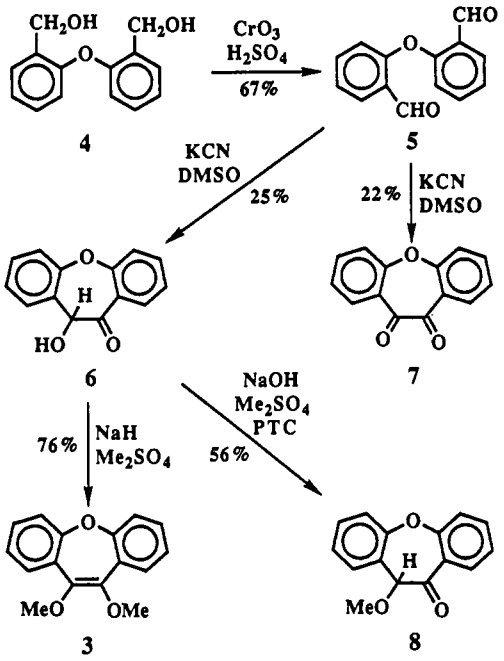
Scheme I



Bis(2-formylphenyl) Ether (5). A solution of CrO_3 (10 g, 0.1 mol) in 2 N H_2SO_4 (200 mL) was added dropwise over 30 min to a solution of compound 4[14a] (11.5 g, 50 mmol) in acetone (200 mL) at 0 °C under N_2. After the addition, the mixture was stirred for a further 15 min and was then quenched by addition of 2-propanol (15 mL). After 15 min, solid $NaHCO_3$ (14 g) was added, and the mixture was filtered through a sintered-glass filter. The filtrate was concentrated under vacuum and the residue was chromatographed on a silica gel column (100 g, hexanes/ethyl acetate 4:1) to give compound 5 (7.5 g, 67%), mp 77–77.5 °C [lit.[16b] mp 74 °C]: ^{1}H-NMR δ 6.96 (d, J = 8.3 Hz, 2 H), 7.31 (m, 2 H), 7.59 (m, 2 H), 8.00 (dd, J_1 = 7.8 Hz, J_2 = 1.8 Hz, 2 H), 10.51 (s, 2 H); ^{13}C-NMR δ 119.02 (CH), 124.43 (CH), 127.37 (C), 129.21 (CH), 135.78 (CH), 158.73 (C), 188.24 (CH); MS (EI) m/e 226 (M^+). Anal. Calcd for $C_{14}H_{10}O_3$: C, 74.33; H, 4.46. Found: C, 74.69; H, 4.51.

10,11-Dihydro-11-hydroxydibenz[*b*,*f*]oxepin-10(11*H*)-one (6) and 10,11-Dihydrodibenz[*b*,*f*]oxepin-10,11-dione (7). To a solution of compound 5 (1.78 g, 7.5 mmol) in DMSO (3 mL) was added KCN (0.2 g, 3 mmol) under N_2. The mixture was stirred at rt for 4 h and was then filtered through a silica gel column (50 g, 70–230 mesh, hexanes/ethyl acetate 3:2) to give a crude mixture of 6 and 7 after evaporation. The crude mixture of 6 and 7 was purified by chromatography on a silica gel column (50 g, hexanes/ethyl acetate 4:1) to afford 6 (0.42 g, 25%) and 7 (0.12 g, 6%), respectively. However, the yields of 6 and 7 were 4% and 22%, respectively, when the reaction was carried out for 20 h and 7.5 mmol of 5 and 6 mmol of KCN were used. Compound 6: yellowish solid, mp 79–81 °C. Compound 7: yellowish solid, mp 114–116 °C [lit.[17a] mp 119 °C].

^{1}H-NMR (6): δ 5.84 (s, 1 H), 7.15 (m, 1 H), 7.22 (m, 3 H), 7.36 (m, 1 H), 7.52 (m, 1 H), 7.3 (m, 1 H), 8.09 (m, 1 H). ^{13}C-NMR (6): δ 75.37 (CH), 120.12 (CH), 121.71 (CH), 123.50 (C), 124.09 (CH), 125.35 (CH), 126.54 (CH), 128.86 (CH), 130.24 (C), 130.82 (CH), 135.88 (CH), 154.32 (C), 160.52 (C), 191.68 (C). MS (EI): m/e 226 (M^+) (6). Anal. Calcd for $C_{14}H_{10}O_3$: C, 74.33; H, 4.46. Found: C, 74.28; H, 4.37.

^{1}H-NMR (7): δ 7.32 (m, 2 H), 7.42 (d, J = 8.2 Hz, 2 H), 7.66 (ABX, J_1 = 8.2 Hz, J_2 = 7.9 Hz, J_3 = 1.7 Hz, 2 H), 7.99 (dd, J_1 = 7.9 Hz, J_2 = 1.7 Hz, 2 H). ^{13}C-NMR (7): δ 121.72 (CH), 125.60 (CH), 126.32 (C), 131.80 (CH), 135.83 (CH), 156.97 (C), 186.53 (C). MS (EI): m/e 224 (M^+) (7). Anal. Calcd for $C_{14}H_8O_3$: C, 74.99; H, 3.59. Found: C, 74.75; H, 3.51.

10,11-Dihydro-11-methoxydibenz[*b*,*f*]oxepin-10(11*H*)-one (8). To a solution of 6 (226 mg, 1 mmol) in THF (5 mL) were added methyltrioctylammonium chloride (2 drops) and a solution of NaOH (170 mg, 4 mmol) in water (0.7 mL) under N_2. To the resulting mixture was added dimethyl sulfate (285 μL, 3 mmol). The mixture was stirred at rt under N_2 for 20 h. $CHCl_3$ (30 mL) was added and the organic layer was washed with water (2 × 5 mL) and dried (Na_2SO_4). The solvent was removed under vacuum and the residue was chromatographed on a silica gel column (30 g, hexanes/ethyl acetate 2:1) to give 8 (136 mg, 56%), mp 179–181 °C: ^{1}H-NMR δ 3.59 (s, 3 H), 5.33 (d, J = 1 Hz, 1 H), 7.16 (m, 4 H), 7.36 (m, 2 H), 7.49 (dd, J_1 = 7.3 Hz, J_2 = 0.8 Hz, 2 H); ^{13}C-NMR δ 53.78 (CH_3), 70.14 (CH), 116.90 (CH), 122.15 (C), 123.49 (CH), 126.76 (CH), 129.95 (CH), 150.50 (C), 174.98 (C); MS (EI) m/e 240 (M^+). Anal. Calcd for $C_{15}H_{12}O_3$: C, 74.99; H, 5.03. Found: C, 74.21; H, 5.26.

10,11-Dimethoxydibenz[*b*,*f*]oxepin (3). To a solution of compound 6 (226 mg, 1 mmol) in THF (5 mL) were added NaH (72 mg, 3 mmol) and dimethyl sulfate (315 mg, 0.24 mL, 2.5 mmol). The mixture was stirred at rt under N_2 for 4 h. The mixture was then diluted with $CHCl_3$ (30 mL). The organic layer was washed with water (2 × 5 mL) and dried (Na_2SO_4). The solvent was removed under vacuum and the residue was chromatographed on a silica gel column (50 g, hexanes/ethyl acetate 4:1) to afford compound 3 as an oil (195 mg, 76%): ^{1}H-NMR δ 3.80 (s, 6 H), 7.15 (m, 4 H), 7.30 (ABX, J_1 = 7.95 Hz, J_2 = 7.66 Hz, J_3 = 1.81 Hz, 2 H), 7.50 (dd, J_1 = 7.66 Hz, J_2 = 1.81 Hz, 2 H); ^{13}C-NMR δ 60.26 (CH_3), 120.89 (CH), 124.87 (CH), 126.94 (CH), 127.5 (C), 129.73 (CH), 143.98 (C), 157.54 (C); MS (EI) m/e 254 (M^+). Anal. Calcd for $C_{16}H_{14}O_3$: C, 75.58; H, 5.55. Found: C, 75.15; H, 5.60.

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Registry No. 3, 141511-32-2; 4, 10038-40-1; 5, 49590-51-4; 6, 141511-33-3; 7, 68978-15-4; 8, 141511-34-4.

Supplementary Material Available: ^{1}H- and ^{13}C-NMR spectra of 3, 11, 12, and 13 (8 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.

Selectivity in Radical-Cation Diels–Alder Reactions of Indole and Electron-Rich Dienes: A Semiempirical Approach

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Introduction

The use of cation radicals in organic chemistry is a field of increasing interest. During the last decade, particularly the radical-cation Diels–Alder reaction[1] has been the subject of many mechanistic/theoretical[2] and preparative investigations.[3] The typical features of this reaction are the increase of reaction rates by several orders of magnitude over these of the neutral reaction coupled with a high regio- and chemoselectivity. Therefore it is a promising tool for organic synthesis. The methods of computational chemistry and MO theory have been highly successful in studies of normal Diels–Alder reactions, so it is not astonishing that for radical-cation cycloadditions, quantum

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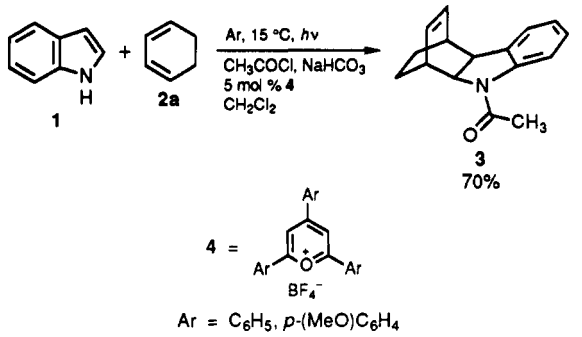
Scheme I



chemical methods have also been used. In these studies, a nonsynchronous, concerted reaction path was calculated. Together with kinetic studies, these methods have proven to be of value in getting insight into the mechanism of this reaction.[2] Up to now, most mechanistic/theoretical studies of the radical-cation Diels–Alder reaction are, however, dealing with simple hydrocarbon compounds.

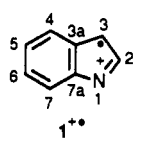
Recently, we reported[4] the use of indole as the electron-rich dienophile in the [4 + 1] cycloaddition with electron-rich dienes catalyzed by photochemically induced electron transfer (PET). As catalyst, triarylpyrylium tetrafluoroborates 4 are used. In most cases, the reaction proceeds with complete regioselectivity, such that a substituent in the 1-position of the diene is found in the 1-position of the tetrahydrocarbazole, whereas a substituent in the 2-position appears in the 3-position of the product. Substituted indoles were relatively unreactive. In this paper, we report the results of a semiempirical study on the features of this reaction (Scheme I).

Method

All calculations were carried out with the AM1-UHF[5] method as implemented in the MNDO89 program.[6] In previous studies, this method has proven to be suitable for predicting the properties of heterocyclic compounds[7] and charged radicals[8] as well as the potential surface for different types of reactions. The geometries of the starting materials and the intermediates were fully optimized using the Broyden–Fletcher–Goldfarb–Shanno (BFGS) algorithm. For the minimum energy reaction pathways (MERP), the C–H bond length and angles in the benzene part of the indole nucleus were kept constant. For the indole radical cation, additional ab initio calculations at the STO-3G-UHF level with the same assumptions were carried out using the GAUSSIAN86 package.[9]

Results and Discussion

The experimental results[4] strongly suggest that only indole is oxidized to its radical cation under the reaction conditions. This is in agreement with the oxidation potential of indole (1.36 V vs NHE), being the lowest in the reaction mixture. Thus, we made the assumption of a free indole radical cation, although the real situation may be more complicated. It will be shown that the main features of the reaction are described correctly by these gas-phase calculations. In Table I, selected results of the semiempirical and ab initio calculations of the indole radical cation are shown. On the basis of these results, the structure of $1^{+\bullet}$ can be represented as shown.



$1^{+\bullet}$

The results of both methods are comparable, showing that $1^{+\bullet}$ is planar with a high positive charge density in the 2-position and the radical character localized in the 3-position. An analysis of the molecular orbital interaction between $1^{+\bullet}$ and the diene within the framework of the frontier molecular orbital theory is not applicable to doublet species because the influence of the singly occupied molecular orbital (SOMO)[10] is difficult to predict. For this reason, such an analysis has been omitted. The differing electronic properties of C_2 and C_3 suggest a nonsynchronous reaction path, a mechanism which is also supported by the calculations of Bauld et al.[2,12] Consequently, the question is whether or not the initial bond is formed in the 2-position or in the 3-position of $1^{+\bullet}$, which leads to the

Table I. Results of AM1 and ab Initio Calculations on $1^{+\bullet}$: Geometric and Electronic Parameters of the Reactive Centers

parameter[a]	AM1-UHF	STO3G-UHF
$R(N_1–C_2)$	134.5	132.3
$R(C_2–C_3)$	146.8	147.9
$R(C_3–C_{3a})$	141.3	141.8
$R(C_{7a}–N_1)$	143.4	144.3
$\alpha(N_1–C_2–C_3)$	110.1	109.4
$\alpha(C_2–C_3–C_{3a})$	106.5	105.5
P_2	0.3173	0.3866
P_3	0.1537	0.1512
Q_2	0.130	0.297
Q_3	0.562	0.770

[a] R = bond length in pm, α = bond angles in degree, P_i = charge density at carbon i with the values for hydrogen summed into the heavy atoms, Q_i = spin density at carbon i.

Table II. Results of the AM1 Calculation for the Intermediates 5 and 6: Geometric and Electronic Parameters

parameter[a]	5	6
ΔH_f [kcal/mol]	234.7	224.3
$R(C_1–C_{9a})$	154.5	372
$R(C_4–C_{4a})$	374	153.2
$R(C_{8a}–C_9)$	134.9	143.4
$R(C_9–C_{9a})$	148.3	132.6
$R(C_{9a}–C_{4a})$	151.8	152.7
$R(C_{4a}–C_{4b})$	138.5	150.8
P_4	−0.154	−0.052
P_{8a}	0.162	−0.078
P_9	−0.176	−0.059
P_{9a}	−0.014	0.111
Q_1	−0.072	0.804
Q_2	0.801	−0.539
Q_3	−0.527	0.808
Q_4	0.800	−0.066
S^2	1.472	1.018

[a] R, P, and Q, same as in Table I.

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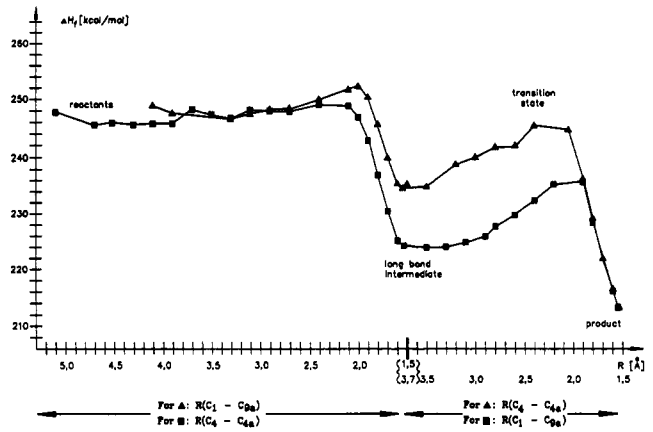
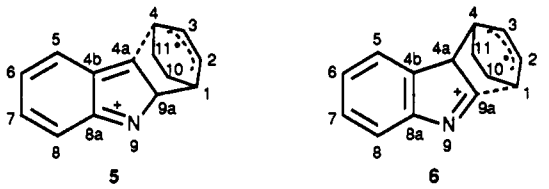


Figure 1. MERP for reaction 1: (▲) MERP for attack in the 2-position of $1^{+\bullet}$ (intermediate **5**); (■) MERP for attack in the 3-position of $1^{+\bullet}$ (intermediate **6**).

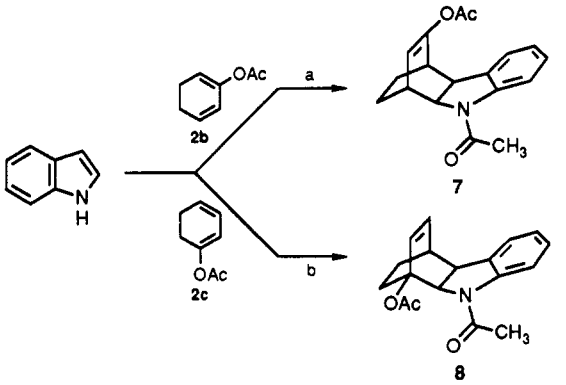
two different intermediates **5** and **6**, respectively. In Table II, selected results[11] of the AM1 calculation for the two intermediates are shown.



5 **6**

The distance between C_4 and C_{4a} in **5** and analogously between C_1 and C_{9a} in **6** (374 and 372 pm, respectively) is much shorter than expected and similar to the distances in the "long bond complex" Bauld et al. found in semiempirical and ab initio calculations of the [3 + 2] cation-radical cycloaddition,[12] which leads to a comparable intermediate. Also in several other processes involving radical cations, long bond intermediates have been calculated.[13] It is not clear whether or not these intermediates are the same as those detected by mass spectroscopic[14] and CIDNP[15] techniques. The long bond complex **6** shows obviously a weak interaction between C_1 and C_{9a}, overcoming the steric repulsion. Hence, the preorientation of the cyclohexenyl ring system towards the reaction center C_{9a} with contact of the van der Waals spheres of C_1 and C_{9a} represents a minimum on the potential surface. The results for the heat of formation suggest that the reaction proceeds via attack of **2a** in the 3-position of $1^{+\bullet}$, forming the intermediate **6** which is 10.4 kcal/mol more stable than **5** (Table II). To get further information on this behavior, we calculated the reaction paths for the two differing attacks of diene **2a** and $1^{+\bullet}$. The reaction proceeds via the approach of the reactive centers C_1–C_{9a} and C_4–C_{4a}. Therefore, we defined $R(C_1–C_{9a})$ and $R(C_4–C_{4a})$ as reaction coordinates, assuming that they describe the MERP correctly. For modeling of the attack in the 2-position (▲ in Figure 1), we started from **5** and successively elongated $R(C_1–C_{9a})$ under optimization of $R(C_4–C_{4a})$ towards the free reactants $1^{+\bullet}$ and **2a** (left part of Figure 1). Towards

Scheme II. Reaction of 1 with Acetoxy-1,3-cyclohexadienes under PET Conditions



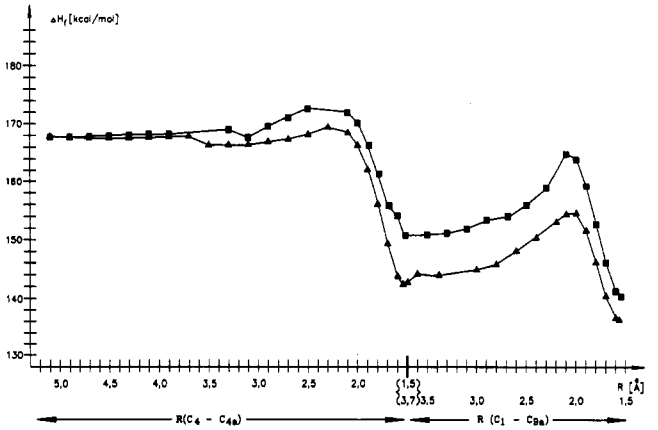


Figure 2. MERP for reaction 2b: (▲) MERP for attack in the 4-position of diene **2c** (intermediate **9**); (■) MERP for attack in the 1-position of diene **2c** (intermediate **10**).

product **3**, $R(C_4–C_{4a})$ was shortened under optimization of $R(C_1–C_{9a})$ (right part of Figure 1). However, during this second step no significant changes in $R(C_1–C_{9a})$ occur. The energy profile for the attack in the 3-position (■ in Figure 1) was calculated analogously starting from **6** by elongation of $R(C_4–C_{4a})$ towards the reactants and shortening of $R(C_1–C_{9a})$ towards product **3**.

From these results, it seems clear that the reaction proceeds via initial attack in the 3-position of $1^{+\bullet}$ because of the more favorable delocalization in **6**, leading to a immonium ion/allyl radical intermediate. The energy barrier for the second step from intermediate **6** to product **3** (18 kcal/mol) is significantly higher than that calculated for the dimerization of 1,3-butadiene (7.9 kcal/mol)[16] and other hydrocarbon compounds.[12] This is a result of the favorable charge delocalization in the immonium ion intermediate. The existence of a relatively stable intermediate having the structure **6** is also supported by our experimental findings[4] that any substitution of the 2-position of **1** inhibits the reaction completely whereas in the case of 3-substitution products were formed in low yield. In these cases, the weak C_1–C_{9a} interaction in the long bond complex **5** is not strong enough to overcome the steric repulsion in the second step of the reaction.[17] In the corresponding case of a 3-substitution the C_4–C_{4a} bond is strong enough to compensate for the steric repulsion in the first step.

(11) The value for S^2 is considerably higher than the expectation value, indicating the participation of higher states. This has, however, no influence on the results. For a discussion of the UHF approach for open shell species, see, e.g.: Dewar, M. J. S.; Olivella, S.; Stewart, J. J. P. *J. Am. Chem. Soc.* **1986**, *108*, 5771 and ref. 8.

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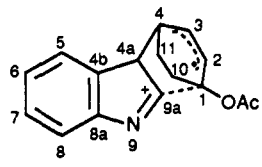
(17) Accordingly, in the calculation of the transition state derived from 2-methylindole and **2**, the relative orientation of the ring systems is changed in a way that $R(C_1–C_{9a})$ is increased.

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.

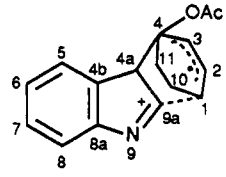
Finally, we examined the regioselectivity of the reaction (Scheme II). As a test system, we chose the reaction of 1 and acetoxy-1,3-cyclohexadienes (**2b** and **2c**) under the PET conditions as in Scheme I.

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

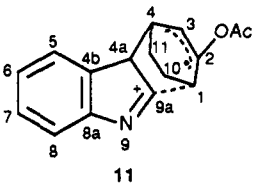
ΔH_f = 142.5 kcal/mol



10

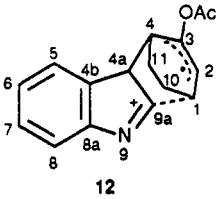
ΔH_f = 150.9 kcal/mol

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.

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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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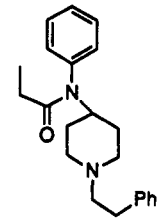
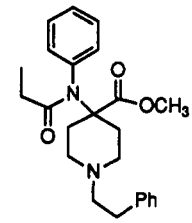
The 4-anilidopiperidine opioid analogues, exemplified by fentanyl (**1**), are widely used in analgetic therapy.[2] While **1** is readily prepared, the 4-alkyl analogues, such as carfentanil (**2**), have been more difficult.[3] Especially, the conversion of nitrile **4** to ester **6** (Scheme I) has 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.

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(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.

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