excess of the nitrosating reagent enabled the formation of **3**. Besides 5% of **2**, the desired product **3** was isolated in 70% yield (entry 2). A reasonable mechanistic explanation might involve the disruption of the intramolecular hydrogen bond in **2** mediated by an additional amount of the reactive nitrosyl cation. It is further noteworthy to state that oximation occurred only at one α-position, although both would be accessible. Adding the acid at low temperatures significantly increased the yield of both **2** (98%) and **3** (85%, entry 3).[13] Interestingly, as the 1,2-dione monoxime formation occurs faster than the subsequent hydrolysis step an increase in the reaction rate of monoxime **2** could be accomplished by using excess sodium nitrite and quenching the reaction after 30 minutes (entry 4). However, applying these conditions in conjunction with prolonged reaction times adversely affected the yield of **3**.[14] Exchanging THF for dioxane had only marginal effects on the reaction (entry 5). Similar results but lower conversion rates were obtained when HCl was replaced with H_2SO_4 (entry 6). On the other hand, using formic acid or acidic acid resulted in essentially no

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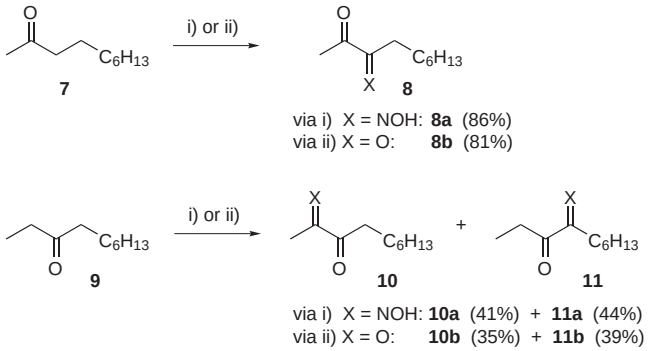
reaction (entries 7 and 8). To our very surprise, replacing HCl with HBr dramatically affected the course of the reaction. Neither of the expected products **2** and **3** could be observed, instead we obtained 2-bromo cyclododecanone in almost quantitative yields (entry 9). In striking contrast to the in situ generated nitrosyl chloride acting as a N-electrophile, its bromide analog offers an excellent Br^+-source.

With optimized conditions in hand, the scope of this reaction was investigated with a range of cyclic ketones by varying ring size and α-substituents (Table 2).[15,16] All reactions were carried out at room temperature in THF using equimolar amounts of sodium nitrite for the preparation of 1,2-dione monoximes **5** while three equivalents were employed to furnish 1,2-diketones **6**. The eight-membered substrate **4a** turned out to be the by far most reactive. Whereas diketone **6a** was obtained quantitatively after 12 minutes the corresponding monoxime **5a** could only be isolated when the reaction was conducted at –20 °C (entry 1). This behavior was even more pronounced by passing to smaller carbocyclic systems. Treating cyclopentanone and cyclohexanone under similar reaction conditions resulted in the exclusive formation of oligo- and/or polymers. However, these substrates were successively converted to the corresponding 1,2-diketones by following the procedure described by Fileti and Ponzio.[10] The medium and large ring cyclic ketones **4b**–**e** broadly followed the above mentioned trends, although longer reaction times were required and the 1,2-diketone formation did not go to completion (ca. 80% conversion). Both the 1,2-diketones **6b**–**e** and their respective monoxime precursors **5b**–**e** were obtained in good yields (entries 2–5). The reaction of unsymmetrical substrates **4f**,**g** having a substituent in α-position also performed well to give the oxidized products in good-to-excellent yields at comparable conversion rates (entries 6 and 7).

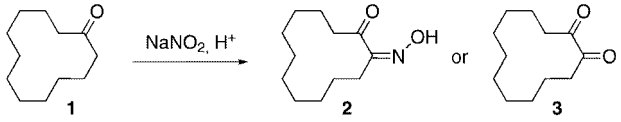
We have further extended our investigations to acyclic substrates (Scheme 2). Oximation of 2-decanone **7** under the same conditions proceeded smoothly via the thermodynamically more stable enol form to give only the methyl ketone derivatives **8a** and **8b**, respectively. On the other hand, the isomeric 3-decanone **9** failed to undergo regioselective oxidation. The decane-2,3-dione **10a**,**b** and decane-3,4-dione counterparts **11a**,**b** were formed in comparable yields.



Scheme 2 *Reagents and conditions*: i) $NaNO_2$ (1 equiv), HCl, THF, 0 °C; ii) $NaNO_2$ (3 equiv), HCl, THF, 0 °C.

In an effort to determine whether this procedure is also applicable to monoterpene derivatives, we treated α-campholanic acid derivative **12**[17] under similar reaction conditions (Scheme 3). In agreement with the results obtained above, the desired diketone **13** was formed in 78% yield (based on recovered starting material),[18] whereas its

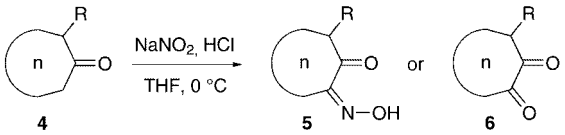
Table 1 Formation of **2** and **3** as a Function of Nature and Stoichiometry of the Nitrosating Reagent



				1,2-Dione Monoxime **2**			1,2-Diketone **3**		
Entry	Solvent	Acid	Temp (°C)	$NaNO_2$ (equiv)	Time (h)	Yield (%)	$NaNO_2$ (equiv)	Time (h)	Yield (%)
1	THF	HCl	25	1	2	75	1	6	0
2	THF	HCl	25	3	8	5	3	8	70
3	THF	HCl	0	1	3	98	3	8	85
4	THF	HCl	0	5	0.5	97	5	5	73
5	Dioxane	HCl	0	1	2	96	3	8	84
6	THF	H_2SO_4	0	1	24	90[a]	3	24	80[b]
7	THF	AcOH	0	3	30	3	6	48	0
8	THF	HCOOH	0	3	30	4	6	48	0
9	THF	HBr	5	1	4	0	3	10	0

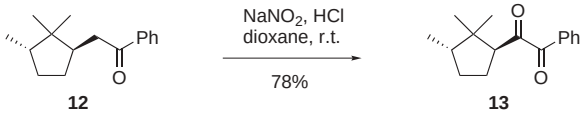
[a] Based on recovered **1** (33%).
[b] Based on recovered **1** (15%) and unhydrolyzed **2** (46%).

Table 2 Ring Size and Substituent Variation



				1,2-Dione Monoxime **5**			1,2-Diketone **6**		
Entry	n	R	Product	$NaNO_2$ (equiv)	Time (h)	Yield (%)[a]	$NaNO_2$ (equiv)	Time (h)	Yield (%)
1	8	H	**a**	1	0.1	55[b]	3	0.2	98[a]
2	10	H	**b**	1	5	84	3	10	87[c]
3	11	H	**c**	1	4	87	3	6	89[c]
4	14	H	**d**	1	5	81	3	12	83[c]
5	15	H	**e**	1	6	85	3	12	84[c]
6	12	Me	**f**	1	4	89	3	8	89[c]
7	12	OMe	**g**	1	3	90	3	8	94[c]

[a] Isolated yield.
[b] The reaction was conducted at –20 °C.
[c] Based on recovered material (ca. 80% conversion).



Scheme 3

monoxime analog could not be observed. Fortunately, **13** suffered no epimerization to give the corresponding *cis*-compound.

In conclusion, we have presented a very convenient α-oximation method that allows for the selective preparation of 1,2-dione monoximes and/or their hydrolyzed 1,2-diketone derivatives simply by using the appropriate amount of the in situ generated nitrosyl chloride. The versatility and very high efficiency coupled with the synthetic significance of 1,2-dicarbonyl compounds makes this procedure a powerful tool in organic synthesis. In addition, the reaction can be run on a preparative scale with no significant change in yield,[19] rendering this procedure also very promising for industrial applications.

Acknowledgment

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(12) The ^{1}H NMR of **2** showed a significantly low field shifted singlet at δ = 8.53 ppm accounting for an OH group being part of a hydrogen bridge.
(13) MS analysis provided evidence for the formation of a minor amount of a dehydrogenated form of **2**, that was purified by silica gel chromatography, characterized and proved to be 2-nitroso-cyclododec-2-enone (1% yield), colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.91 (t, ^3J = 7.7 Hz, 1 H), 2.74 (t, ^3J = 6.7 Hz, 2 H), 2.46 (dt, ^3J = 7.7 Hz, ^3J = 6.2 Hz, 2 H), 1.80–1.66 (m, 2 H), 1.46 (quint., ^3J = 6.2 Hz, 2 H), 1.34–1.23 (m, 10 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 198.23 (s, C1), 140.99 (d, C3), 133.57 (s, C2), 37.53 (t), 29.07 (t), 26.55 (t), 25.66 (t), 24.79 (t), 24.75 (2 C, t), 24.72 (t), 23.95 (t)ppm. MS (EI): m/z (%) for $C_{12}H_{19}NO_2$ (209.29) = 209 (19) $[M - NO]^+$, 161 (16), 149 (10), 143 (23), 132 (27), 111 (32), 98 (100), 84 (67), 55 (71).
(14) In a control experiment we could show that diketone **3** did not react further to give the corresponding 1,2,3-trione, even if large excess of sodium nitrite in combination with longer reaction times was used.
(15) **General Procedure for the Prearation of 1,2-Diketones and 1,2-Dione Monoximes**.
A suspension of the starting ketone (50 mmol) and $NaNO_2$ (10.35 g, 150 mmol) in THF (100 mL) was cooled to 0 °C. To this mixture, concd HCl (65 mL) was added in such a way that the temperature did not exceed 10 °C. In order to avoid the evolution of nitrous gases the acid was added via cannula that was immerged into the reaction mixture. After the addition the cooling bath was removed and the suspension turned dark yellow. The progress of the reaction was monitored by GC. After the starting material had vanished (0.1–12 h) the reaction mixture containing the crude 1,2-diketone was poured into a separatory funnel containing crushed ice (200 g) and Et_2O (100 mL). The organic layer was separated, and the aqueous phase extracted with Et_2O (3 × 100 mL). The combined organic layers were washed with a sat. aq solution of $NaHCO_3$ (100 mL) and with brine (100 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by filtration over a pad of silica gel (5:1) using hexane–EtOAc (50:1) as eluent. The corresponding 1,2-dione monoximes were prepared accordingly by using only 3.45 g (50 mmol) of $NaNO_2$ and 25 mL of concd HCl. The crude product was purified either by filtration over a pad of silica gel (5:1) using hexane–EtOAc (50:1) as eluent or by crystallization from hexane–EtOAc.
(16) All new compounds were fully characterized. Selected data for novel compounds:
3-Methylcyclododecane-1,2-dione (6f): yellow oil (1.42 g). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.52 (qdd, ^3J = 7.0 Hz, ^3J = 6.9 Hz, ^3J = 3.5 Hz, 1 H, H–C3), 3.36–3.27 (m, 1 H), 2.26–2.17 (m, 1 H), 1.82–1.68 (m, 3 H), 1.38–1.17 (m, 13 H), 1.10 (d, ^3J = 6.9 Hz, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 204.07 (s, C2), 201.93 (s, C1), 38.34 (d, C3), 36.47 (t, C12), 29.86 (t), 26.34 (t), 26.17 (t), 24.95 (t), 23.79 (t), 23.70 (t), 22.09 (t), 14.45 (q, CH_3) ppm. MS (EI): *m/z* (%) $C_{13}H_{22}O_2$ (210.32) = 210 (7) $[M^+]$, 192 (1), 167 (3), 153 (6), 139 (8), 125 (22), 112 (29), 98 (37), 83 (24), 69 (51), 55 (100). Anal. Calcd for $C_{13}H_{22}O_2$ (210.32): C, 74.24; H, 10.54. Found: C, 74.44; H, 10.60.
(*Z*)-3-Methylcyclododecane-1,2-dione-1-oxime (5f): colorless crystals (0.99 g); mp 97–98 °C (from hexane–EtOAc). ^{1}H NMR (300 MHz, $CDCl_3$): δ = ca. 8 (s, 1 H, NOH), 3.62 (qdd, ^3J = 7.0 Hz, ^3J = 6.9 Hz, ^3J = 3.6 Hz, 1 H, H–C12), 2.89–2.80 (m, 1 H), 2.65–2.57 (m, 1 H), 1.84–1.76 (m, 1 H), 1.66–1.42 (m, 3 H), 1.37–1.16 (m, 12 H), 1.09 (d, ^3J = 6.9 Hz, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 203.15 (s, C1), 160.06 (s, C2), 39.64 (d, C12), 31.38 (t, C3), 26.09 (t, 2 C), 25.04 (t), 23.42 (t), 22.87 (t), 22.65 (t), 21.89 (t), 21.19 (t), 15.12 (q, CH_3) ppm. MS (EI): *m/z* (%) $C_{13}H_{23}NO_2$ (225.32) = 225 (4) $[M^+]$, 208 (26), 197 (5), 180 (42), 168 (11), 138 (18), 124 (26), 110 (28), 96 (34), 82 (37), 69 (45), 55 (100). Anal. Calcd for $C_{13}H_{23}NO_2$ (225.33): C, 69.29; H, 10.29; N, 6.22. Found: C, 69.18; H, 10.19; N, 6.11.
3-Methoxycyclododecane-1,2-dione (6g): yellow oil (1.23 g). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.85 (t, ^3J = 4.4 Hz, 1 H, H–C3), 3.38 (s, 3 H, OCH_3), 2.23–2.14 (m, 1 H), 1.90–1.83 (m, 2 H), 1.73–1.66 (m, 2 H), 1.53–1.49 (m, 1 H), 1.39–1.02 (m, 12 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 202.10 (s), 199.00 (s), 81.14 (d, C3), 57.61 (q, OCH_3), 36.71 (t, C12), 27.30 (t), 26.21 (t), 26.17 (t), 24.33 (t), 23.29 (t), 22.03 (t), 21.83 (t), 19.48 (t) ppm. MS (EI): *m/z* (%) $C_{13}H_{22}O_2$ (210.32) = 226 (1) $[M^+]$, 198 (8), 148 (5), 138 (8), 127 (6), 109 (13), 96 (19), 82 (43), 71 (100), 55 (34). Anal. Calcd for $C_{13}H_{22}O_3$ (226.32): C, 68.99; H, 9.80. Found: C, 69.12; H, 9.85.
(*Z*)-3-Methoxycyclododecane-1,2-dione-1-oxime (5g): colorless crystals (1.86 g); mp 100–102 °C (from hexane–EtOAc). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.50 (s, 1 H, NOH), 4.88–4.86 (m, 1 H, H–C12), 3.37 (s, 3 H, OCH_3), 2.94–2.84 (m, 1 H), 2.65–2.58 (m, 1 H), 1.97–1.86 (m, 2 H), 1.55–1.37 (m, 2 H), 1.36–1.02 (m, 12 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 198.16 [s, C(1)], 159.63 [s, C(2)], 82.52 [d, C(12)], 57.46 (q, OCH_3), 29.03 (t), 26.24 (t), 26.16 (t), 24.02 (t), 22.81 (t), 22.50 (t), 21.91 (t), 21.78 (t), 18.80 (t)ppm. MS (EI): *m/z* (%) $C_{13}H_{23}NO_2$ (225.33) = 241 (2) $[M^+]$, 224 (58), 196 (95), 182 (17), 166 (14), 120 (23), 110 (21), 96 (27), 71 (100), 55 (52). Anal. Calcd for $C_{13}H_{23}NO_3$ (241.33): C, 64.70; H, 9.61; N, 5.80. Found: C, 64.83; H, 9.70; N, 5.88.
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(18) **(+)-*trans*-2-(2,2,3-Trimethylcyclopentyl)-1-phenylethanedione (13)**: bright yellow oil; $[\alpha]_D^{23}$ +39.2 (*c* 1.6, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.03 (dd, ^3J = 8.2 Hz, ^4J = 1.4 Hz, 2 H), 7.64–7.59 (m, 1 H), 7.52–7.47 (m, 2 H), 3.61 (dd, ^3J = 8.3, 6.4 Hz, 1 H), 2.10–1.24 (m, 5 H), 0.97 (s, 3 H), 0.95 (s, 3 H), 0.87 (d, ^3J = 6.9 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 205.83 (s), 192.16 (s), 135.10 (s), 134.17 (d), 130.40 (d), 128.70 (d), 55.64 (d), 45.75 (s), 44.27 (d), 31.74 (t), 24.92 (q), 24.81 (t), 24.22 (q), 14.44 (q) ppm. MS (EI): *m/z* (%) $C_{16}H_{20}O_2$ (244.33) = 244 (3) $[M^+]$, 139 (59) $[M - COPh]^+$, 111 (97), 105 (82) $[COPh^+]$, 77 (75), 69 (100), 55 (94).
(19) Several reactions were conducted on a 20 g scale.