JOC Notes

Selective Opening of Ring C in the Morphine Skeleton by an Unexpected Cleavage of the C5−C6 Bond in Cycloadducts of Thebaine and Acyl Nitroso Compounds

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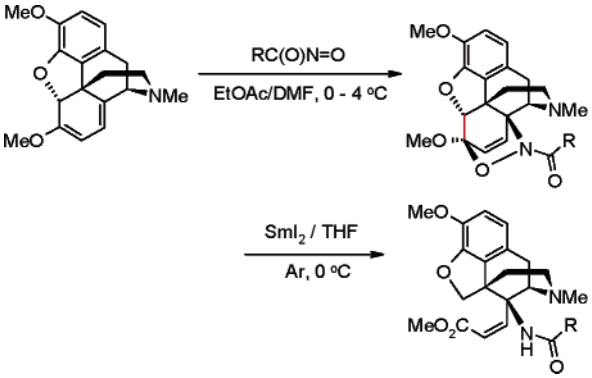

Acyl nitroso cycloadducts of the alkaloid thebaine undergo an unexpected cleavage of the C5−C6 bond when treated with 2 equiv of samarium(II) iodide in THF to give novel hexahydrobenzazocine products. A proposed mechanism for the transformation involves rearrangement of the initial radical anion.

Few areas of alkaloid chemistry have been studied as widely as the morphine skeleton in the search for more effective analgesics with fewer adverse side effects. In the huge body of reported work on the structural features of the morphine skeleton required for activity, hundreds of compounds have been prepared with one or more of the five rings (see Figure 1) systematically removed or modified, but very few examples have been reported in which only ring C is missing.

One successful route into the generation of novel morphine-like compounds has been via Diels−Alder cycloadditions of dienophiles with the alkaloid thebaine **1**. It has been shown that β-functionalization of the C14 position of thebaine can lead to compounds with greatly enhanced analgesic properties, for example, the oripavines **2** derived from the Diels−Alder reaction of thebaine with methyl vinyl ketone[1] (Scheme 1).

The cycloadditions of heterodienophiles with thebaine have also been studied, and the first examples of transient acyl nitroso compounds as dienophiles were reported by Kirby et al.[2] These hetero-Diels−Alder reactions are usually regioselective to give

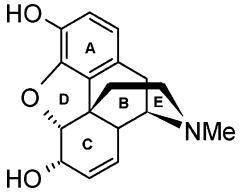

FIGURE 1. Morphine with conventional ring labeling.

the 5*O*-,14*N*-oxazine products **3** shown in Scheme 2. As expected, adducts of this type gave 14β-hydroxyamino substituted codeinones **4** under acid or base hydrolysis[3] or 14β-amino codeinones **5** with catalytic hydrogenation[4] (Scheme 2).

In this Note, we report that reduction of adducts such as **3** with 2 equiv of the single-electron reducing agent samarium(II) iodide follows a different and unexpected pathway resulting in cleavage of the C5−C6 bond.

A series of acyl nitroso dienophiles **7a**−**f** were generated in situ by the oxidation of the corresponding hydroxamic acids[5] **6a**−**f** with benzyltrimethylammonium periodate[6] in the presence of thebaine **1** as diene to give the adducts **8a**−**f** in good to excellent yields (Table 1). In each case, the only observed

TABLE 1. Yields of Thebaine Acyl Nitroso Diels−Alder Adducts 8 and Corresponding SmI_2 Reduction Products 9

entry	adduct	yield (%)	product	yield (%)
1	**8a**	71	**9a**	77
2	**8b**	61	**9b**	69
3	**8c**	31	**9c**	55
4	**8d**	38	**9d**	41
5	**8e**	90	**9e**	65
6	**8f**	95	**9f**	0[a]

[a] Complex mixture of products obtained, none of which could be identified as **9f**.

diastereoisomer was the 6β*O*-,14β*N*-adduct shown. Treatment of these adducts with two molar equivalents of samarium(II) iodide in THF[7] at 0 °C did not give the expected codeinones, but instead the major product in each case (except for **8f**) was

(1) Bentley, K. W.; Hardy, G. G.; Meek, B. *J. Am. Chem. Soc.* **1967**, *89*, 3273−3280.

(2) Kirby, G. W.; Sweeny, J. G. *J. Chem. Soc., Chem. Commun.* **1973**, 704−705.

(3) (a) Kirby, G. W.; McLean, D. *J. Chem. Soc., Perkin Trans. 1* **1985**, 1443−1446. (b) Kirby, G. W.; Sweeney, J. G. *J. Chem. Soc., Perkin Trans. 1* **1981**, 3250−3254. (c) Kirby, G. W.; McGuigan, H.; Mackinnon, J. W. M.; McLean, D. J.; Sharma, R. P. *J. Chem. Soc., Perkin Trans. 1* **1985**, 1437−1452. (d) Kirby, G. W.; Bladon, C. *J. Chem Soc., Chem Commun.* **1982**, 1402−1404. (e) Kirby, G. W.; Gourlay, R. I. *J. Chem. Res., Miniprint* **1997**, 1001−1020. (f) Schwab, L. S. *J. Med. Chem.* **1980**, 698−702.

(4) (a) Horsewood, P.; Kirby, G. W. *J. Chem. Soc., Perkin Trans. 1* **1980**, 1587−1591. (b) Sebastian, A.; Bidack, J. M.; Jiang, Q.; Deecher, D.; Teitler, M. *J. Med. Chem.* **1993**, 3154−3160.

(5) Benzohydroxamic acid **6a** was purchased from Aldrich; the other hydroxamic acids were prepared by standard methods from the corresponding carboxylic acids (Defoin, A.; Pires, J.; Streith, J. *Helv. Chim. Acta* **1991**, *74*, 1653−1670) or from carboxylate esters (Liguori, A.; Sindona, G.; Uccella, N. *Gazz. Chim. Ital.* **1986**, *116*, 377−380.

(6) Dang, H.-S.; Davies, A. G. *J. Chem. Soc., Perkin Trans. 2* **1991**, 721−734.

(7) We found freshly prepared SmI_2 in THF to be superior in performance to any of the commercially available solutions. SmI_2−THF was prepared according to the method of Kagan et al. (Girard, P.; Namy, J. L.; Kagan, H. B. *J. Am. Chem. Soc.* **1980**, *102*, 2693−2698).

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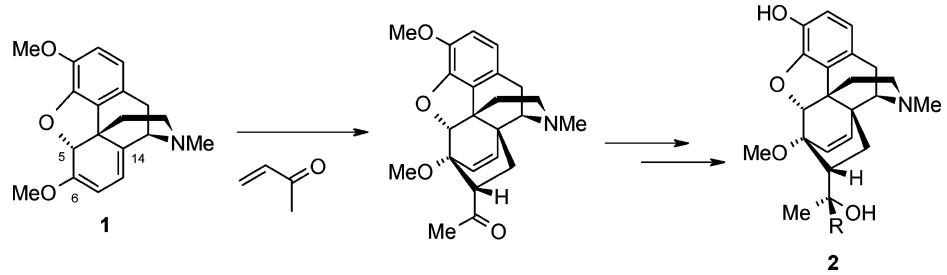
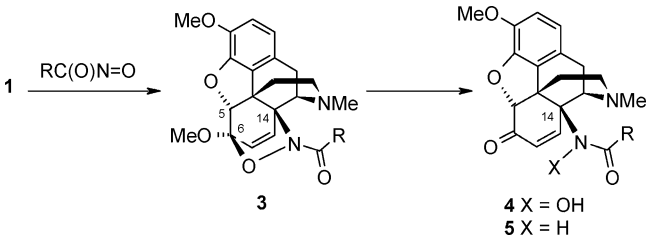
SCHEME 1. Synthesis of Oripavine Analgesics from Thebaine



SCHEME 2



the hexahydrobenzazocine product **9** in which C6 of the Diels−Alder adducts **8** has become the methyl ester carbonyl carbon and the C5−C6 bond has been cleaved (Scheme 3).

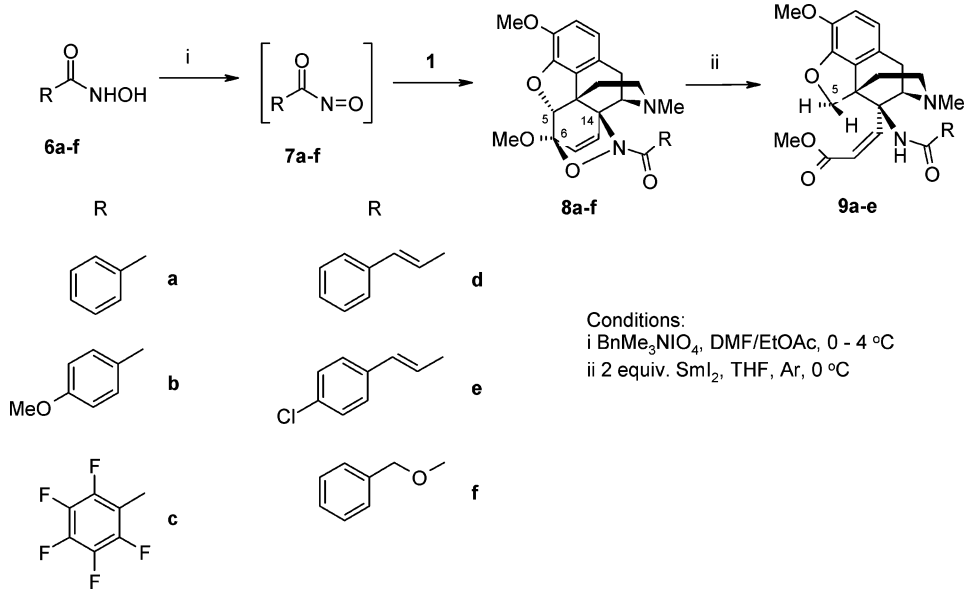
The assignment of the proposed structures for **9a**−**e** is clear from the ^{1}H and ^{13}C NMR spectra. In the ^{1}H NMR spectra, in each case the singlet for 5-H in the adducts **8** has been replaced by two coupled doublets corresponding to 5-Hα and 5-Hβ of the newly formed methylene group in the reduced hexahydrobenzazocine product **9**. Furthermore, in the ^{13}C NMR spectra, the signal for the acetal carbon (6-C) in the adducts has been replaced by an ester carbonyl signal in the product. Full spectroscopic data for **8a**−**f** and **9b**−**e** may be found in the Supporting Information.

We believe this to be an unprecedented transformation and are unaware of any other published examples of the *selective* opening of ring C of the morphine structure. A possible mechanism for this reaction becomes apparent when comparing the structural similarities between the thebaine adduct **8a** and the oxazine cycloadduct **10** (Scheme 4). We reported previously[8] that **10** undergoes a reductive rearrangement with SmI_2 to give a mixture of the cyclopentane **15** and the cyclobutane **16**. If the same initial steps apply to both cycloadducts, then it might be expected that the radical anions **11** and **12** produced by electron transfer from SmI_2 could fragment to give the intermediates **13** and **14**, respectively. The polycyclic skeleton of **13** lacks the conformational flexibility of the open chain intermediate **14**, and it is our proposal that the radical anion **13** is unable to undergo either of the ring closures observed for **14** but instead is reduced by a second equivalent of SmI_2, leading to the observed product **9a** after protonation. It appears that the conversion of **8** to **9** requires conjugation of the amide carbonyl group of the adduct to an aromatic ring either directly (Table 1, entries 1−3) or vinylagously (entries 4 and 5). When this conjugation is absent (entry 6), then the ring cleavage product is not observed. It is possible that this conjugation is necessary to stabilize the initial radical anion allowing the C−C bond cleavage to take place.

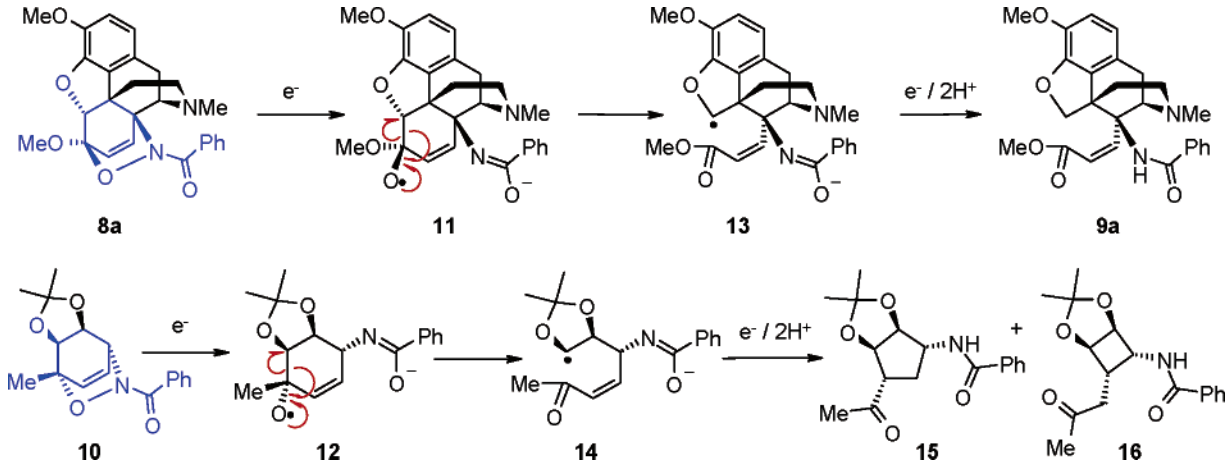
Experimental Section

General Procedure for the Reduction of Thebaine Acyl Nitroso Adducts with SmI_2. Freshly prepared 0.1 M samarium(II) iodide in dry THF[7] was added dropwise to the adduct (0.12 mmol) in dry THF (0.5 mL) under argon at 0 °C until a blue color just persisted (2.6 mL, 0.26 mmol). After 3 h, a 10% aqueous solution of 1:1 K_2CO_3/Rochelle salt[9] (1 mL) was added to the mixture, which was then extracted with EtOAc (3 × 2 mL). The organic phases were combined, washed with saturated brine (2 × 1 mL), dried ($MgSO_4$), and concentrated under reduced pressure

SCHEME 3



SCHEME 4



to give a crude product that was purified by preparative TLC using Et_2O/hexane (60:40) as eluant.

11*β*-Benzoylamino-11α-[*cis*-2-(methoxycarbonyl)ethenyl]-8-methoxy-3-methyl-1,2,3,4,5,6-hexahydro-6α,7-(methyleneoxy)-2,6-methano-3-benzazocine (9a). The pure product was obtained as an off-white solid in 77% yield (41.2 mg, 0.09 mmol); mp 138−140 °C; $[\alpha]_D$ +23.6 (*c* 1.3, CH_2Cl_2); IR (KBr): ν = 1203, 1478, 1507 (s), 1653, 1722, 2927, 3429 (br) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 1.56 (m, 1H), 2.01 (dt, J = 5.0, 12.7 Hz, 1H), 2.14 (dt, J = 3.7, 12.1 Hz, 1H), 2.35 (d, J = 5.0 Hz, 1H), 2.48 (s, 3H), 2.51 (dd, J = 18.3, 5.7 Hz, 1H), 3.06 (d, J = 18.6 Hz, 1H), 3.33 (s, 3H), 3.82 (s, 3H), 3.89 (d, J = 5.5 Hz, 1H), 4.29 (d, J = 10.1 Hz, 1H), 5.03 (d, J = 10.1 Hz, 1H), 5.75 (d, J = 12.6 Hz, 1H), 6.21 (d, J = 12.6 Hz, 1H), 6.57 (d, J = 8.0 Hz, 1H), 6.70 (d, J = 8.0 Hz, 1H), 7.41 (m, 3H), 7.77 (m, 2H), 7.83 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 20.0 (CH_2), 30.2 (CH_2), 42.0 (CH_3), 45.0 (CH_2), 47.9 (C), 50.3 (CH_3), 55.4 (CH_3), 57.8 (C), 62.1 (CH), 81.9 (CH_2), 112.8 (CH), 117.3 (CH), 120.6 (CH), 125.6 (C), 126.2 (CH), 127.5 (CH), 128.7 (C), 130.3 (CH), 133.6 (C), 140.9 (CH), 141.7 (C), 145.3 (C), 164.5 (C), 165.8 (C); MS (EI) *m*/*z* (relative intensity) 448 (M^+, 32), 230 (60), 105 (40), 97 (18), 86 (70), 84 (100), 77 (23), 69 (25), 57 (40), 47 (30), 43 (40). HRMS (EI): calcd for $C_{26}H_{28}N_2O_5$ 448.199822, found 448.200058.

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Supporting Information Available: General experimental details, complete experimental details and spectroscopic data for the thebaine acyl nitroso adducts **8a**−**f** and the hexahydrobenzazocine products **9b**−**e**, and NMR spectra for compounds **8a** and **9a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(8) McAuley, B. J.; Nieuwenhuyzen, M.; Sheldrake, G. N. *Org. Lett.* **2000**, *2*, 1457−1459.

(9) Rochelle salt is potassium sodium tartrate tetrahydrate.