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# A MILD METHOD FOR THE CONVERSION OF ACTIVATED ARYL METHYL GROUPS TO CARBOXALDEHYDES VIA THE UNCATALYZED PERIODATE CLEAVAGE OF ENAMINES

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**Summary:** A mild procedure for the oxidative cleavage of aryl enamines to aryl aldehydes by periodate without the need for transition metal catalysis is presented.

We were interested in a convenient large scale preparation of *o*-nitrobenzaldehydes such as 3 for use as intermediates in subsequent chemistry. Oxidation of the readily available *o*-nitro toluene 1 by the Kröhnke aldehyde procedure[1] provided pure product but with inconsistent yields. Numerous alternative reagents are available for oxidation of aromatic methyl groups. Many involve chromium ($CrO_2Cl_2$, Étard reaction, $CrO_3/Ac_2O$),[2] which can present disposal and isolation problems, while radical mediated oxidations (e.g. the Kröhnke aldehyde synthesis[1] or ceric ammonium nitrate,[2] etc.) had proven to be capricious. We therefore pursued an alternative approach exploiting the activation of the methyl group by the *o*-nitro substituent in 3. The formation of enamines of *o*-nitrotoluenes using N,N-dimethylformamide dimethyl acetal is well established[3] and oxidative cleavage of 2 would generate the desired aldehyde 3. This cleavage has been accomplished with a wide variety of reagents including ozone,[4a] singlet oxygen,[4b,c] sodium dichromate,[4d,e,f] and $RuO_4/NaIO_4$.[4g,h]

Enamine 2, obtained in 80% yield as purple crystals,[3] was first subjected to standard Lemieux-Johnson conditions:[5] rapid oxidation with $OsO_4/NaIO_4$ occurred to produce 3 in 95% yield (see Scheme). On a 50 gram scale-up, we premixed 2 with 3.0 eq. of $NaIO_4$ in 50% aqueous THF and observed a mildly exothermic reaction accompanying the rapid discharge of color *without added osmium tetroxide.!* The enamine was cleanly converted at room temperature to the desired aryl aldehyde 3 within 1 h. in 95% yield. This methodology has proven to be quite general and reproducible for the preparation of a number of aryl aldehydes.[6]

## Scheme

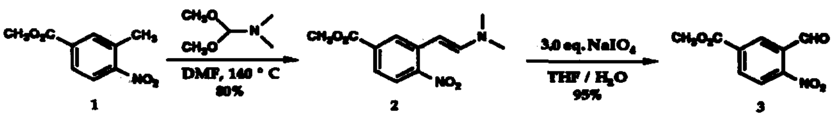
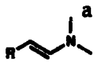
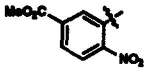
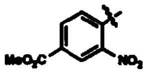
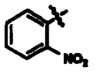
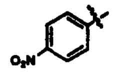
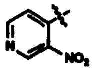
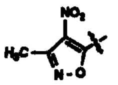
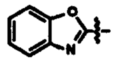
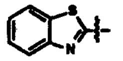
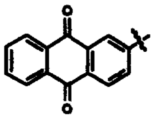
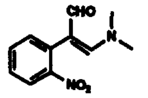


**Table** Enamine Formation and Periodate Cleavage of Activated Aryl Methyl Groups

| entry | RCH$_3$ |  [a] yield (%) | m.p. | NaIO$_4$ cleavage reaction time (h) | RCHO yield (%) | m.p. |
|---|---|---|---|---|---|---|
| 1 |  | 80% | 76-77°C | 1 | 95% | 67-68 °C |
| 2 |  | 99% | 54-55°C$^{b}$ | 2 | 95% | 54-55 °C |
| 3 |  | 88% | oil | 1 | 80% | 44-46 °C |
| 4 |  | 72% | 132-133 °C$^{b}$ | 1 | 72% | 106-108 °C |
| 5 |  | 80% | 97-98 °C$^{b}$ | 1 | 75% | oil |
| 6 |  | 69% | 95-98 °C | 24 | 42% | oil |
| 7 |  | 66% | 101-102 °C | 1 | 63% | 132-133 °C |
| 8 |  | 77% | 82-83 °C | 0.5 | 77% | oil |
| 9 |  | 86% | 172-173 °C | 2 | 79% | 151-152 °C |
| 10 |  |  |  | 18 | 71% | 147-148 °C$^{c}$<br>2-nitrobenzoic acid |

a) Substrate warmed to 140 °C in DMF (1 Molar) with 1.3 eq. $(CH_3O)_2CHN(CH_3)_2$ for 24 h under nitrogen. Concentration affords product. Recrystallization from methanol where mp indicated. b) Enamine formation complete in 2 h. c) 4 eq. NaIO$_4$, standard aqueous acidic workup.

With other substrates, enamine formation under standard conditions[3] provided essentially pure materials after a single crystallization from methanol. This transformation has been accomplished on the activated aryl methyl derivatives in the table; less activated systems fail to react under these conditions.[7] Entry 10 exemplifies the conversion of a β-formylaryl enamine to 2-nitrobenzoic acid involving two oxidative cleavage steps.[8]

While the mechanism of this transformation is uncertain, oxidations of activated methylene compounds with periodate are known.[9] By analogy, we presume that oxidation of the enamine β-carbon generates a hydroxy-iminium ion which is hydrated to an α-hydroxy aldehyde or aminal: oxidative cleavage of this species by periodate generates product. Experiments are underway to elucidate the mechanistic course of this process and will be reported in due course.

## Experimental

In a typical procedure, enamine **2** (47.9 g, 195 mmol) and $NaIO_4$ (125.3 g, 586 mmol) were mechanically stirred in 50% aqueous THF (1 L) at ambient temperature for 1 h or until judged complete by TLC. The insolubles ($NaIO_3$) were removed by filtration and washed with EtOAc. The organic layer was washed with sat. $NaHCO_3$ solution (3 x 100 mL) then dried over $MgSO_4$. Concentration and elution through a silica gel pad (150 g) with 50% $CH_2Cl_2$/hexanes provides pure **3**, (38.8 g, 95%).

## References and Notes

1. Kröhnke, F. *et. al., Ber.* **1936,** *69,* 2006.

2. For leading references see, March, J. *Advanced Organic Chemistry* (Wiley, N.Y., 4th ed. 1992), pp. 1190 - 1191.

3. Leimgruber, W.; Batcho, A. D.; Abstracts of Papers, Third International Congress of Heterocyclic Chemistry, Tohoku University, Sendai, Japan, Aug. 1971; A. D. Batcho and W. Leimgruger, U. S. Patent 3,976,639, (1976); *Chem. Abstr.*, 86, 29624t (1977); Clark, R. D.; Repke, D. B. *Heterocycles,* **1984,** 22, 195.

4. a) Herr, M. E.; Heyl, F. W. *J. Am. Chem. Soc.* **1952**, *74*, 3627. b) Foote, C. S.; Lin, J. W. *Tetrahedron Lett.* **1968**, *9*, 3267, c) Huber, J. E. *Tetrahedron Lett.* **1968**, *9*, 3271. d) Shephard, D. A. *et. al.* *J. Am. Chem. Soc.* **1955**, *77*, 1212. e) Slomp, G. *et. al.* *J. Am. Chem. Soc.* **1955**, *77*, 1216. f) Trivedi, G. K.; Kalsi, P. S.; Chakravarti, K. *Tetrahedron* **1964**, *20*, 2631. g) Desai. M. C.; Chawla, H. P. S.; Dev, S. *Tetrahedron* **1982**, *38*, 379. h) Torii, S.; Inokuchi, T.; Kondo, K. *J. Org. Chem*, **1985**, *50*, 4980.

5. Pappo, R.; Allen, D. S. Jr.; Lemieux, R. U.; Johnson, W. S. *J. Org. Chem.* **1956**, *21*, 478.

6. $NaIO_4$ oxidation of 2,3-disubstituted indoles has been observed, see Dolby, L. J.; Booth, D. L. *J. Am. Chem. Soc.* **1966**, *88*, 1049.

7. 2-Methylquinoline, 2-methylpyridine, 2-methylpyrazine, 2-methyl-quinoxoline, 3-nitrotoluene, 2-ethyl nitrobenzene, 2-methylbenzofuran and methyl 4-methylbenzoate failed to form enamines under standard conditions.$^3$ 4-methylpyrimidine formed enamine in 89% yield but decomposed under the $NaIO_4$ cleavage conditions.

8. We have found that the oxidation of 2'-nitro-dimethylaminostyrene (entry 3) with $KMnO_4$ (2.1 eq in 5/1 t-BuOH/$H_2O$ with 2.2 eq $K_2CO_3$) produces 2-nitrobenzoic acid in quantitative yield.

9. See a) Fieser. L. F.; Fieser, M. *Reagents for Organic Synthesis*, Vol. 1, p. 809, **1967**; b) *Oxidation in Organic Chemistry*, Part A, (Academic Press, 1965) pp. 368 - 398.; and for a related example see Wolfrom, M. L.; Bobbitt, J. M. *J. Am. Chem. Soc.* **1956**, *78*, 2489.

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