of dimethylthallium chloride and 1.8 mmol of MeLi) in 20 mL of ether was added dropwise 0.18 g (1.8 mmol) of phenylacetylene and the reaction mixture was stirred for 17 h. Decanoyl chloride (0.34 g, 1.8 mmol) was then added and the heterogeneous mixture that resulted was stirred for an additional 5 min. Addition of 0.5 mL of a 0.1 M aqueous HCl solution followed by filtration and a standard workup gave the crude ketone, which was further purified by reverse-phase HPLC (eluant, 20:80 water/acetonitrile) to afford 0.35 g (75%) of pure material: MS, EI 155, CI 257, 274; IR (neat, cm^{-1}) 2910, 2850, 2190, 1665, 1555; 220-Mz NMR ($CDCl_3$) δ 7.55 (2 H, d, J = 8 Hz), 7.37 (3 H, m), 2.55 (1 H, t, J = 7.5 Hz), 1.75 (2 H, m), 1.25 (12 H, m), 0.85 (3 H, t, J = 8 Hz).

Acknowledgment. I.E.M. is grateful to the Department of Chemistry of the University of Sheffield for financial support, to Peter Ashton and Ian Johnstone for running so efficiently the MS, to Ian Staton and David Andrews for the HPLC and GC, respectively, and to all my collegues of the Chemistry Department for their numerous suggestions, criticisms, and constructive support.

Registry No. 1, 3003-15-4; 2, 687-82-1; 3, 3003-04-1; **5a**, 84907-66-4; **5b**, 1817-57-8; TlI, 7790-30-9; Me_2TlCl, 16834-14-3; TlBr, 7789-40-4; $TlBr_3$, 13701-90-1; $PhB(OH)_2$, 98-80-6; Ph_2TlBr, 10192-61-7; PhC≡CH, 536-74-3; $C_9H_{19}C(O)Cl$, 112-13-0; H_2C=$CH(CH_2)_8C(O)Cl$, 38460-95-6; $MeOC(O)(CH_2)_8C(O)Cl$, 14065-32-8; PhC(O)Cl, 98-88-4; $MeOC_6H_4$-*p*-C(O)Cl, 100-07-2; MeC(O)Cl, 75-36-5; $C_9H_{19}C(O)Me$, 112-12-9; H_2C=$CH(CH_2)_8C(O)Me$, 5009-33-6; $MeOC(O)(CH_2)_8C(O)Me$, 18993-09-4; PhC(O)Me, 98-86-2; $MeOC_6H_4$-*p*-C(O)Me, 100-06-1; PhC(O)Et, 93-55-0; $C_9H_{19}C(O)Et$, 1534-27-6; PhC(O)Ph, 119-61-9; cyclopentanecarbonyl chloride, 4524-93-0; acetylcyclopentane, 6004-60-0.

Synthesis of 6-Aryl-4,5-dibenzamido-1,2,3,6-tetrahydropyridines

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In 1928 van der Merwe[1] reported the reaction sequence, shown in Scheme I starting with histamine and *p*-anisaldehyde. The three steps are Schiff base formation, reduction of the anil double bond, and a Bamberger ring fission reaction.[2] Information on yields was not provided. Only elemental analyses were given in support of structures **2** and **3**, but that evidence was not convincing because the experimental values van der Merwe reported for the nitrogen content of the dipicrate of the secondary amine **2** (-0.49%) and the carbon content of the Bamberger product **3** (-0.80%) did not check within acceptable limits.

In 1966 we reported[3] on some histamine research that included evidence that compound **1** of van der Merwe's proposed sequence was actually 4-(4-methoxyphenyl)-4,5,6,7-tetrahydro-1*H*-imidazo[4,5-*c*]pyridine (**4a**) formed by thermal cyclization of the Schiff base **1**. In the light of that finding it seemed reasonable to presume that van der Merwe's final step employing Bamberger reaction conditions produced 4,5-dibenzamido-1-benzoyl-6-(4-methoxyphenyl)-1,2,3,6-tetrahydropyridine (**5a**) (Scheme II). The current research was undertaken, in part, to confirm this assumption.

Further motivation for the project came from a literature search that revealed that many substituted 1,2,3,6-tetrahydropyridines exhibit interesting and potentially useful pharmacological properties.[4] Thus, a major objective of the current research was to study the potential of Scheme II as a pathway to a series of new 1,2,3,6-tetrahydropyridines.

Our first effort was simply to repeat van der Merwe's work to allow us to test our assumptions concerning the actual structure of his Bamberger reaction product and to determine the reaction yield. The product we obtained was a solid that, contrary to the expected properties of a Bamberger product such as **3** or **5**, was largely (80-90%) soluble in dilute aqueous acid.

Examination of the small amount of acid-insoluble residue by means of elemental analyses and spectroscopy (^1H NMR and MS) proved it to be the expected Bamberger product **5a**. The corrected melting point of our analytical sample was approximately 12 °C higher than the 205 °C reported by van der Merwe, suggesting our isolation scheme afforded a product of higher purity. The yield, however, was only 10% and various attempts to improve the yield by either manipulating reaction conditions or by using a large excess of benzoyl chloride met with failure. During this phase of our work **4b** was also subjected to the Bamberger reaction. By means of a similar workup, **5b** was isolated in 9% yield.

We then turned our attention to the acid-soluble portion of the Bamberger reaction product. Spectral data (^1H NMR and MS) of this material showed that it was the monobenzoylated derivative 5-benzoyl-4-(4-methoxyphenyl)-4,5,6,7-tetrahydro-1*H*-imidazo[4,5-*c*]pyridine (**6a**). Convincing evidence that the benzoyl group was at the 5-position was provided by the strong downfield shifts of the absorptions of neighboring protons at C-4 and C-6 in the ^1H NMR spectrum.[6] This rapid, initial benzoylation occurring at the more basic (and more nucleophilic) 5-position of the tetrahydropyridine ring[7] evidently produced

(1) van der Merwe, P. *Z. Physiol. Chem.* **1928**, *177*, 30.

(2) For a comprehensive review of the Bamberger reaction, see: Hofmann, K. *Imidazole and Its Derivatives, Part I*, in the series the Chemistry of Heterocyclic Compounds; Weissberger, A.; Ed.; Interscience; New York, 1953; pp 48-49, 156, 273-276.

(3) Stocker, F. B.; Fordice, M. W.; Larson, J. K.; Thorstenson, J. H. *J. Org. Chem.* **1966**, *31*, 2380.

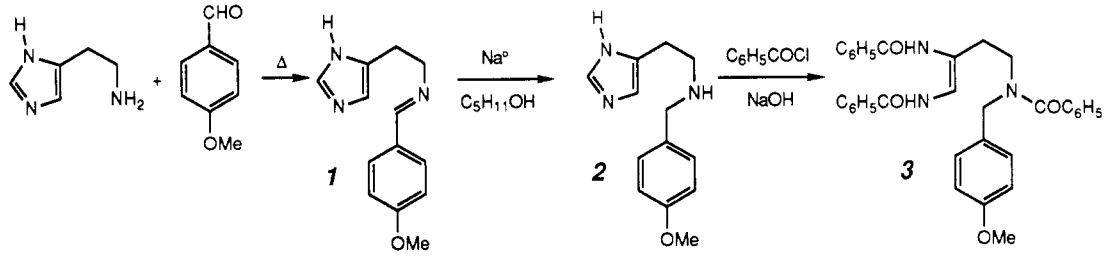
(4) A number of di- and trisubstituted 1,2,3,6-tetrahydropyridines have been shown to have pharmacological activity. See: Boettcher, H.; Fuchs, A.; Seyfried, C. Ger. Pat. DE 1986 3, 438,394 (tranquilizers); *Chem. Abstr.* **1986**, *105*, 97328k. McCall, J. M.; TenBrink, R. E.; Kamdar, B. V.; Skaletzky, L. L.; Perricone, S. C.; Piper, R. C.; Delehanty, P. J. *J. Med. Chem.* **1986**, *29*, 133 (hypotensive agents). Pall, H. S.; Williams, A. C.; Ramsden, D. B. *J. Clin. Hosp. Pharm.* **1986**, *11*, 229 (involvement with Parkinson's disease). Eur. Pat. Appl. EP 1982 60,179 (CL. CO7D211/70); *Chem. Abstr.* **1983**, *98*, 71939k (appetite suppressants). Martin, L. L.; Klioze, S. S.; Worm, M.; Crichlow, C. A.; Geyer, H. M., III; Kruse, H. *J. Med. Chem.* **1979**, *22*, 1347 (anti-depressants). F. Hoffman-La Roche and Co., A.-G. Neth. Pat. Appl. 1965 6,407,413 (Cl. C 07d); *Chem. Abstr.* 1965, *63*, 1774b (analgesics).

(5) When slightly more than 3 equiv of benzoyl chloride was allowed to react with 1 equiv of **4c** in pyridine at 85 °C for 45 min, monobenzoylation at the 5-position occurred in 92% yield. (See Experimental Section.)

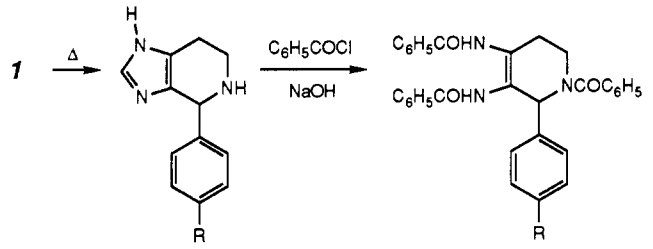
(6) The ^1H NMR methylene proton absorption at C-6 was shifted from 3.0 and 3.15 ppm downfield to 3.24 and 3.61 ppm, whereas the methine proton absorption at C-4 was shifted from 4.9 downfield to 6.9 ppm. Reference data from Silverstein et al. [Silverstein, R. M.; Bassler, G. G.; Morrill, T. C. *Spectrometric Identification of Organic Compounds*, 4th ed.; John Wiley and Sons: New York, 1981; p 220, 222] give a predicted methylene shift of approximately 0.6 ppm and a predicted methine shift of approximately 0.9 ppm. The observed methylene shift is close to the predicted value but the observed methine shift is approximately 1 ppm farther downfield than the predicted value. If one assumes that the bulk 4-methoxyphenyl and the benzoyl groups are trans to one another on the tetrahydropyridine ring, the benzoyl group then is cis to the methine C-4 proton. We surmise that anisotropic deshielding by the nearby benzoyl group is responsible for the unexpectedly large downfield shift of the methine proton.

0022-3263/90/1955-3370$02.50/0

Scheme I



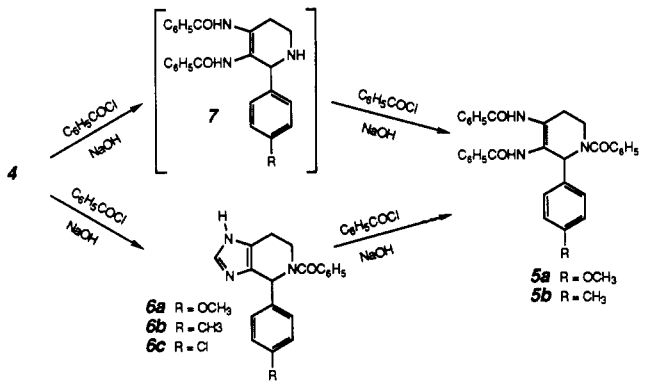
Scheme II



4a R = OCH_3
4b R = CH_3
4c R = Cl

5a R = OCH_3
5b R = CH_3

Scheme III



6a R = OCH_3
6b R = CH_3
6c R = Cl

5a R = OCH_3
5b R = CH_3

a derivative that is resistant to further reaction. In fact, resubjecting this material to the Bamberger reaction left it virtually unchanged.

Scheme III shows the two possible pathways from **4** to **5**. We have never detected intermediate **7** in any of our reaction attempts, whereas intermediate **6** was consistently found to be the major product when the reaction was conducted in aqueous sodium hydroxide solution. We have surmised that production of **7** would be slow, but once formed would be rapidly converted to **5**. On the other hand, we have surmised that **6** accumulated rapidly but then either failed to proceed to **5** or did so only with great difficulty. What remained to be answered was why **6** was not an efficient precursor of **5**. We considered such factors as the possible insolubility of **6** in the reaction medium and a combination of unfavorable steric and electronic effects introduced by the 5-benzoyl group. Following this early work in aqueous media, and after establishing the fact that both **4** and **6** were appreciably soluble in pyridine, we attempted the synthesis of **5** in a pyridine–water cosolvent system using sodium hydroxide as the base. Unfortunately, yields of **5** did not improve by using that approach.[5] That result led us, temporarily, to believe that the low yields were not due solely to solubility problems. In fact, for a time we thought that unfavorable inductive effects might be a significant factor in reducing yields. Unpublished information recently provided to us[8] has caused us to discount the importance of electronic effects in inhibiting the reaction. By modification of the Bamberger cleavage conditions to include an acetonitrile–water cosolvent system and sodium bicarbonate as the base, we very recently have repeated the preparation of **5a** and the yield rose to 60%. Evidently, the insolubility of **6** in purely aqueous media strongly inhibits further reaction even in the presence of a large excess of benzoyl chloride. In retrospect, we now attribute the inefficiency of our early preparations in pyridine–water to be due to an increased tendency of benzoyl chloride to suffer hydrolysis via the pyridine complex in the presence of hydroxide ion.

At an early point in this project when we were consistently obtaining unfavorable yields in both aqueous media and in pyridine–water, we decided to place a blocking group at the 5-position of **4** to prevent the benzoylation at that site. After considering a variety of possible blocking reactions, we selected the Eschweiler–Clarke methylation[9] for this purpose. Among the pharmacologically active 1,2,3,6-tetrahydropyridines, one of the most common N-substituents was the methyl. Some earlier work in our laboratories had shown that this procedure fails to methylate the 1-position of the imidazole ring. Upon applying Eschweiler–Clarke conditions to **4**, we observed CO_2 evolution in a volume consistent with monomethylation and obtained yields of **8** averaging 75%. The Bamberger reaction was then carried out on **8** in yields averaging over 65%, to produce 6-aryl-4,5-dibenzamido-1-methyl-1,2,3,6-tetrahydropyridines **9** (Scheme IV). The Eschweiler–Clarke step was convenient because we found it was not necessary to purify the methylated intermediates before use in the Bamberger reaction.

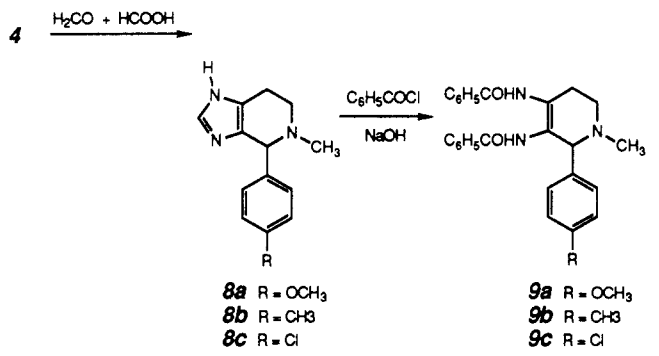
The new tetrahydropyridines, **5** and **9**, are being evaluated for their pharmacological properties.

(7) That the aliphatic amino group rather than the NH of the imidazole ring is the more reactive site for benzoylation can be seen from results with histamine. The latter, with 1 equiv of benzoyl chloride in aqueous base gives side-chain benzoylation exclusively. When the *N*-benzoylhistamine is treated with an additional equivalent of benzoyl chloride in benzene, the imidazole ring NH is also benzoylated. Hofmann, K. *Imidazole and Its Derivatives, Part I* in the series The Chemistry of Heterocyclic Compounds; Weissberger, A.; Ed.; Interscience: New York, 1953, p 155.

(8) J. C. Hodges, Parke-Davis, Ann Arbor, MI (private communication), reported successful Bamberger reactions (i.e., 70% yields) on two different 4,5,6,7-tetrahydroimidazo[4,5-*c*]pyridines using an acetonitrile/saturated sodium bicarbonate medium and 5 equiv of benzoyl chloride. The reactants were mixed at 5 °C and allowed to warm to room temperature over a 2-h period. We are indebted to Dr. Hodges for helpful comments on our work and for sharing these unpublished experimental results with us.

(9) Eschweiler, W. *Chem. Ber.* **1905**, *38*, 880. Clarke, H. T.; Gillespie, H. B.; Weishaus, S. Z. *J. Am. Chem. Soc.* **1933**, *55*, 4571. Moore, M. L. *Organic Reactions V*; Adams, R., Ed.; John Wiley and Sons: New York, 1949; p 301. Cope, A. C.; Ciganek, E.; Fleckenstein, L. J.; Meisinger, M. A. P. *J. Am. Chem. Soc.* **1960**, *82*, 4651.

Scheme IV



Experimental Section

General. All NMR spectra were determined on either a JEOL C-60 HL or a Bruker AC-200 spectrometer using $CDCl_3$ as the solvent unless otherwise indicated. For 60-MHz spectra, TMS was used as an internal standard and for 200-MHz spectra, residual solvent was used as an internal standard. Chemical shifts are reported in ppm downfield. Mass spectral data were obtained on an AEI MS-30 spectrometer. Melting points were determined on a Kofler micro hot stage and are corrected unless otherwise indicated. Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, TN. All spectra were in accord with assigned structures. The elemental analyses of each compound were within 0.3% of the theoretical values. Yields reported were the highest obtained for each crude product.

Materials. Commercial reagents were utilized without further purification.

4-Aryl-4,5,6,7-tetrahydro-1*H*-imidazo[4,5-*c*]pyridines 4a–c. These materials were prepared by the method of Stocker et al.[3]

Eschweiler–Clarke Methylation. Preparation of 4-Aryl-5-methyl-4,5,6,7-tetrahydro-1*H*-imidazo[4,5-*c*]pyridines 8a–c: General Procedure. In a typical reaction, 0.06 mol of chilled 88% formic acid was added dropwise to 0.03 mol of the tetrahydroimidazopyridine **4a–c**, with stirring and chilling in an ice bath during the addition. Formaldehyde solution (37%, 0.031 mol) was added in a similar manner, and the reaction mixture was heated over steam until evolution of CO_2 terminated (typically from 0.75 to 1.5 h). The product was dissolved in 6 M HCl, and the solution was filtered and brought to pH 11 with 30% KOH solution. After the gummy mass of tan-colored product was separated from the basic aqueous solution, it was washed with distilled water and then triturated under distilled water until a fine powdery suspension formed. If a powder failed to form, trituration of the dried gummy mass under ligroin or cyclohexane was used to produce a powdery suspension. The product was then collected on a filter and dried. Usually these compounds were not purified further before use in the Bamberger reaction.

5-Methyl-4-(4-methoxyphenyl)-4,5,6,7-tetrahydro-1*H*-imidazo[4,5-*c*]pyridine (8a) was obtained as a tan powder in 65% yield. Recrystallization from water gave pale yellow microcrystals, mp 200–204 °C. ^1H NMR (200 MHz, $CDCl_3$) δ 7.25 (s, 1 H), 7.15 (d, J = 8.6 Hz, 2 H), 6.82 (d, J = 8.6 Hz, 2 H), 4.10 (s, 1 H), 3.77 (s, 3 H), 3.10 (m, 1 H), 2.95 (m, 1 H), 2.66 (m, 2 H), 2.25 (s, 3 H).

5-Methyl-4-(4-methylphenyl)-4,5,6,7-tetrahydro-1*H*-imidazo[4,5-*c*]pyridine (8b) was obtained as a tan-colored solid in 66% yield. Recrystallization from benzene provided pale yellow microcrystals, mp 205–206 °C. ^1H NMR (60 MHz, $CDCl_3$) δ 8.6 (s, 1 H), 7.35 (s, 1 H), 7.08 (s, 4 H), 4.11 (s, 1 H), 3.0 (m, 2 H), 2.7 (m, 2 H), 2.30 (s, 3 H), 2.26 (s, 3 H). Anal. Calcd for $C_{14}H_{17}N_3$: C, 73.97; H, 7.54; N, 18.49. Found: C, 74.01; H, 7.62; N, 18.23.

5-Methyl-4-(4-chlorophenyl)-4,5,6,7-tetrahydro-1*H*-imidazo[4,5-*c*]pyridine (8c) was obtained as a tan-colored solid in 94% yield. Recrystallization from ethyl acetate gave pale yellow needles, mp 188–191 °C. ^1H NMR (60 MHz, $CDCl_3$) δ 8.26 (br s, 1 H), 7.20–7.05 (m, 5 H), 4.01 (s, 1 H), 3.04 (m, 2 H), 2.61 (m, 2 H), 2.18 (s, 3 H).

Bamberger Reaction. Preparation of 6-Aryl-4,5-dibenzamido-1-methyl-1,2,3,6-tetrahydropyridines 9a–c: General Procedure. In a representative reaction, 0.03 mol of methylated tetrahydroimidazopyridine **8a–c** compound was pulverized and suspended in 100 mL of an aqueous solution containing 0.12 mol of KOH. Benzoyl chloride (0.09 mol) was added dropwise over 30 min, with constant stirring with a magnetic stirrer during the addition. Stirring was continued and care was taken to keep the reaction solution basic until the tarry mass of product broke up and a powdery suspension remained. In most cases this process took several hours but in some instances stirring was continued overnight. The product was then collected on a filter, washed with water, and dried.

4,5-Dibenzamido-6-(4-methoxyphenyl)-1-methyl-1,2,3,6-tetrahydropyridine (9a) was obtained as an amber-colored solid in 68% yield. Recrystallization from acetonitrile gave pale yellow crystals, mp 217–221.5 °C. ^1H NMR (200 MHz, $CDCl_3$) δ 9.22 (s, 1 H), 7.94 (m, 2 H) 7.49–7.26 (bm, 11 H), 6.90 (d, J = 8.6 Hz, 2 H), 3.87 (s, 1 H), 3.80 (s, 3 H), 3.33 (m, 1 H), 2.97 (m, 1 H), 2.55 (m, 2 H), 2.12 (s, 3 H). D_2O exchange caused a loss of a total of two NH proton adsorptions, one at δ 9.22 and the other at δ 7.49–7.26. Anal. Calcd for $C_{27}H_{27}N_3O_3$: C, 73.44; H, 6.17; N, 9.52. Found: C, 73.15; H, 6.05; N, 9.53.

4,5-Dibenzamido-6-(4-methylphenyl)-1-methyl-1,2,3,6-tetrahydropyridine (9b) was obtained as a pale yellow solid in 68% yield. Several recrystallizations from acetone gave clear colorless microcrystals (prisms), mp 198.5–202.7 °C. ^1H NMR (200 MHz, $CDCl_3$) δ 9.22 (s, 1 H), 7.93 (m, 2 H), 7.48–7.12 (bm, 13 H), 3.85 (s, 1 H), 3.39 (s, 1 H), 2.98 (m, 1 H), 2.55 (m, 2 H), 2.35 (s, 3 H), 2.16 (s, 3 H). D_2O exchange caused a loss of a total of two NH proton absorptions, one at δ 9.22 and the other at δ 7.48–7.12. Anal. Calcd for $C_{27}H_{27}N_3O_2$: C, 76.21; H, 6.40; N, 9.87. Found: C, 76.43; H, 6.45; N, 9.87.

4,5-Dibenzamido-6-(4-chlorophenyl)-1-methyl-1,2,3,6-tetrahydropyridine (9c) was obtained as a tan-colored solid in 65% yield. Several recrystallizations from benzene gave white microcrystals, mp 211.3–213.7 °C. ^1H NMR (200 MHz, $CDCl_3$) δ 8.95 (s, 1 H), 7.95 (m, 2 H), 7.71 (s, 1 H), 7.54–7.26 (bm, 12 H), 4.05 (s, 1 H), 3.07 (m, 1 H), 2.84 (m, 1 H), 2.50 (m, 2 H), 2.04 (s, 3 H). D_2O exchange caused a loss of a total of two NH proton absorptions, one at δ 8.95 and the other at δ 7.71. Anal. Calcd for $C_{26}H_{24}N_3O_2Cl$: C, 70.34; H, 5.45; N, 9.47. Found: C, 70.50; H, 5.57; N, 9.29.

Bamberger Reaction. Isolation of Tribenzoylated Derivatives. Preparation of 6-Aryl-4,5-dibenzamido-1-benzoyl-1,2,3,6-tetrahydropyridines 5a,b: General Procedure. The reaction was the same as outlined above, except for the following. The tetrahydroimidazopyridine compound (0.03 mol) (**4a,b**) was allowed to react with 0.12 mol of benzoyl chloride in an aqueous solution containing 0.15 mol of KOH. After the product was separated by filtration, it was stirred for 1 h with a magnetic stirrer in 50 mL of 10% HCl solution. The undissolved solid product was then collected on a filter, washed with water, dried, and recrystallized from acetonitrile.

4,5-Dibenzamido-1-benzoyl-6-(4-methoxyphenyl)-1,2,3,6-tetrahydropyridine (5a) was obtained as an pale yellow solid in 10% yield, mp 201–207 °C. Several recrystallizations from acetonitrile gave white micro needles, mp 211.5–215 °C. ^1H NMR (200 MHz, $CDCl_3$) δ 9.59 (s, 1 H), 9.52 (s, 1 H), 7.96 (m, 2 H), 7.66–6.89 (bm, 18 H), 3.83 (s, 3 H), 3.49 (m, 2 H), 3.22 (m, 1 H), 2.36 (m, 1 H). D_2O exchange caused a loss of a total of two NH proton absorptions, one at δ 9.59 and the other at δ 9.52. LRMS m/z (relative intensity) 531 (M^+, 2), 426 (8), 305 (12), 105 (100), 77 (29). Anal. Calcd for $C_{33}H_{29}N_3O_4$: C, 74.56; H, 5.50; N, 7.91. Found: C, 74.41; H, 5.50; N, 7.78.

4,5-Dibenzamido-1-benzoyl-6-(4-methylphenyl)-1,2,3,6-tetrahydropyridine (5b) was obtained as a white solid in 9% yield. Several recrystallizations from acetonitrile gave white microcrystals, mp 223–226 °C. ^1H NMR (200 MHz, $CDCl_3$) δ 9.58 (s, 1 H), 9.07 (s, 1 H), 7.95 (m, 2 H), 7.65–7.02 (bm, 18 H), 3.46 (bm, 2 H), 3.22 (bm, 1 H), 2.44 (m, 1 H), 2.36 (s, 3 H). D_2O exchange caused loss of a total of two NH protons, one at δ 9.58 and the other at δ 9.07. LRMS m/z (relative intensity) 425 (17), 320 (34), 199 (21), 105 (100), 77 (29). Anal. Calcd for $C_{33}H_{29}N_3O_3$: C, 76.87; H, 5.67; N, 8.15. Found: C, 76.68; H, 5.53; N, 8.07.

Bamberger Reaction. Preparation of Tribenzoylated Product 5a in an Acetonitrile–Water Cosolvent System.[10]

(10) We are indebted to Erik Severin, a Macalester College senior, for conducting this experiment.

Finely divided **4a** (1.1192 g, 4.88 mmol) was dissolved in 35 mL of hot acetonitrile. Cooling the solution to 5 °C produced a saturated suspension, to which was added 30 mL of saturated aqueous sodium bicarbonate solution. While holding the temperature of the reaction mixture at or below 5 °C, a solution of benzoyl chloride (3.10 g, 21.8 mmol) in 20 mL of acetonitrile was added slowly (1 drop/s). When the addition was complete, the reaction mixture was allowed to warm slowly (2 h) to room temperature and remain at that temperature for an additional 2 h. The initial precipitate was filtered off (sodium bicarbonate, 1.413 g). The mixture of two clear phases was then set aside for a few days during which time crystallization occurred. The white solid product **5a** (needles, 498.5 mg, mp 205–210 °C, uncorrected) was collected on a filter and the filtrate was evaporated to dryness. The residue was dissolved in a solvent mixture of 100 mL of water and 100 mL of chloroform. The organic layer was removed and extracted 3 times with 10% HCl and 3 times with 5% aqueous sodium bicarbonate. The organic layer was then evaporated to dryness to give crude **5a** (2.2370 g) as a tan-colored glass. Recrystallization of the crude product from acetonitrile yielded another crop of white needles (1.0665 g, mp 205–207 °C, uncorrected). The total yield was 60.3%. Mixture melting point of each crop of crystals with an authentic sample of **5a** showed no depression.

Bamberger Reaction. Isolation of Monobenzoylated Derivatives. 5-Benzoyl-4-(4-methoxyphenyl)-4,5,6,7-tetrahydro-1*H*-imidazo[4,5-*c*]pyridine (6a). The acid-wash solution from the previously described preparation of compound **5a** was made basic with KOH, and the tarry mass that formed was stirred in the alkaline solution until a powdery suspension remained. The nearly white powder product was collected on a filter, washed with distilled water, and dried. The yield was 63%. Recrystallization from absolute ethanol afforded white crystals, mp 215.5–218 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.38–7.26 (bm, 10 H), 6.87 (s, 1 H), 6.81 (d, J = 8.6 Hz, 2 H), 3.74 (s, 3 H), 3.61 (bm, 1 H), 3.25 (bm, 1 H), 2.73 (bm, 1 H), 2.48 (m, 1 H). D_2O exchange caused a loss of a total of one NH proton absorption at δ 7.38–7.26. LRMS m/z (relative intensity) 333 (M^+, 57), 228 (100), 212 (27), 169 (19), 105 (63), 77 (23).

5-Benzoyl-4-(4-methylphenyl)-4,5,6,7-tetrahydro-1*H*-imidazo[4,5-*c*]pyridine (6b) was isolated as a white powder in 30% yield by basifying the acid-wash solution from the preparation of **5b**. Recrystallization from acetonitrile afforded white microcrystals mp 223–224 °C (uncorr). ^{1}H NMR (200 MHz, $CDCl_3$) δ 10.0 (bm, 1 H), 7.34–7.07 (bm, 10 H), 6.90 (s, 1 H), 3.61 (bm, 1 H), 3.24 (bm, 1 H), 2.47 (bm, 1 H), 2.45 (m, 1 H), 2.29 (s, 3 H). D_2O exchange caused loss of a total of one NH proton absorption at δ 10.0.

5-Benzoyl-4-(4-chlorophenyl)-4,5,6,7-tetrahydro-1*H*-imidazo[4,5-*c*]pyridine (6c). Finely divided **4c** (467 mg, 2 mmol) was dissolved in 5 mL of warm pyridine and the solution was cooled to room temperature. Benzoyl chloride (850 mg, 6.05 mmol) was added dropwise, with stirring over a 2–3-min period. The clear pale yellow solution was heated over steam for 45 min and allowed to cool to room temperature. This solution was then added dropwise with vigorous stirring to 100 mL of aqueous 2% KOH. A white precipitate formed during the addition. After being stirred an additional 75, min the white precipitate was collected on a filter, washed with distilled water, and dried. The yield was 92%. Recrystallization from absolute ethanol afforded white microcrystals, mp 276–280 °C (uncorr.). ^{1}H NMR (200 MHz, DMSO-d_6) δ 7.79–7.44 (bm, 12 H), 3.64 (m, 1 H), 3.18 (m, 1 H), 2.84 (m, 1 H), 2.61 (m, 1 H). LRMS m/z (relative intensity) 337 (M^+, 31), 232 (80), 169 (25), 105 (100), 77 (39).

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Registry No. **4a**, 4875-49-4; **4b**, 4875-43-8; **4c**, 4875-41-6; **5a**, 126036-46-2; **5b**, 126036-47-3; **6a**, 126036-48-4; **6b**, 126036-49-5; **6c**, 126036-50-8; **8a**, 126036-42-8; **8b**, 126036-43-9; **8c**, 126036-44-0; **9a**, 126036-45-1; **9b**, 126061-76-5; **9c**, 126061-77-6.

N-Fluorolactams: Rapid, Mild, and Regiospecific Fluorinating Agents[1]

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Regiospecific aromatic fluorination reactions have received much attention because of the presence of fluoroaryl moieties in a large number of compounds of biological significance and potential pharmaceutical use.[2] The utility of ^{18}F-labeled aromatic compounds in positron emission tomography (PET) has elevated the interest in the field of radiofluorination reactions.[3] The relatively short half-life of the ^{18}F isotope ($t_{1/2}$ = 110 min) imposes stringent demands on the reaction times and efficient utilization of the radiolabel. Particularly noteworthy in this regard is the focus on electrophilic fluorinations of activated aromatic compounds and cleavage of several aryl–metal bonds with fluorine and acetyl hypofluorite.[3,4] The high toxicity of the starting materials, such as arylmercury derivatives, or possible isomer formation makes some of these methods less attractive.[3] Moreover, the high reactivity and oxidizing properties of various fluorinating reagents could prove to be detrimental to compounds containing sensitive functional groups.

Recently, as milder alternatives, several groups have reported *N*-fluoro compounds as useful fluorinating reagents.[5-7] Interestingly, *N*-fluoro-2-pyridone has been prepared and used as a fluorinating reagent. It is speculated that after fluorination, the tautomerization of the pyridone nucleus to 2-hydroxypyridine would be a driving force for the reaction.[8] Actually, 2-hydroxypyridine exists almost exclusively as the pyridone tautomer.[9] Hence it is likely that the pyridone nucleus is not a prerequisite, and *N*-fluoroamides in general could behave as fluorinating agents. Thus, we investigated the properties of *N*-fluoroamides as a general class of fluorinating reagents and in this report we describe our results on the preparation and reactions of *N*-fluorolactams with Grignard reagents.

N-Fluoroamides have been prepared in modest yields by the reactions of amides with CF_3OF.[10] Barton's original method[10] has recently been optimized[12] for the synthesis of fluorolactams. However, CF_3OF is expensive, not readily available, has only a finite shelf life, and is an unattractive choice for radiolabeling techniques. Also, fluorination of

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