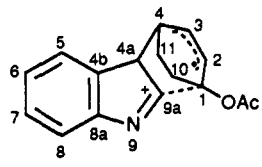
The small energy barrier against bond formation in the first step has to be viewed critically, because in high level (6-31G* and MP2/6-31G*//3-21G) calculations of model systems it has been established that this energy barrier leading to the long bond intermediate vanishes with increasing level of computational rigour.[18] However, from Figure 1, the reaction has to be classified as nonsynchronous-nonconcerted.

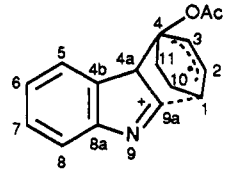
Finally, we examined the regioselectivity of the reaction (Scheme II). As a test system, we chose the reaction of 1 and acetoxy-1,3-cyclohexadienes (**2b** and **2c**) under the PET conditions as in Scheme I.

According to the previous results, we only examined the attack on the 3-position. For the possible regioisomers of the reaction, the calculations were performed as discussed before. Starting from the two possible intermediates **9** (▲) and **10** (■) of reaction b, the MERP is shown in Figure 2.



9

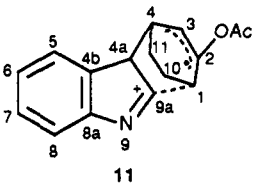
ΔH_f = 142.5 kcal/mol



10

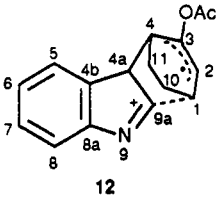
ΔH_f = 150.9 kcal/mol

Again, the MERP is in excellent agreement with the experimental results. The calculated ΔH_f for the intermediate **9** leading to the exclusively observed product **8** is 9.3 kcal/mol more favorable than that of the regioisomer **10**, hence describing the regioselectivity of the reaction correctly. Also in the very similar case of the reaction of



11

ΔH_f = 155.8 kcal/mol



12

ΔH_f = 143.2 kcal/mol

1 and **2b** (reaction a), the intermediate **11** leading to the exclusively observed product **7** is 12.5 kcal/mol more stable than its regioisomer **12**.

In conclusion, the results of the calculations are in good agreement with the experimental results and the mechanism we proposed earlier.[4] Though the approximation of free, unsolvatized radical cations is made, the regioselectivity and the influences of substituents in the 2- or 3-position are described properly. On the basis of experimental results and calculations, the reaction is nonsynchronous-nonconcerted, involving a relatively stable intermediate.

Acknowledgment. The calculations were performed at the Institut für Physikalische und Theoretische Chemie and the Regionales Hochschulrechenzentrum der Universität Bonn. Financial support by the Deutsche Forschungsgemeinschaft (Ste 227\14-2), the Fonds der Chemischen Industrie, and the BASF Aktiengesellschaft is gratefully acknowledged. We like to thank Dipl. Chem. P. Bündgen (Fredericton) and Dipl. Chem. P. M. Windscheif (Bonn) for helpful discussions.

Registry No. 1, 120-72-9; $1^{\bullet+}$, 57212-28-9; **2b**, 93914-93-3; **2c**, 74502-18-4; **5**, 141583-21-3; **6**, 141583-22-4; **9**, 141583-23-5; **10**, 141583-24-6; **11**, 141583-25-7; **12**, 141583-26-8.

(18) Bellville, D. J.; Bauld, N. L. *Tetrahedron* **1986**, *42*, 6167.

Supplementary Material Available: The Z-matrices of the fully optimized AM1 calculations of the intermediates $1^{+\bullet}$, **5**, **6**, and **9–12** (9 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

Amide to Ester Conversion: A Practical Route to the Carfentanil Class of Analgetics

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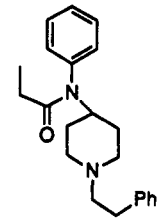
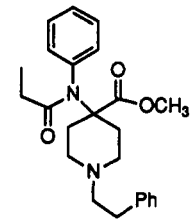
The 4-anilidopiperidine opioid analogues, exemplified by fentanyl (**1**), are widely used in analgetic therapy.[2] While **1** is readily prepared, the 4-alkyl analogues, such as carfentanil (**2**), have been more difficult.[3] Especially, the conversion of nitrile **4** to ester **6** (Scheme I) has been plagued by low yields. We report a simple solution to this problem, the key to which is the direct conversion of an amide to the corresponding methyl ester.[4]



1



2

The first step in the synthesis (Scheme I) in Strecker addition of aniline and HCN to *N*-benzyl-4-piperidone **3**. While the direct reaction works fairly well, the use of trimethylsilyl cyanide has been recommended[3a] for this step. As a less expensive alternative, we have found that *sonication*[5] of the aniline/HCN addition significantly enhances the yield.

(1) Permanent address: Department of Chemistry, Mashhad University, Mashhad, Iran.

(2) For an overview of the analgetic activity of these piperidine derivatives, see: Jaffe, J. H.; Martin, W. R. In *The Pharmacological Basis of Therapeutics*, 6th ed.; Gilman, A. G., Goodman, L. S., Gilman, A., Eds.; Macmillan: New York, 1980; pp 513–518.

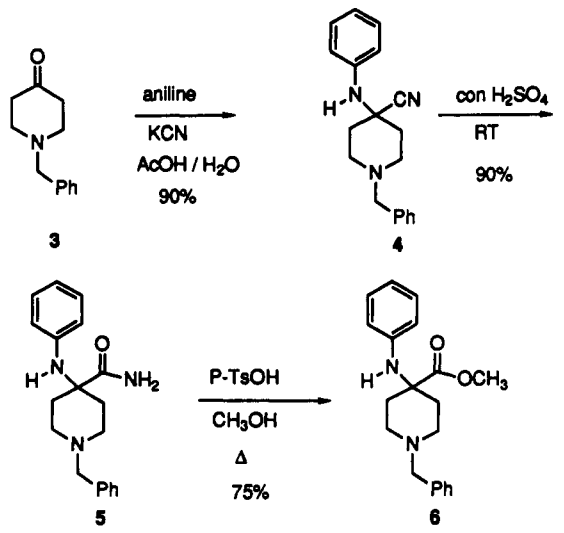
(3) For recent synthetic approaches to this class of analgetics, see the following. (a) Feldman, P. L.; Brackeen, M. F. *J. Org. Chem.* **1990**, *55*, 4207. (b) Colapret, J. A.; Diamantidis, G.; Spencer, H. K.; Spaulding, T. C.; Rudo, F. G. *J. Med. Chem.* **1989**, *32*, 1968. (c) Bagley, J. R.; Wynn, R. L.; Rudo, F. G.; Doorley, B. M.; Spencer, H. K.; Spaulding, T. *J. Med. Chem.* **1989**, *32*, 663. (d) Casey, A. F.; Huckstep, M. R. *J. Pharm. Pharmacol.* **1988**, *40*, 605. (e) Janssens, F.; Torremans, J.; Janssen, P. A. *J. Med. Chem.* **1986**, *29*, 2290. (f) Van Daele, P. G. H.; DeBruyn, M. F. L.; Boey, J. M.; Sanczuk, S.; Agten, J. T. M.; Janssen, P. A. *J. Arzeneim.-Forsch. Drug. Res.* **1976**, *26*, 1521. (g) Van Beaver, W. F. M.; Niemegeers, C. J. F.; Janssen, P. A. *J. Med. Chem.* **1974**, *17*, 1047. (h) Kudzma, L. V.; Severnak, S. A.; Benvenga, M. J.; Ezell, E. F.; Ossipov, M. H.; Knight, V. V.; Rudo, F. G.; Spencer, H. K.; Spaulding, T. *J. Med. Chem.* **1989**, *32*, 2534.

(4) Four procedures have previously been reported for effecting this transformation. (a) HCl/EtOH: Bobbit, J. M.; Scola, D. A. *J. Org. Chem.* **1960**, *25*, 560. (b) $BF_3{\cdot}Et_2O/CH_3OH$: Hamilton, D. J.; Price, M. J. *J. Chem. Soc., Chem. Commun.* **1969**, 414. (c) Sulfonic acid resin/CH_3OH: Greenlee, W. J.; Thorsett, E. D. *J. Org. Chem.* **1981**, *46*, 5351. (d) $Cu(ClO_4)_2/CH_3OH$: Nanjappan, P.; Czarnik, A. M. *J. Am. Chem. Soc.* **1987**, *109*, 1826.

(5) Menendez, J. C.; Trigo, G. G.; Sollhuber, M. M. *Tetrahedron Lett.* **1986**, *27*, 3285.

0022-3263/92/1957-4037$03.00/0

Scheme I



Methanolysis of the nitrile would be the most direct way to convert **4** to **6**. We and others[3] have found, however, that while some **6** is formed, the dominant products from such attempts derive from reversal of the Strecker addition. The alternative has been[3] hydrolysis to the difficult-to-handle amino acid, followed by methylation of the carboxylate salt. The esterification is a competition between O-methylation and N-methylation, resulting in mediocre yields.

There are scattered reports[4] of the direct alcoholysis of amides to the corresponding methyl esters. After some experimentation, we found that *p*-toluenesulfonic acid monohydrate gave the cleanest conversion of **5** to **6**. The reaction, slow in refluxing methanol, is best run in a sealed bottle. The optimal temperature for the conversion of **5** to **6** is 105 °C, at which temperature the reaction takes 36 h. We expect that less hindered amides will react more rapidly. (**CAUTION**: A volatile material, presumably dimethyl ether,[4b] is formed during the methanolysis. The reaction should be run behind a shield, and pressure bottles should be opened slowly, after cooling.)

With these modifications, ester **6**, the key intermediate for the synthesis of carfentanil (**2**), is available in 61% overall yield from *N*-benzyl-4-piperidone (**3**).

Experimental Section

4-(Phenylamino)-1-(phenylmethyl)-4-piperidinecarbonitrile (4). A mixture of 1-benzyl-4-piperidone (**3**) (17.01 g, 90 mmol), KCN (14.64 g, 225 mmol), aniline (12.57 g, 135 mmol), acetic acid (450 mL), and water (75 mL) was maintained at 45 °C with irradiation from an ultrasonic cleaning bath, for 45 h. The mixture was cooled and then poured over 200 g of ice in 600 mL of concentrated aqueous NH_4OH. An additional 15 mL of NH_4OH was added to complete neutralization (pH = 7 by pH paper). The mixture was extracted with $CHCl_3$ (3 × 150 mL), and the combined extracts were dried (Na_2SO_4), filtered, and evaporated. The residue was crystallized from Et_2O to give nitrile **4** as a white solid (23.7 g, 90%), mp = 145–146 °C (lit.[3] mp = 145–146 °C).

4-(Phenylamino)-1-(phenylmethyl)-4-piperidinecarboxamide (5). Nitrile **4** (15.0 g, 51.5 mmol) was added portionwise to 400 mL of concentrated H_2SO_4 at rt. After 48 h the mixture was cooled and then added slowly to 400 g of ice in 1300 mL of concentrated aqueous NH_4OH. The resultant white precipitate was filtered, washed with water, and vacuum dried to give amide **5** (14.35 g, 90%), mp = 190–191 °C. ^1H NMR (δ): 7.38–7.22 (m, 5 H); 7.19 (t, 2 H, J = 7.7 Hz); 6.87 (bs, 1 H); 6.80 (t, 1 H, J = 7.5 Hz); 6.63 (d, 2 H, J = 7.7 Hz); 5.43 (bs, 1 H); 4.02 (s, 1 H); 3.48 (s, 2 H); 2.74 (dt, 2 H, J = 12.1, 2.1 Hz); 2.31 (dt, 2 H, J = 3.9, 12.6 Hz); 2.10 (dt, 2 H, J = 2.0, 11.9 Hz); 1.92 (bd, 2 H, J = 12.2 Hz). ^{13}C NMR (δ): 178.7, 144.0, 138.5, 129.4, 129.2, 128.4, 127.3, 119.5, 116.4, 63.2, 58.5, 49.0, 31.7; MS (*m*/*z*, rel intensity): 309 (17.6), 266 (9.7), 265 (62.5), 264 (100), 216 (54.6), 172 (28.4).

Methyl 4-(Phenylamino)-1-(phenylmethyl)-4-piperidinecarboxylate (6). Amide **5** (4.65 g, 15.0 mmol), *p*-toluenesulfonic acid monohydrate (10.0 g, 52 mmol), and methanol (55 mL) were sealed in a glass pressure vessel and maintained at 105 °C (internal) for 36 h. (**CAUTION**: PRESSURE BUILD-UP! The reaction should be run behind a shield.) The vessel was cooled and vented. The solvent was evaporated, the residue was taken to pH = 8 (pH paper) with concentrated aqueous NH_4OH, and the mixture was extracted with ethyl acetate (3 × 100 mL). The combined organic extracts were dried (Na_2SO_4), evaporated, and chromatographed on silica gel to give 3.63 g (75%) of ester **6**, TLC R_f = 0.64 (10% CH_3OH/CH_2Cl_2), as a clear viscous oil. On standing in the refrigerator and seeding, this material crystallized, mp = 80–80.5 °C (lit.[3f] mp = 80.5 °C). The ^{13}C and ^1H NMR spectra for **6** are identical with those recently reported,[3a] with the exception that the peak at 3.56 (5, 3 H) cited should be 3.56 (s, 3 H).

Acknowledgment. We thank CRDEC/Aberdeen and the donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this work. We thank Dr. John A. Colapret for sharing with us his procedure for the conversion of **4** to **5**. M.R. thanks the University of Mashhad for a sabbatical leave.

Registry No. **2**, 59708-52-0; **3**, 3612-20-2; **4**, 968-86-5; **5**, 1096-03-3; **6**, 61085-60-7; aniline, 62-53-3.

(6) A general experimental procedure was recently published: Taber, D. F.; Hoerrner, R. S.; Hagen, M. D. *J. Org. Chem.* **1991**, *56*, 1287.

The Tautomerism of a Phosphono Enamine

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The Emmons reaction, a popular modification of the Wittig reaction because of the ease of removal of the water-soluble byproducts, typically involves the formation of a diethoxyphosphono intermediate such as **1**. This is converted by a strong base to an anion and treated with a ketone or aldehyde to provide the desired olefin from the elimination of a more oxygenated phosphorus species. We have used such an approach in the synthesis of unsaturated 1-pyrrolines, **2**, identified in the venom of the ant *Megalomyrmex foreli*.[1] Thus, the butylpyrroline phosphonate intermediate **3** was readily prepared by phosphonylation of the anion of the corresponding 2-methyl-1-pyrroline under conditions of kinetic control. The Emmons product of this material and hexanal or 2-hexenal produced the required venom alkaloids, **2**.

Several groups preparing phosphono intermediates with a nitrogen substituent have characterized them with divergent results. Russian and American groups have prepared examples corresponding to **4** and **5**, with the proportions of the *E* and *Z* isomers varying with various substituents.[2] In light of the observations below, it is

(1) Jones, T. H.; DeVries, P. J.; Escoubas, P. *J. Chem. Ecol.* **1991**, *17*, 2507.

(2) (a) Chattha, M. S.; Aguiar, A. M. *J. Org. Chem.* **1973**, *38*, 820. (b) Alikin, A. Y.; Liorber, B. G.; Sokolov, M. P.; Razumov, A. I.; Zykova, T. V.; Salakhutdinov, R. A. *Z. Obsch. Khim.* **1982**, *52*, 316.