Bicyclic Imides with Bridgehead Nitrogen. Synthesis of an Anti-Bredt Bicyclic Hydantoin

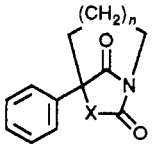
M. Shamim Akhtar, Wayne J. Brouillette,* and D. Vincent Waterhous

Department of Chemistry, University of Alabama at Birmingham, Birmingham, Alabama 35294

Received January 11, 1990

The first synthesis of an anti-Bredt bicyclic hydantoin containing an imide bridghead nitrogen was accomplished. In this procedure 3-bromo-ϵ-caprolactam (**14**) was converted to 3-cyano-ϵ-caprolactam (**15**). A key reaction was the phenylation of **15** using Ph_5Bi to provide 3-cyano-3-phenyl-ϵ-caprolactam (**18**), although limitations of this procedure were revealed by unsuccessful efforts with closely related structures. Nitrile **18** was hydrolyzed to the 3-carboxamide **20**, which underwent a Hofmann rearrangement in the presence of $Pb(OAc)_4$ and 2,6-lutidine. The rearrangement of **20** was accompanied by intramolecular attack of the lactam nitrogen on the intermediate isocyanate to give the final product, 1,7-diaza-8,9-dioxo-6-phenylbicyclo[4.2.1]nonane (**5**). Thus **5** was formed from **14** in five steps and an overall yield of 17%. The structural assignment of **5** was supported by an ^{15}N NMR study.

Bicyclic imides such as **1–6** were first proposed and their syntheses attempted by Smissman,[1] and we thus refer to this class of compounds as "smissmanones".[2] We have been interested in the synthesis of such compounds as stereochemically defined probes of anticonvulsant receptor site structure.[3,4] Our previous synthetic efforts[5] revealed that **1** and **4** (n = 1) could not be easily prepared, suggesting that instability may result when the tetrahedral geometry of the bridgehead nitrogen prevents efficient delocalization of the lone electron pair into the π-orbitals of the carbonyls. Accordingly, such compounds may be termed anti-Bredt imides. However, our more recent efforts[2] with bicyclic 2,4-oxazolidinediones **2** and **3**, which contain larger methylene bridges (n = 2 and 3, respectively) than **1** and thus more nearly planar imide nitrogens, resulted in the first successful syntheses of examples from this class.



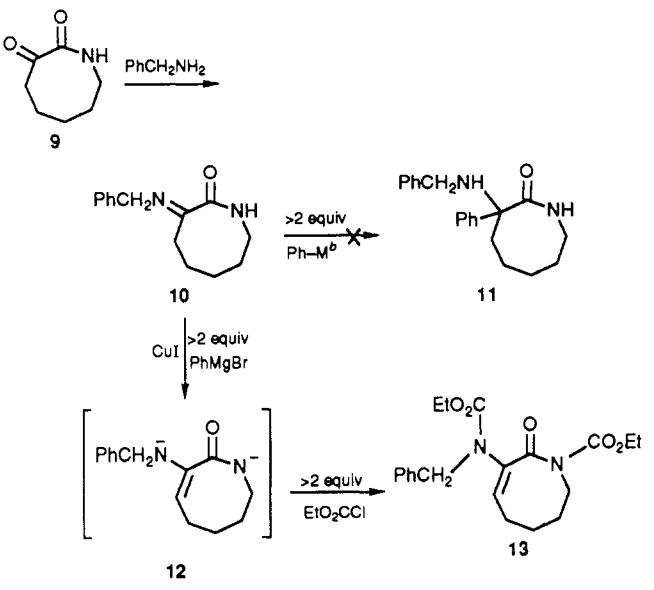
X	n	
O	1	**1**
O	2	**2**
O	3	**3**
HN	1	**4**
HN	2	**5**
HN	3	**6**

Here we describe the first synthesis of an anti-Bredt bicyclic imide from the hydantoin class, structure **5** (n = 2). As was also observed for the 2,4-oxazolidinedione class (**1–3**),[2,5] bicyclo[4.2.1]nonane **5** appears to contain the smallest methylene bridge that allows for preparation, isolation, and handling under normal conditions (e.g., ≥25 °C).

Results and Discussion

Two synthetic approaches to **5** were considered. In the first it was envisioned that an intermediate monocyclic hydantoin, such as 5-(4-bromobutyl)-5-phenylhydantoin (**7**), under basic conditions may undergo intramolecular N-alkylation at the more acidic imide nitrogen to provide **5**. However, this approach to **5** was previously attempted by Smissman[6] and was shown to result in intramolecular alkylation of the amide rather than the imide nitrogen. In the second approach it was proposed that 3-amino-3-phenyl-ϵ-caprolactam (**8**) could be cyclized via insertion of a carbonyl group between the two nitrogens to form the bicyclic hydantoin. (A similar approach was successful for the preparation of **2** and **3**.)[2] However, general methods for the preparation of 3-amino-3-phenyllactams such as **8** have not been previously reported.

Scheme I[a]



[a] The N-methyl derivative of **9** gave similar results. [b] Ph–M = PhMgBr, PhMgBr + CuI, PhLi, PhLi + Me_3SiOTf, or PhLi + $BF_3{\cdot}Et_2O$.

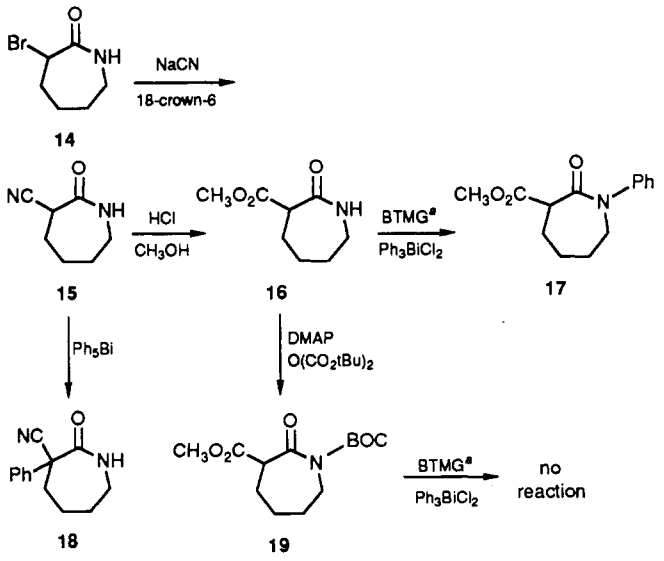
Two methods for α-functionalization of ϵ-caprolactam to give **8** were considered. Approach A is based upon the reported[7] addition of organometallic reagents to selected N-alkylketimines to provide α-substituted amines, which would require an α-iminolactam (or an N-substituted derivative such as **10**, Scheme I). Approach B takes advantage of a recently reported method for the C-

* Address correspondence to this author.

(1) Smissman, E. E.; Matuszack, A. J. B.; Corder, C. N. *J. Pharm. Sci.* **1964**, *53*, 1541.
(2) Brouillette, W. J.; Einspahr, H. M. *J. Org. Chem.* **1984**, *49*, 5113.
(3) Brouillette, W. J.; Brown, G. B.; DeLorey, T. M.; Shirali, S. S.; Grunewald, G. L. *J. Med. Chem.* **1988**, *31*, 2218.
(4) Brouillette, W. J.; Grunewald, G. L.; Brown, G. B.; DeLorey, T. M.; Akhtar, M. S.; Liang, G. L. *J. Med. Chem.* **1989**, *32*, 1577.
(5) Brouillette, W. J.; Smissman, E. E.; Grunewald, G. L. *J. Org. Chem.* **1979**, *44*, 839.
(6) Smissman, E. E.; Chien, P. L.; Robinson, R. A. *J. Org. Chem.* **1970**, *33*, 3818.
(7) Huet, W. *Bull. Soc. Chim. Fr.* **1964**, 952.

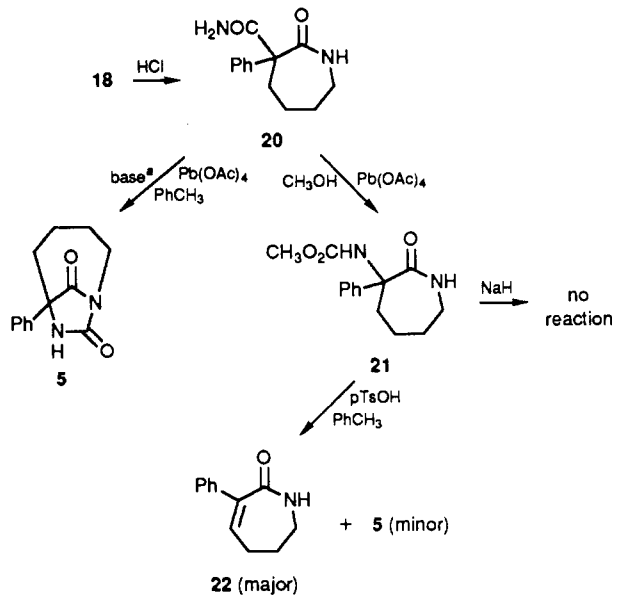
0022-3263/90/1955-5222$02.50/0

Scheme II



[a] No reaction occurred with Ph_5Bi. BTMG = *tert*-butyltetramethylguanidine.

Scheme III



[a] Base (isolated yield) = DMAP (20%), pyridine (25%), and 2,6-lutidine (48%).

phenylation of 2-(ethoxycarbonyl)cyclohexanone at the most acidic carbon using *tert*-butyltetramethylguanidine (BTMG) and Ph_3BiCl_2 or Ph_5Bi.[8] It was anticipated that α-(methoxycarbonyl)lactam **16** (Scheme II) could be similarly phenylated under these conditions. The resulting product could then be transformed to the α-carboxamide, which should undergo a Hofmann rearrangement to give **8**.

Scheme I summarizes results that were typical of our efforts with approach A. Since quantities of the 8-membered α-oxolactam **9** were available from a previous study,[2] this system was used as a model for approach A in the 7-membered system. Compound **9** was converted to the *N*-benzyl Schiff base **10**, and the addition of 2 equiv of phenylmetallic reagents to form **11** was then attempted. Generation of the amide anion of **10** with the first equivalent of organometallic reagent was anticipated to protect the lactam carbonyl from nucleophilic attack, hopefully allowing for selective addition of the second equivalent to the imino carbon. However, the reaction of **10** with 2 equiv of either PhLi or PhMgBr under a variety of conditions failed to yield any detectable amount of **11**. As shown in Scheme II, it was determined that treatment of **10** with 2 equiv of PhMgBr resulted in formation of the dianion **12**, since reaction of this intermediate with 2 equiv of ethyl chloroformate provided **13**. Interestingly, similar results were obtained when the lactam nitrogen of **10** contained a methyl substituent in that treatment with 1 equiv of PhMgBr followed by 1 equiv of ethyl chloroformate gave the lactam *N*-methyl analogue of **13**. This approach was therefore abandoned.

Scheme II summarizes our initial studies with approach B. In this study α-bromolactam **14**, prepared as previously described,[9] was converted to the α-cyano derivative **15**, which was in turn converted to the methyl ester **16**. Although pentacoordinate phenylbismuth reagents were reported[8] to C-phenylate 2-(ethoxycarbonyl)cyclohexanone in high yield, the major product observed for the treatment of lactam **16** under identical conditions was the *N*-phenyl derivative **17**. The *N*-BOC derivative of **16** (**19**) did not react. However, **15** reacted with Ph_5Bi to produce **18** in high yield. The reasons for the differences in reactivity of 2-(ethoxycarbonyl)cyclohexanone, **15**, **16**, and **19** toward C-phenylation using Ph_5Bi are not clear, but these results suggest that the success of this procedure (with lactams) is highly dependent upon structure.

Scheme III details studies which resulted in the conversion of **18** to bicyclic hydantoin **5**. Nitrile **18** was hydrolyzed to the carboxamide **20**, which underwent a Hofmann rearrangement in the presence of $Pb(OAc)_4$ and MeOH to give the carbamate **21**. Surprisingly, the reaction of **21** with NaH (1–3 equiv) in DME gave only recovered starting material. This result suggests that the carbamate NH may be more acidic than the lactam NH, since generation of the carbamate anion would be expected to be nonproductive. (Alternatively, the lactam anion of **21** may not have cyclized due to ring strain.) The reaction of **21** with pTsOH in toluene under azeotroping conditions provided the unsaturated lactam **22** as the major product and a small amount (5%) of a product whose ^1H and ^{13}C NMR, IR, and mass spectra were consistent with **5**. Attempts to improve the yields of **5** under acidic conditions were unsuccessful. Compound **20** was therefore rearranged to the isocyanate in the absence of alcohol and in the presence of a pyridine base. Under these conditions the major product was identical with that assigned as **5** from the reaction of **21**. Studies with three pyridine bases revealed that the yield of **5** from **20** improved as the base strength was decreased. More specifically, the use of DMAP resulted in a 20% isolated yield, pyridine gave a 25% isolated yield, and 2,6-lutidine gave a 48% isolated yield of **5**.

Compound **5** presumably formed in the latter reaction via an intramolecular attack by the lactam nitrogen on the intermediate isocyanate, and this proposal is consistent with literature reports on the intermolecular N-alkylation of amides by simple isocyanates.[10] However, amides are ambident nucleophiles and, in this case, intramolecular O-alkylation to produce **23** (Figure 1) could not be convincingly excluded based upon routine spectral data. In

(8) Barton, D. H. R.; Finet, J. P.; Giannotti, C.; Halley, F. *J. Chem. Soc., Perkin Trans. 1* **1987**, 241.
(9) Wineman, R. J.; Hsu, E. P.; Anagnospopoulos, C. E. *J. Am. Chem. Soc.* **1958**, *80*, 6233.
(10) Wiley, Paul F. *J. Am. Chem. Soc.* **1949**, *71*, 1310.

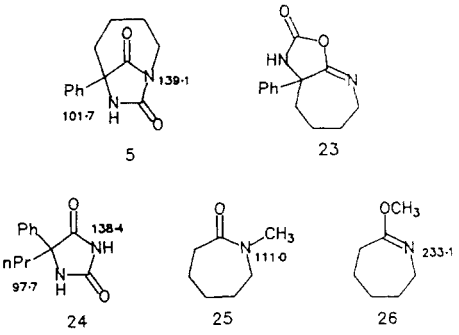


Figure 1.

particular, **5** and **23** should have very similar ^1H NMR, IR, and mass spectra. While ^{13}C NMR data might be expected to distinguish the imino ether carbon of **23** as compared to the lactam carbonyl carbon of **5**, model studies reveal similar chemical shifts for these types of carbon. For example, the carbonyl carbon in **25** (Figure 1) undergoes resonance at 175.5 ppm, while the imine carbon in **26** (Figure 1) resonates at 169.6 ppm. We therefore performed an ^{15}N NMR study on **5** (or **23**) and model compounds **24–26** to resolve this question. The results are summarized in Figure 1. As indicated, the Schiff base nitrogen of model **26** resonates roughly 100 ppm downfield of amide or imide nitrogens in the other models, and the nitrogen resonances for model hydantoin **24** are very similar to those observed for **5**. The ^{15}N chemical shift assignments thus clearly distinguish structure **5** from **23**.

Experimental Section

Bromohydantoin **14** was synthesized from ϵ-caprolactam according to a literature method.[9] NMR model compounds **25** and **26** were purchased from Aldrich, and model hydantoin **24** was synthesized from butyrophenone according to a literature procedure.[11]

General methods were essentially the same as those previously reported.[2] Additionally, all mass spectra were obtained at 70 eV, and the ^{15}N NMR [30.4 MHz, referenced externally to the nitro resonance of doubly enriched (95% ^{15}N) NH_4NO_3 at 374.4 ppm] spectra were obtained on a GE NT spectrometer (300.1 MHz for ^1H) at ambient temperature in $CDCl_3$.

1,7-Diaza-8,9-dioxo-6-phenylbicyclo[4.2.1]nonane (5). A mixture of **20** (100 mg, 0.430 mmol), $Pb(OAc)_4$ (762 mg, 1.72 mmol), and either DMAP (105 mg, 0.860 mmol), pyridine (68 mg, 0.86 mmol), or 2,6-lutidine (92 mg, 0.86 mmol) in anhydrous toluene (10 mL) was heated at reflux under a N_2 atmosphere for 2, 3, and 1 h, respectively (until TLC indicated disappearance of starting material). The solvent was removed, and the oily residue was purified by preparative silica TLC (ether). The band at R_f 0.52 (ether) was removed to give **5** (20 mg, 20% using DMAP; 25 mg, 25% using pyridine; 48 mg, 48% using 2,6-lutidine): mp 150–151 °C ($CHCl_3$/hexane); ^1H NMR ($CDCl_3$) δ 7.6–7.3 (m, 5 H, aromatic), 6.7–6.5 (br s, 1 H, NH), 3.8–3.4 (m, 2 H, NCH_2), 2.3–1.4 (m, 6 H, $CH_2CH_2CH_2$); ^{13}C NMR ($CDCl_3$) δ 180.4, 164.0, 134.2, 128.8, 128.7, 126.3, 70.5, 43.3, 41.8, 25.0, 21.6; IR (KBr) 1780, 1700 (C=O) cm^{-1}; MS *m/e* 230 (M^+, 70). Anal. Calcd for $C_{13}H_{14}N_2O_2$: C, 67.80; H, 6.12; N, 12.16. Found: C, 67.69; H, 6.13; N, 12.12. (See also the preparation of **22**, in which **5** was a minor byproduct.)

3-(*N*-Benzylimino)tetrahydro-1*H*,4*H*-azocin-2-one (10). A solution of **9** (560 mg, 3.9 mmol), benzylamine (620 mg, 5.8 mmol), and pTsOH (5 mg) in anhydrous benzene (40 mL) was heated at reflux using a Dean Stark trap for 5 h. The solvent was removed, water (20 mL) was added, and the mixture extracted with $CHCl_3$ (40 mL). The organic layer was washed with water (2 × 20 mL), dried (Na_2SO_4), and concentrated on a rotary evaporator to provide an oil. Trituration with 25% ether/hexane gave **10** (600 mg, 65%) as a white solid: mp 105–107 °C; ^1H NMR ($CDCl_3$) δ 7.2 (br s, 5 H, aromatic), 6.3 (br s, 1 H, NH), 4.5 (s, 2 H, CH_2Ph), 3.1 (m, 2 H, NCH_2), 2.6 (m, 2 H, allylic CH_2), 1.6 (m, 6 H, $CH_2CH_2CH_2$); IR (KBr) 1650 (C=O, C=N) cm^{-1}; MS *m/e* 230 (M^+, 31). Anal. Calcd for $C_{14}H_{18}N_2O$: C, 73.01; H, 7.87; N, 12.15. Found: C, 72.86; H, 7.90; N, 12.12.

3-[*N*-Benzyl-*N*-(ethoxycarbonyl)amino]-1-(ethoxycarbonyl)-5,6,7,8-tetrahydro-1*H*-azocin-2-one (13). To freshly dried DME (5 mL) at 0 °C under N_2 was added a 3.0 M solution (diethyl ether) of PhMgBr (1.0 mL, 3.0 mmol). To this was added CuI (190 mg, 1.0 mmol), and a solution of **10** (230 mg, 1.0 mmol) in anhydrous DME (10 mL) was then slowly added at 0 °C. The resulting mixture was warmed to room temperature and stirred for 15 h. Ethyl chloroformate (220 mg, 2.0 mmol) was added, and the resulting solution was stirred for an additional 24 h. Water (20 mL) was added, the mixture extracted with ether (20 mL), the organic layer was dried (Na_2SO_4), and the solvent was removed on a rotary evaporator to provide an oil. This was applied to a preparative silica TLC plate and eluted with 6% $Et_2O/CHCl_3$. The band at R_f 0.4 was removed by washing with $CHCl_3$, and the solution was concentrated to provide **13** (200 mg, 53%) as a colorless oil: ^1H NMR ($CDCl_3$) δ 7.3 (m, 5 H, aromatic), 5.7 (t, 1 H, vinyl CH), 4.8 (m, 2 H, CH_2Ph), 4.2 (m, 6 H, 2 $CO_2CH_2CH_3$ and NCH_2), 1.9 (m, 6 H, $CH_2CH_2CH_2$), 1.3 (m, 6 H, 2 $CO_2CH_2CH_3$); IR (liquid film) 1710, 1690 (C=O), 1670 (C=C) cm^{-1}; MS *m/e* 374 (M^+, 6). Anal. Calcd for $C_{20}H_{26}N_2O_5$: C, 64.15; H, 6.99; N, 7.48. Found: C, 64.21; H, 6.72; N, 7.63.

3-Cyanohexahydro-2*H*-azepin-2-one (15). To a solution of bromolactam **14** (5.2 g, 0.025 mol) and 18-crown-6 (50 mg) in anhydrous CH_3CN (50 mL) was added dry, powdered NaCN (7.4 g, 0.15 mol). The reaction mixture was heated at reflux for 36 h and filtered, and the solvent was removed to yield an oily residue (5.5 g). This was flash chromatographed on silica (5 × 21 cm, 5:3:2 EtOAc/THF/hexane). Fractions containing material with R_f 0.52 (5:3:2 EtOAc/THF/hexane) were combined and concentrated to give an oil. This was crystallized from hexane to provide **15** (1.9 g, 55%) as a white solid: mp 98–99 °C; ^1H NMR ($CDCl_3$) δ 7.3 (br s, 1 H, NH), 3.7 (m, 1 H, CH), 2.9 (m, 2 H, NCH_2), 1.9 (m, 6 H, $CH_2CH_2CH_2$); ^{13}C NMR ($CDCl_3$) δ 170.1, 117.0, 41.9, 39.2, 28.6, 28.0, 27.8; IR (KBr) 2220 (CN), 1660 (C=O) cm^{-1}; MS *m/e* 138 (M^+, 18). Anal. Calcd for $C_7H_{10}N_2O$: C, 60.84; H, 7.29; N, 20.28. Found: C, 60.59; H, 7.36; N, 20.18.

3-(Methoxycarbonyl)hexahydro-2*H*-azepin-2-one (16). A solution of **15** (0.20 g, 1.4 mmol) in anhydrous ether (15 mL) and methanol (0.6 mL) was cooled to 0 °C. Gaseous HCl was bubbled through the cold solution for 20 min, and the resulting mixture was stirred at 0 °C for 20 min and allowed to warm to room temperature during 45 min. Ice-cold water (10 mL) was added, and the mixture was extracted with EtOAc (2 × 30 mL). The combined extracts were dried (Na_2SO_4) and concentrated on a rotary evaporator to yield an oil. This was crystallized from hexane to give **16** (90 mg, 36%): mp 79–80 °C; ^1H NMR ($CDCl_3$) δ 6.8 (br s, 1 H, NH), 3.7 (s, 3 H, CO_2CH_3), 3.5 (m, 1 H, CH), 3.2 (m, 2 H, NCH_2), 1.8 (m, 6 H, $CH_2CH_2CH_2$); IR (KBr) 1730, 1665 (C=O) cm^{-1}; MS *m/e* 171 (M^+, 64). Anal. Calcd for $C_8H_{13}NO_3$: C, 56.12; H, 7.65; N, 8.17. Found: C, 56.09; H, 7.70; N, 8.09.

3-(Methoxycarbonyl)-1-phenylhexahydro-2*H*-azepin-2-one (17). To a solution of **16** (60 mg, 0.35 mmol) in anhydrous benzene (2 mL) was added *tert*-butyl tetramethylguanidine (BTMG, 85 mg, 0.50 mmol) and Ph_3BiCl_2 (260 mg, 0.50 mmol). The mixture was heated at reflux under N_2 for 1.5 h, the solvent was removed, and the oily residue was triturated with 25% ether/hexane to give **17** (54 mg, 62%) as a white solid: mp 104–105 °C; ^1H NMR ($CDCl_3$) δ 7.5–7.1 (m, 5 H, aromatic), 4.0–3.5 (m, 6 H, CH_3, CH, and NCH_2), 2.3–1.5 (m, 6 H, $CH_2CH_2CH_2$); IR (KBr) 1730, 1650 (C=O) cm^{-1}; MS *m/e* 247 (M^+, 31). Anal. Calcd for $C_{14}H_{17}NO_3$: C, 67.99; H, 6.92; N, 5.66. Found: C, 67.85; H, 6.71; N, 5.58.

3-Cyano-3-phenylhexahydro-2*H*-azepin-2-one (18). To freshly prepared Ph_5Bi[12] (6.00 g, 10.1 mmol) under N_2 was added a solution of **15** (1.3 g, 9.4 mmol) in dry benzene (32 mL). The resulting mixture was stirred at room temperature for 15 h, and the solvent was removed on a rotary evaporator. The oily residue was triturated with 25% ether/hexane to provide crude **18** (1.5

(11) Novelli, A. *Anal. Asoc. Quim. Arg.* **1941**, *29*, 83; *Chem. Abstr.* **1941**, *35*, 6567.

(12) Wittig, G.; Clauss, K. *Justus Liebigs Ann. Chem.* **1952**, *578*, 136.

g, 74%) as a white solid: mp 136–137 °C ($CHCl_3$/hexane); ^1H NMR ($CDCl_3$) δ 7.3 (m, 6 H, NH and aromatic), 3.3 (m, 2 H, NCH_2), 2.4 (m, 2 H, CH_2), 1.8 (m, 4 H, CH_2CH_2); ^{13}C NMR ($CDCl_3$) δ 170.7, 135.0, 128.9, 128.5, 127.1, 119.0, 54.1, 41.9, 34.5, 28.3, 25.2; IR (KBr) 2210 (CN), 1660 (C=O) cm^{-1}; MS *m/e* 214 (M^+, 22). Anal. Calcd for $C_{13}H_{14}N_2O$: C, 72.87; H, 6.58; N, 13.07. Found: C, 72.99; H, 6.63; N, 13.10.

1-(*tert*-Butyloxycarbonyl)-3-(methoxycarbonyl)hexahydro-2*H*-azepin-2-one (19). DMAP (12 mg, 0.10 mmol) was added to a stirred solution of **16** (150 mg, 0.87 mmol) in anhydrous CH_3CN (5 mL) under N_2. After 5 min, di-*tert*-butyl dicarbonate (440 mg, 2.0 mmol) was added, and the resulting mixture was stirred at room temperature for 15 h. EtOAc (25 mL) was added, and the solution was washed with 1 M $KHSO_4$ (10 mL) followed by saturated aqueous NaCl (2 × 10 mL). The organic layer was dried (Na_2SO_4) and concentrated to yield an oily residue (290 mg). This was placed on a silica preparative TLC plate and eluted with ether. The band at R_f 0.68 was removed by washing with $CHCl_3$, and the washings were concentrated to give **19** (260 mg, 63%) as a colorless oil: ^1H NMR ($CDCl_3$) δ 3.7 (s, 3 H, CO_2CH_3), 3.5 (m, 3 H, CH, NCH_2), 2.4 (m, 2 H, $CHCH_2$), 1.5 (m, 13 H, *tert*-butyl, CH_2CH_2); IR (liquid film) 1750, 1710, 1690 (C=O) cm^{-1}.

3-(Aminocarbonyl)-3-phenylhexahydro-2*H*-azepin-2-one (20). In a pear-shaped pressure bottle was placed a suspension of **18** (1.5 g, 7.0 mmol) in concentrated HCl (1.5 mL), and gaseous HCl was bubbled through the mixture at 0 °C for 20 min. The bottle was sealed, and the mixture stirred at room temperature for 48 h. The solution was adjusted to pH 7 by adding saturated aqueous $NaHCO_3$, and the resulting mixture was extracted with $CHCl_3$ (2 × 50 mL). The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo to provide crude **20** (1.4 g, 86%): mp 192–193 °C ($CHCl_3$/hexane); ^1H NMR ($CDCl_3$) δ 7.3 (m, 5 H, aromatic), 6.8 (br s, 1 H, NH), 5.9 (br s, 2 H, NH_2), 2.8 (m, 2 H, NCH_2), 2.6 (m, 2 H, CCH_2), 1.6 (m, 4 H, CH_2CH_2); ^{13}C NMR (1:1 $CDCl_3$/DMSO-d_6) δ 176.7, 175.3, 136.1, 129.0, 127.8, 127.6, 63.7, 41.6, 30.8, 27.9, 24.1; IR (KBr) 1680, 1655 (C=O) cm^{-1}; MS *m/e* 232 (M^+, 61). Anal. Calcd for $C_{13}H_{16}N_2O_2$: C, 67.22; H, 6.93; N, 12.06. Found: C, 67.16; H, 6.97; N, 12.10.

3-[*N*-(Methoxycarbonyl)amino]-3-phenylhexahydro-2*H*-azepin-2-one (21). To a stirred solution of **20** (1.0 g, 4.3 mmol) in anhydrous CH_3OH (50 mL) under N_2 was added $Pb(OAc)_4$ (7.62 g, 17.2 mmol). The mixture was warmed to 55–58 °C while stirring for 19 h. The solvent was removed on a rotary evaporator, 10% aqueous $NaHCO_3$ (20 mL) added to the residue, and the resulting mixture extracted with $CHCl_3$ (2 × 60 mL). The combined organic extracts were washed with water (2 × 30 mL) and dried (Na_2SO_4), and the solvent was removed. The residual oil was triturated with 25% ether/hexane to provide **21** (0.80 g, 71%) as a white solid: mp 149–150 °C; ^1H NMR ($CDCl_3$) δ 7.3 (m, 5 H, aromatic), 6.8 (m, 2 H, 2 NH), 3.5 (s, 3 H, $NHCO_2CH_3$), 2.7 (m, 2 H, NCH_2), 1.2 (m, 6 H, $CH_2CH_2CH_2$); IR (KBr) 1710, 1650 (C=O) cm^{-1}; MS *m/e* 262 (M^+, 30). Anal. Calcd for $C_{14}H_{18}N_2O_3$: C, 64.10; H, 6.91; N, 10.68. Found: C, 64.18; H, 6.94; N, 10.63.

3-Phenyl-1,5,6,7-tetrahydro-2*H*-azepin-2-one (22). A solution of **21** (40 mg, 0.15 mmol) and pTsOH (1 mg) in dry toluene (20 mL) was heated at reflux for 36 h using a Dean–Stark trap. TLC indicated no reaction. Additional pTsOH (30 mg, 0.15 mmol) was added, and heating was continued for an additional 12 h. TLC revealed starting material and several new products. A third portion of pTsOH (30 mg, 0.15 mmol) was added, and heating was continued for an additional 12 h. The solvent was removed on a rotary evaporator, and the residual oil was placed on a preparative silica TLC plate (EtOAc). Two bands were removed by washing with $CHCl_3$. The minor one (R_f 0.61) was **5** (2 mg, 5%), which was identical with that produced from **20** (described above). The major band (R_f 0.42) provided **22** (18 mg, 63%) as a white solid: mp 138–139 °C; ^1H NMR ($CDCl_3$) δ 7.3 (m, 5 H, aromatic), 7.1 (br s, 1 H, NH), 6.6 (t, 1 H, vinyl CH), 3.3 (m, 2 H, NCH_2), 2.4 (m, 2 H, allylic CH_2), 1.9 (m, 2 H, NCH_2CH_2); ^{13}C NMR ($CDCl_3$) δ 173.0, 139.1, 137.0, 131.6, 128.4, 127.7, 127.0, 39.6, 29.6, 23.9; IR (KBr) 1640 (C=O, C=C) cm^{-1}; MS *m/e* 187 (M^+). Anal. Calcd for $C_{12}H_{13}NO$: C, 76.98; H, 6.99; N, 7.47. Found: C, 76.81; H, 6.86; N, 7.40.

Acknowledgment. This work was supported by the National Institutes of Health (Grant NS23866).

Nitrile Additions to *C,N*-Diacylimines. Formation of 4-Amidooxazoles[1]

Bilha Fischer and Alfred Hassner*

Department of Chemistry, Bar-Ilan University, Ramat-Gan 52100 Israel

Received August 3, 1989

Nitriles are shown to react with *C,N*-diacylimines **2**, generated in situ from **1** or **4** in the presence of Lewis acids, to produce 4-amidooxazoles **5** and **6** in good to excellent yield. Diamides are sometimes also produced. The reaction was followed by NMR spectroscopy, and mechanistic pathways are discussed.

Introduction

The ability of the imine function to add to other multiple bond compounds has been used extensively for the construction of heterocyclic molecules.[2] Among imines, the *N*-acylimine moiety has been shown to readily undergo amidoalkylations with olefins, acetylenes, and aromatic compounds,[3] as well as to act as dienophiles[4a–d] or as diene components[4e] in hetero-Diels–Alder reactions. It was of interest to compare the behavior of a rare series of imines,[4f] namely *C,N*-diacylimines **2**, to that of their simpler analogues.

As a possible entry to **2** we chose the *N*-(α-methoxy-β,β-dimethoxyalkyl)benzamides **1**, or the *N*-(α-methoxy-β-ketoalkyl)amides **4**, which in turn are readily obtained

(1) Synthetic Methods 35. For part 34, see: Rai, L. K. M.; Hassner, A. *Heterocycles* **1990**, *31*, 817.

(2) (a) Govindachari, T. R.; Chinnasamy, P.; Rajeswari, S.; Chandrasekaran, S.; Premila, M. S.; Natarajan, S.; Nagarajan, K.; Pai, B. R. *Heterocycles* **1984**, *22*, 585. (b) Maryanoff, B. E.; McComsey, D. F.; Almond, H. R., Jr.; Mutter, M. S.; Bemis, G. W.; Whittle, R. R.; Olofson, R. A. *J. Org. Chem.* **1986**, *51*, 1341. (c) Ben-Ishai, D.; Peled, N.; Sataty, I. *Tetrahedron Lett.* **1980**, *21*, 569.

(3) Zaugg, H. E. *Synthesis* **1984**, 85 and references cited.

(4) (a) Weinreb, S. M.; Staib, R. R. *Tetrahedron* **1982**, *38*, 3087. (b) Weinreb, S. M. *Acc. Chem. Res.* **1985**, *18*, 16. (c) Ben-Ishai, D.; Goldstein, E. *Tetrahedron* **1971**, *27*, 3119. (d) Jung, M. E.; Shishido, K.; Light, L.; Davis, L. *Tetrahedron Lett.* **1981**, *22*, 4611. (e) Scola, P. M.; Weinreb, S. M. *J. Org. Chem.* **1986**, *51*, 248. (f) Boger, D. L.; Weinreb, D. N. *Hetero Diels–Alder Methodology in Organic Synthesis*; Academic Press: San Diego, 1987; p 39.

0022-3263/90/1955-5225$02.50/0