showed $[\alpha]^{20}_D$ +43°. The two alcohols were converted into the esters with (+)-MTPA. In the derivative from the *R* alcohol, the CH_3CH doublet adsorbs at δ, 1.21 whereas in the derivative obtained from the *S* enantiomer it adsorbs at δ 1.19.

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Registry No. 1, 87900-45-6; 2, 87841-57-4; 3, 87841-58-5; 4, 87841-59-6; 5, 87841-60-9; 6, 87841-61-0; (*R*)-7, 87900-46-7; (*S*)-7, 87900-47-8; (*S*)-7 (+)-MTPA ester, 87841-72-3; 8, 87841-62-1; 9, 87841-63-2; 10, 87841-64-3; 11, 87841-65-4; 12, 87841-66-5; 13, 87841-67-6; 14, 23406-52-2; 15, 87841-68-7; 16, 87841-69-8; 17, 81445-45-6; (*R*)-18, 87037-69-2; (*S*)-18, 33106-64-8; (*R*)-18 (+)-MTPA ester, 87841-70-1; (*S*)-18 (+)-MTPA ester, 87841-71-2; (+)-2-methoxy-2-(trifluoromethyl)-2-phenylacetic acid, 20445-31-2.

Reaction of Substituted *N*-Methylbenzimidoyl Chlorides with Pyrrole-2-acetate Esters

John E. Mills,* Robin M. Cosgrove, Rekha D. Shah, Cynthia A. Maryanoff, and Vasken Paragamian

McNeil Pharmaceutical, Spring House, Pennsylvania 19477

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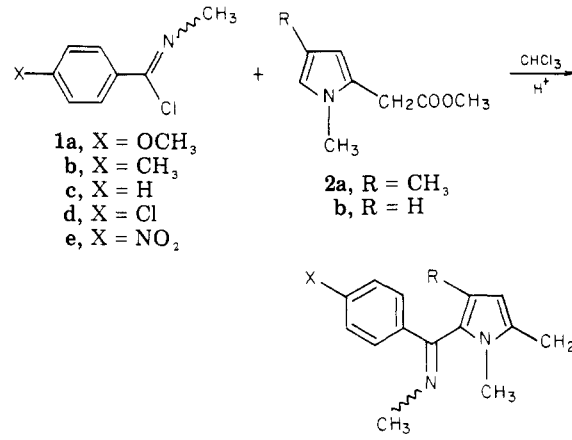
This paper expands the scope of the Vilsmeier–Haack reaction. Stable ketimines are isolated from the reaction of benzimidoyl chlorides with pyrrole derivatives.

The classical Vilsmeier–Haack reaction is the formylation of electron-rich aromatic or heterocyclic compounds or compounds containing activated double bonds, using disubstituted formamides activated by phosphoryl chloride.[1] The term "Vilsmeier reagent" is now often used to denote an amide derivative activated by any one of a number of inorganic or organic acid halides.[2] Depending upon the structure of the Vilsmeier reagent, the products isolated are usually ketones or aldehydes. An exception to this generalization is the Bischler–Napieralski reaction.[3]

Results

The scope of the Vilsmeier–Haack reaction has been extended with the discovery that isolable ketimines are produced in the acid-catalyzed condensation[5] of *N*-methylbenzimidoyl chlorides, **1a–e**, with pyrroleacetates, as shown in Scheme I and Table I. In the absence of added acid catalysts,[6] little or no condensation was observed even at reflux in toluene.

Scheme I



1a, X = OCH_3
b, X = CH_3
c, X = H
d, X = Cl
e, X = NO_2

2a, R = CH_3
b, R = H

3a, X = OCH_3, R = CH_3
b, X = CH_3; R = CH_3
c, X = H; R = CH_3
d, X = Cl; R = CH_3
e, X = NO_2; R = CH_3
f, X = CH_3; R = H

Table I. Summary of Yield and Physical Constant Data[c]

compd	mp (bp, mmHg), °C	% yield isolated	% yield (GLC)[a]
1a	(75-80, 0.1)	76	
1b	(57, 0.1)	80	
1c	(80-90, 0.1)	91	
1d	(125, 15)	83	
1e	67-73	98	
3a	123-129 dec[b]	64	(82.4)
3b	119-124 dec[b]	61	(82.4)
3c	145-147 dec[b]	61	(87.1)
3d	168-171 dec[b]	69	(86.0)
3e	108 dec[b]	65	(92.8)
3f	138-143 dec[b]	30	(39)

[a] GLC yields (using dodecane as internal standard) are not corrected for recovered pyrrole. In all cases, the yield is essentially quantitative when corrected for recovered pyrrole. [b] Isolated as a perchlorate salt. [c] Satisfactory analyses (±0.2% for C, H, N, and Cl) were reported for compounds **3a–f**.

Kinetic data generated to date indicate that unlike the Vilsmeier–Haack reaction of *N*,*N*-disubstituted benzamides,[7] this reaction is not first order in pyrrole, acid halide, or acid. However, the relative order of reactivity of imidoyl chlorides **1a–e** with **2a** is the same as that reported in the Vilsmeier–Haack aroylation of pyrroles. In both reactions, electron-withdrawing groups on the phenyl ring increase the rate of the condensation, while electron-donating groups decrease the rate relative to the unsubstituted case. The half-life values for the reactions of imidoyl halides **1a–d** with pyrrole **2a** when [1] = [**2a**] = 0.17 M and the initial [chlorosulfuric acid] = 1.7×10^{-2} M at 22 °C in chloroform were found to be 20, 13, 8.5, and 6.25 h, respectively. Under the above conditions, the reaction of **1e** with **2a** never proceeded to the point where half of the pyrrole was consumed but stopped at about 38% conversion to products. When [**1e**] = 1.5 M and [**2a**] = 0.35 M, the reaction half-life was 1.38 h.

Irreversibility of product formation was demonstrated by crossover experiments. In the first experiment, pure ketimine **3b** (as its hydrochloride salt) was treated with

(1) A. Vilsmeier and A. Haack, *Chem. Ber.*, **60**, 119 (1927).
(2) For a review of the Vilsmeier–Haack reaction, see: S. Seshadri, *J. Sci. Ind. Res.*, **32**(3), 128 (1973).
(3) The Bischler–Napieralski reaction is an intramolecular Vilsmeier–Haack reaction that leads to dihydroisoquinoline derivatives. Recent modifications of this reaction have used trifluoroacetic anhydride or trifluoromethanesulfonyl anhydride[4a] as activating reagents. Isolated and purified *N*-(2-phenethyl)benzimidoyl chlorides have been shown to cyclize in the presence of Lewis acids.[4b]
(4) (a) S. Nagubandi and G. Fodor, *Heterocycles*, **15**, 165 (1981); (b) S. Nagubandi and G. Fodor, *J. Heterocycl. Chem.*, **17**, 1457 (1980).
(5) The ketimines prepared in this study were surprisingly stable to both acid and base hydrolysis. In most cases, the ketimine may be hydrolyzed to the corresponding ketone in aqueous methanol containing an eightfold excess of sodium acetate in 60–65% yield. Alternatively, the ketimine may be alkylated with dimethyl sulfate and then hydrolyzed with aqueous methanolic sodium bicarbonate in about 75% yield.
(6) Suitable acid catalysts are protic acids, e.g., chlorosulfuric acid and hydrochloric acid. Some imidoyl halides condense with pyrroleacetates in the presence of diethylaluminum chloride. The effect of other Lewis acids has not been studied in detail. For convenience, all work reported in this paper was done with use of chlorosulfuric acid as the catalyst.
(7) (a) J. White and G. McGillivray, *J. Chem. Soc., Perkin Trans. 2*, 259 (1982); (b) *ibid.*, 943 (1979); (c) J. White and G. McGillivray, *J. Org. Chem.*, **42**, 4248 (1977).

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1 molar equiv of imidoyl chloride **1d** and 10 mol % of chlorosulfuric acid. After 24 h at room temperature, GLC showed no evidence of ketimine **3d**. In the second experiment, equimolar quantities of imidoyl chloride **1b** and pyrrole **2a** were treated with a catalytic amount of chlorosulfuric acid. The reaction was allowed to proceed to 85% conversion and then treated with imidoyl chloride **1d**. The reaction was allowed to proceed until only traces of pyrrole were observed by GLC. At this point, the ratio of ketimine **3b** to **3d** was found to be 86:14.

All the perchlorate salts prepared in this study gave ^{1}H NMR spectra that were consistent with the ketiminium salt being a mixture of *E* and *Z* isomers. The isomer ratio varied from ~3:1 in the case of **3e** to ~28:1 for **3b**. The structure of the major isomer for each of the compounds has not been definitely established.[8]

Discussion

Ketimines have been prepared through the condensation of ketones with amines in the presence of titanium tetrachloride,[9] through the condensation of nitriles with organometallic reagents,[10] and several other miscellaneous methods.[11] The current reaction makes ketimines derived from pyrroles available under essentially neutral conditions which are compatible with a variety of functional groups.

Experimental conditions are undemanding. Unlike the Vilsmeier–Haack reaction, this condensation need not be run under strictly anhydrous conditions[7b] in order to obtain good yields of clean products. If the imidoyl halide is used in excess, water is removed through the formation of amide. The resulting amide byproduct does not interfere with the condensation reaction.

Experimental Section

General Procedures. Infrared (IR) spectra were recorded on Perkin-Elmer 727B or 283 spectrophotometers. Unless noted otherwise, ^{1}H NMR spectra were obtained on JEOL JNM-FX60Q (60 MHz) or Perkin-Elmer R32 (90 MHz) instruments with $CDCl_3$ as solvent and Me_4Si as internal reference (20 mg of compound in 0.3 mL of solvent). GLC analyses were performed on a Perkin-Elmer Sigma 2B instrument equipped with flame-ionization detectors. All GLC analyses were performed with 6-ft, 3% SE-30 on 100–200-mesh Chromosorb W glass columns, temperature programmed 2 min 125–260 °C, 10 °C/min, with dodecane as internal standard.

Experiments in $CHCl_3$ were run with either MCB OmniSolv grade chloroform or chloroform with the alcohol stabilizer removed by elution through an activity I alumina column. Chloroform with no stabilizer was stored in amber bottles under argon in a refrigerator at 0 °C prior to use.

Preparation of Benzimidoyl Chlorides 1a–e. The procedure is a modification of that reported by Bartholomew and Kay.[12] The *N*-methylbenzamide (84.5 mmol) and thionyl chloride (33 g, 278 mmol) were placed in a 50-mL, round-bottom flask equipped with a magnetic stirrer, heating mantle, and condensor attached to a trap containing aqueous base. The reaction was stirred and heated at reflux until gas evolution ceased (1–3 h depending upon the amide). The excess thionyl chloride was distilled at ~15 mmHg. The benzimidoyl chlorides were purified by distillation as shown in Table I. In the case of *N*-methyl-4-nitrobenzimidoyl chloride, purification was effected through recrystallization from petroleum ether.

Preparation of Ketimines 3a–f. The appropriate *N*-methylbenzimidoyl chloride (35 mmol) was placed in a dry, 50-mL, round-bottom flask and treated with chloroform (13 mL) and chlorosulfuric acid (0.42 g, 3.6 mmol). The appropriate pyrrole (35 mmol) was added dropwise with stirring over a period of about 5 min, and the reaction was stirred overnight. The orange reaction mixture was quenched into saturated aqueous sodium bicarbonate, the phases were separated, and the organic phase was washed with saturated sodium bicarbonate and water then dried over sodium sulfate, and filtered. The chloroform was removed under reduced pressure. The residue was dissolved in absolute ethanol (~20 mL), cooled, and treated with 70% perchloric acid (5.5 g, 38 mmol). The resulting solution was cooled, stirred, and treated with diethyl ether to induce crystallization. The solid was isolated by filtration, washed with cold ethanol, and air-dried.[13] The IR spectra typically show absorption bands between 1730 and 1745 cm^{-1} and between 1598 and 1608 cm^{-1}. Melting points are given in Table I.

Registry No. **1a**, 78554-86-6; **1b**, 55174-52-2; **1c**, 21737-87-1; **1d**, 39887-78-0; **1e**, 64594-45-2; **2a**, 84145-71-1; **2b**, 51856-79-2; **3a**, 87937-72-2; **3a**·$HClO_4$, 87937-73-3; **3b**, 87937-74-4; **3b**·$HClO_4$, 87937-75-5; **3c**, 87937-76-6; **3c**·$HClO_4$, 87937-77-7; **3d**, 87937-78-8; **3d**·$HClO_4$, 87937-79-9; **3e**, 87937-80-2; **3e**·$HClO_4$, 87937-81-3; **3f**, 87937-82-4; **3f**·$HClO_4$, 87937-83-5; 4-methoxy-*N*-methylbenzamide, 3400-22-4; *N*,4-dimethylbenzamide, 18370-11-1; *N*-methylbenzamide, 613-93-4; 4-chloro-*N*-methylbenzamide, 6873-44-5; *N*-methyl-4-nitrobenzamide, 2585-23-1; thionyl chloride, 7719-09-7.

Supplementary Material Available: Table II, giving IR, UV, and ^{1}H NMR data for ketimine salts **3a–f**, and Table III, giving IR and ^{1}H NMR data for benzimidoyl chlorides **1a–e** (2 pages). Ordering information is given on any current masthead page.

(8) *E*/*Z* isomeric mixtures have been well-documented for a number of ketimines and aldimines as the free bases (see W. B. Jennings, V. E. Wilson, D. R. Boyd, and P. B. Coulter, *Org. Magn. Reson.*, **21**, 279 (1983) and references therein). Work is continuing to establish the structure of the major isomer and to determine substituent effects in this system.

(9) H. Weingarten, J. P. Chupp, and W. A. White, *J. Org. Chem.*, **32**, 3246 (1967).

(10) (a) F. H. Pinkerton and S. F. Thames, *J. Heterocycl. Chem.*, **9**, 725 (1972); (b) P. L. Pickard and D. J. Vaughan, *J. Am. Chem. Soc.*, **72**, 876 (1950).

(11) R. W. Layer, *Chem. Rev.*, **63**, 489 (1963).

(12) D. Bartholomew and I. T. Kay, *Tetrahedron Lett.*, **30**, 2827 (1979).

(13) No shock sensitivity was observed with any of these compounds; however, due care should be exercised in their preparation and handling.

Absolute Configuration of (–)-Vincatine, the Unique 2,16-Seco *Aspidosperma* Alkaloid

Bruno Danieli,* Giordano Lesma, Giovanni Palmisano,* Renata Riva, and Stefano Tollari

Istituto di Chimica Organica della Facoltà di Scienze, Università degli Studi di Milano, 20133 Milano, Italy

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In our continuing study of the chemistry in indole alkaloids,[1] our attention was drawn by (–)-vincatine (VCT, **1**,[2] Chart I) which represents a unique type of alkaloid formally derived from a ring-C-cleaved *Aspidosperma* skeleton. Prompted by the natural occurrence of VCT and of both antipodal vincadifformines (VDF, **2a,b**) in *Vinca minor* L., we set out to correlate **2a,b** → **1** in order to clear up the stereochemistry, relative and absolute, of VCT. While our work was in progress, Ali and Pakrashi[3a] described the results of a similar study. Our findings led to the assignment of the 7*R*,20*S*,21*R* configuration for (–)-

(1) Part of this paper was presented as a communication at the 12th IUPAC International Symposium on the Chemistry of Natural Products at Tenerife, Spain, Sept 21–27 1980.

(2) (a) Döpke, W.; Meisel, H.; Fehlhaber, H. W. *Tetrahedron Lett.* **1969**, 1701. For synthetic studies on VCT, see: Castedo, L.; Harley-Mason, J.; Caplan, M. *Chem. Commun.* **1969**, 1444. Hugel, G.; Laronze, J. Y.; Laronze, J.; Lévy, J. *Heterocycles* **1981**, *16*, 581.

(3) (a) Ali, E.; Roy, S.; Chakraborty, P. K.; Pakrashi, S. C. *Tetrahedron Lett.* **1983**, *24*, 2497. (b) Ali, E.; Chakraborty, P. K.; Chakravarty, A. K.; Pakrashi, S. C. *Heterocycles* **1982**, *9*, 1667.

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