

Oxime Derivatives as α -Electrophiles. From α -Tetralone Oximes to Tetracyclic Frameworks

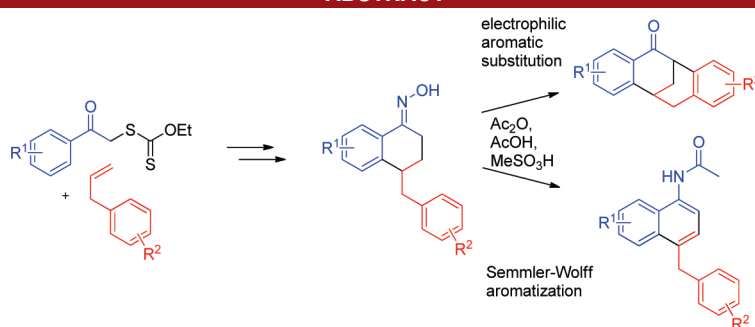
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ABSTRACT



When subjected to the conditions of a Semmler–Wolff/Schroeter aromatization, the oximes of 4-benzyl-substituted tetralones undergo an electrophilic aromatic substitution reaction to form tetracyclic frameworks.

Various synthetic applications for oximes have been reported since their first application to the identification of ketones and aldehydes in the late 19th century.¹ The Beckmann rearrangement of ketoximes is a classical textbook reaction, which has found widespread utility.² Oximes are known to react as O or N nucleophiles,³ and their use as $C=N$ electrophiles has been reported.⁴ Additionally, their $C-H$ acidity is often sufficient for α -alkylation-reactions, and coordination of transition metal atoms can lead to a β - $C-H$ activation through cyclopalladation reactions for example.⁵ A lesser known reaction is the aromatization under acidic conditions of oximes derived from α,β -unsaturated cyclohexanones, first described by Semmler and

Wolff and later extended to oximes of α -tetralones by Schroeter and his collaborators.⁶

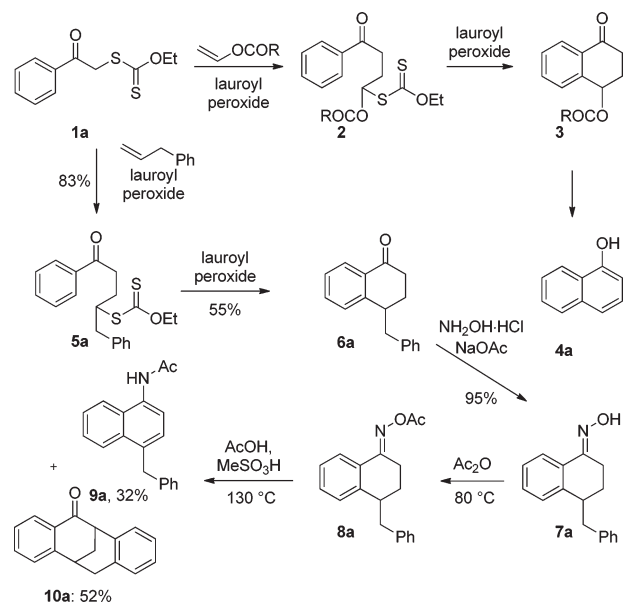
A few years ago, we devised a concise route to α -tetralones⁷ based on the radical xanthate transfer technology⁸ and applied it to the total synthesis of a number of natural products such as norparvulenone, *O*-methyl asparvenone, and shinanolone.⁹ We also found that α -tetralones **3**, obtained by the

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(4) (a) Yoshida, M.; Uchiyama, K.; Narasaka, K. *Heterocycles* **2000**, *52*, 681. (b) Hoch, J. *Compt. Rend.* **1934**, *198*, 1865. (c) Campbell, K. N.; McKenna, J. F. *J. Org. Chem.* **1939**, *4*, 198. (d) Rodrigues, K. E.; Basha, A.; Summers, J. B.; Brooks, D. W. *Tetrahedron Lett.* **1988**, *29*, 3455.
(5) Dunina, V. V.; Zalevskaya, O. A.; Potapov, V. M. *Russ. Chem. Rev.* **1988**, *57*, 250.

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(9) (a) Cordero Vargas, A.; Quiclet-Sire, B.; Zard, S. Z. *Org. Lett.* **2003**, *5*, 3717. (b) Cordero Vargas, A.; Quiclet-Sire, B.; Zard, S. Z. *Tetrahedron Lett.* **2004**, *45*, 7355. (c) Cordero-Vargas, A.; Quiclet-Sire, B.; Zard, S. Z. *Org. Biomol. Chem.* **2005**, *3*, 4432. (d) Cordero-Vargas, A.; Quiclet-Sire, B.; Zard, S. Z. *Bioorg. Med. Chem.* **2006**, *14*, 6165. (e) Petit, L.; Zard, S. Z. *Chem. Commun.* **2010**, *46*, 5148.

addition–cyclization of an *S*-phenacyl xanthates **1** to vinyl acetate or vinyl pivalate, underwent facile aromatization upon heating with acid to give the corresponding naphthols **4** (Scheme 1).¹⁰

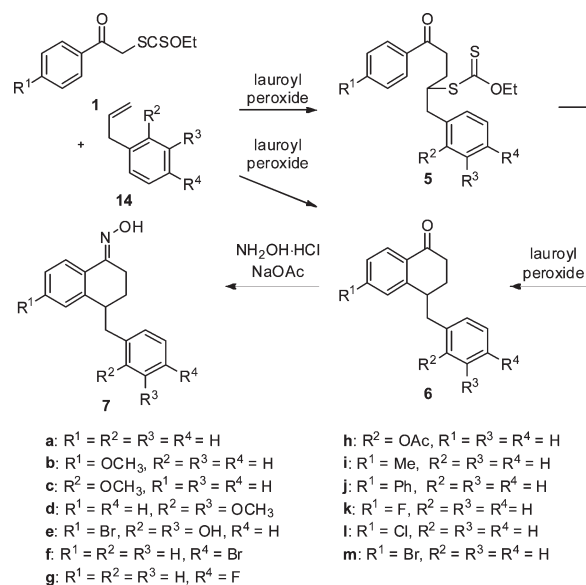
Scheme 1. Unexpected Formation of a Tetracyclic Product



To complement this very effective synthesis of naphthols (and naphthalenes, more generally), we contemplated applying the Semmler–Wolff/Schroeter reaction to obtain α -naphthylamines. We therefore prepared α -tetralone **6a** by addition of xanthate **1a** to allylbenzene, and the resulting adduct **5a** was ring closed by exposure to stoichiometric amounts of lauroyl peroxide. The corresponding oxime **7a** was then heated to 80 °C for 40 min in neat acetic anhydride to form the *O*-acetate **8a**, followed by addition of a mixture of acetic and methanesulfonic acid and heating to 130 °C for 30 min. We were surprised to find after purification of the crude mixture that the major product was not the expected *N*-acetyl naphthylamine **9a** (32%) but tetracyclic compound **10a**, isolated in 52% yield.

In order to explore the scope of this new transformation, we prepared variously substituted α -tetralone oximes **7b–m** by the same three-step sequence outlined in Scheme 1 for the parent substrate **7a**. The structures and yields are summarized in Table 1. Exposure of these oximes to the combination of acetic anhydride and acetic acid/methanesulfonic acid under the same conditions previously used for **7a** furnished the corresponding tetracyclic ketones **10b–m** after workup in addition to variable amounts of the *N*-acetyl-naphthylamines **9** resulting from the normal Schroeter reaction (Table 2).

Table 1. Synthesis of α -Tetralone Oximes **7a–m**



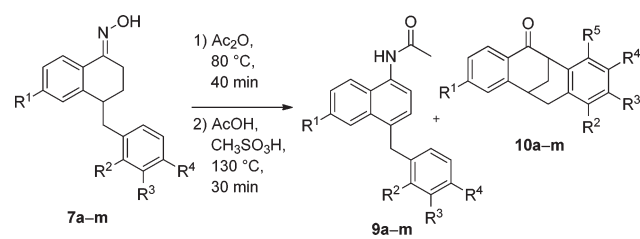
entry	yield 5 [%]	yield 6 [%]	yield 7 [%]
a	83	55	95
b	87	62	94
c	86	48	94
d	72	48	76
e	69	50	78
f	^a	48	87
g	96	42	83
h	^a	32	81
i	^a	51	98
j	^a	53	98
k	89	51	92
l	85	54	96
m	87	57	88

^a One pot procedure from **1/14** to **6**.

In most cases, the yield of the tetracyclic ketone was of the order of 40–50%, and it was shown for several examples that the corresponding *N*-acetyl-naphthylamine constituted most of the material balance. The presence of electron-donating methoxy groups caused significant erosion in the yield (entries **b**, **d–e**). The effect was most noticeable when the methoxy group was attached to the pendent aromatic ring (entries **c–e**). Furthermore, the reactions were not clean for these cases. Numerous side products were observed, which appeared to result from Friedel–Crafts acylation of both the starting material and the tetracyclic ketone and *N*-acetyl-naphthylamine products. Indeed, the products of the electrophilic aromatic substitution reaction of **7c** could be characterized as the monoacetylated tetracycles **10ci** (R³ = H, R⁵ = acetyl) and **10cii** (R⁵ = H, R³ = acetyl) in a ratio of 7:3. Furthermore, model experiments showed that the treatment of (3,4-dimethoxyphenyl)acetic acid or 4-allyl-1,2-dimethoxybenzene under the reaction conditions resulted in complete conversion into the mono-, di-, and

(10) Cordero-Vargas, A.; Pérez-Martin, I.; Quiclet-Sire, B.; Zard, S. Z. *Org. Biomol. Chem.* **2004**, *2*, 3018.

Table 2. Influence of the Electronic Nature of the Aromatic Rings on the Ratio of the Products **9** and **10**, Respectively



entry		yield 9 [%]	yield 10 [%]
a		32	52
b		n.d. ^a	29
c		n.d. ^a	48 ^b
d		n.d. ^a	18
e		n.d. ^a	18
f		n.d.	49
g		n.d.	41
h		n.d.	40 ^c
i		n.d.	50
j		n.d.	49
k		n.d. ^a	37
l		37	44
m		29	50

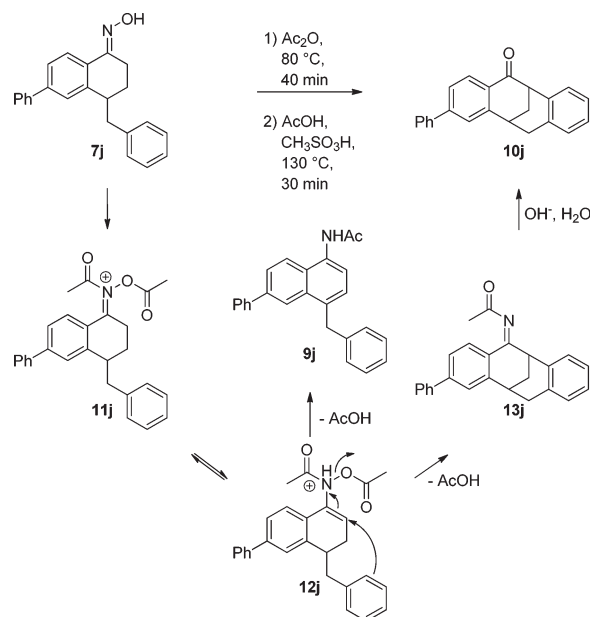
^aComplex mixture of byproducts. ^bTwo acetylated products: **10ci** ($R^3 = H$, $R^5 = \text{acetyl}$): **10cii** ($R^5 = H$, $R^3 = \text{acetyl}$) = 7:3. ^cAfter reacetylation of the crude product.

triacylated compounds along with noncharacterized degradation products.

A plausible mechanism accounting for the formation of tetracyclic derivatives **10** is displayed in Scheme 2 for the case of **10j**. The combination of acetic anhydride and methanesulfonic acid is sufficiently powerful to further acetylate oxime acetate **8** to give intermediate **11**, which is in equilibrium with enamide **12**. This reaction is almost certainly reversible and may not be complete. Enamide **12** normally would evolve into *N*-acetyl naphthylamide **9** by

the Semmler–Wolff/Schroeter reaction. However, the presence of a pendant aromatic ring opens up another reaction pathway involving a Friedel–Crafts reaction and leading to acetylimine **13**. Hydrolysis during a basic work-up would finally give rise to ketone **10**.

Scheme 2. Proposed Mechanism of the Electrophilic Aromatic Substitution Reaction



Evidence for such a pathway was obtained by modifying the workup procedure to avoid as much as possible the hydrolysis of intermediate **13j**. Thus, by diluting the crude reaction mixture with methanol, a very brief treatment with aqueous sodium bicarbonate followed by separation of the organic layer, drying, evaporation, and rapid chromatography furnished *N*-acetylamine **13j** in 34% yield.

The use of unsubstituted oximes as precursors of α -electrophiles in a C–C-bond formation process is unprecedented as far as we can tell. The closest analogy is in a very recent report by the group of Miyata, where reaction of a cyclic *N*-alkoxy enamine with trialkyl- or triaryl-aluminum reagents results in α -alkylation or α -arylation.¹¹

Tetracyclic frameworks such as those present in **10** are very rare. Two syntheses, depicted in Scheme 3, have been reported so far. Both rely on intramolecular Friedel–Crafts reactions. The first, by Roberts and co-workers,¹² involves generation of the requisite intermediate cation by a hydride transfer from tetralin **16** and furnishes 2,3:6,7-dibenzobicyclo[3.3.1]nona-2,6-diene **17**. The second, by Stetter and Reischl, hinges on a more classical double

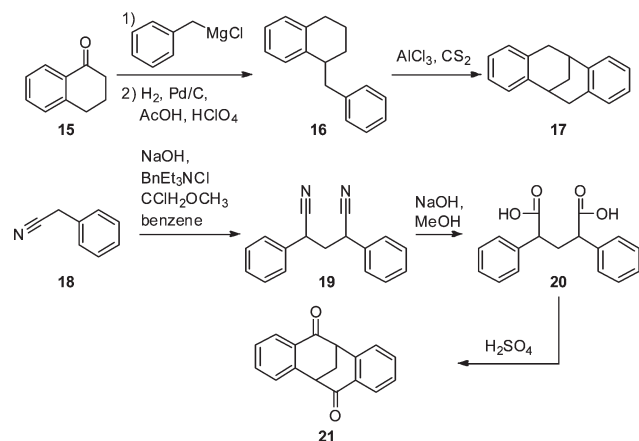
(11) Miyoshi, T.; Miyakawa, T.; Ueda, M.; Miyata, O. *Angew. Chem., Int. Ed.* **2011**, 50, 928.

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intramolecular Friedel–Crafts reaction to generate the central bicyclic scaffold in diketone **21**.¹³

Scheme 3. Synthetic Routes to Symmetric Tetracycles **3** and **7**



Despite the modest yields, due mostly to the existence of the competing normal Schroeter reaction, the present approach is short, convergent, and flexible. It allows a rapid entry to variously substituted tetracyclic ketones not readily accessible otherwise. But perhaps more importantly, this work brings to the fore an aspect of oxime reactivity hitherto unappreciated, and this could have more far reaching synthetic consequences.

Acknowledgment. We dedicate this paper with respect and admiration to Professor Andrew S. Kende (University of Rochester). We thank Ecole Polytechnique and SFERE for financial support to N.T. and S.N.Z.

Supporting Information Available. Experimental procedures, full spectroscopic data and copies of ¹H and ¹³C NMR spectra for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.