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TOTAL SYNTHESIS OF (+)-PEDERINE. A SIMPLE SYNTHETIC METHOD FOR N-(1-METHOXYALKYL)AMIDES

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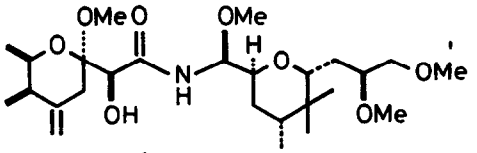
Abstract: A mild one-pot method for the synthesis of acyclic N-(1-methoxyalkyl)amides starting from carboxylic acids and methyl imidates had been developed and applied to the total synthesis of the insect poison pederine 1.

The most characteristic feature of pederine 1[1], the potent insect poison isolated from Paederus fuscipes, is the presence of a rare functionality, acyclic N-(1-methoxyalkyl)amide group[2]. We should like to report here a new, simple and mild synthetic method for this class of compounds and its application to the first total synthesis of pederine 1.



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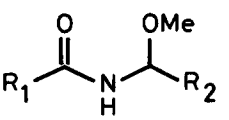

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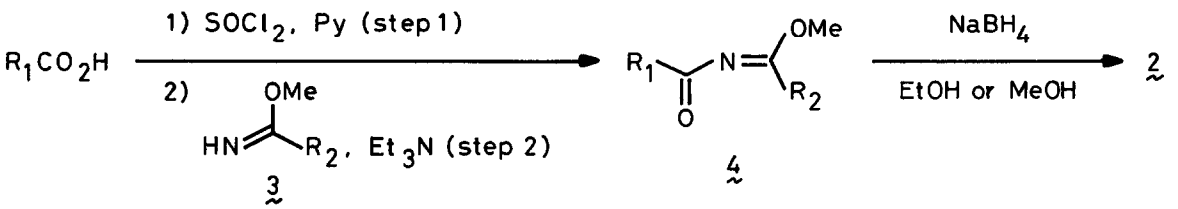
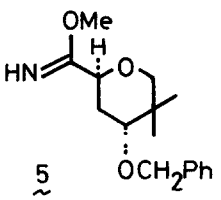
The catalytic effect of a small amount of pyridine in the reaction of thionyl chloride and carboxylic acids is well known. Usually rather drastic conditions, for example excess thionyl chloride and a long period of heating[3], are used. It turned out, however, that carboxylic acids are converted into acid chlorides[4] very rapidly and almost quantitatively, with a nearly stoichiometric amount of thionyl chloride in the presence of pyridine (1.3 - 2.8 equiv.) at room temperature in methylene chloride. Treatment of the resultant acid chlorides in situ with methyl imidates[5] (0.67 equiv.) afforded the corresponding methyl N-acylimidates[6] in high yields. Methyl N-acylimidates thus obtained in turn were reduced with sodium borohydride in alcoholic solvents (0 °C, 10 - 15 min) to give N-(1-methoxyalkyl)amides in excellent yields. Examples of this synthetic method are given in the table. In most cases (entry 1 - 6), carboxylic acids were activated sufficiently within 6 min (step 1). Employing triethylamine (1.2 equiv.) as a base, methyl N-acylimidates were formed usually within 5 min (step 2). By contrast, (+)-acetylpederic acid 6[1b] (entry 7) required a long period of reaction (10 h) to give methyl N-pederoylbenzoimidate 7. Upon

Table Synthesis of N-(1-methoxyalkyl)amides[a] from Carboxylic Acids and Methyl Imidates.



Entry	Carboxylic Acid	Imidate	Step 1			Time for Acylation (Step 2)	Overall Yield[b] of 2 (%)
			$SOCl_2$ equiv.	Py equiv.	Time min		
1	$MeCO_2H$	HN=C(OMe)Ph	1.1	1.4	2	5 min	85[f]
2	$iPrCO_2H$	HN=C(OMe)Ph	1.2	1.3	6	5 min	85[f]
3	$MeCH(OAc)CO_2H$[c]	HN=C(OMe)Ph	1.1	2.8	6	5 min	87[f]
4	$PhCH(OAc)CO_2H$[d]	HN=C(OMe)Ph	1.1	2.8	2.5	5 min	88[f]
5	$MeCH(OAc)CO_2H$	5	1.1	2.8	6	5 min	78[g]
6	$PhCH(OAc)CO_2H$	5	1.1	2.8	2.5	5 min	79[g]
7	6	HN=C(OMe)Ph	1.5	2.1	5	10 h	82[f]



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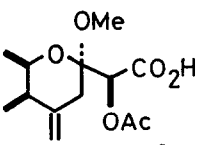

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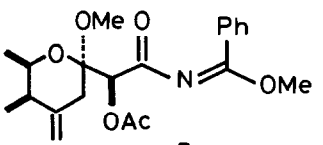

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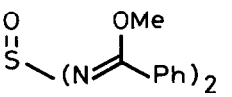

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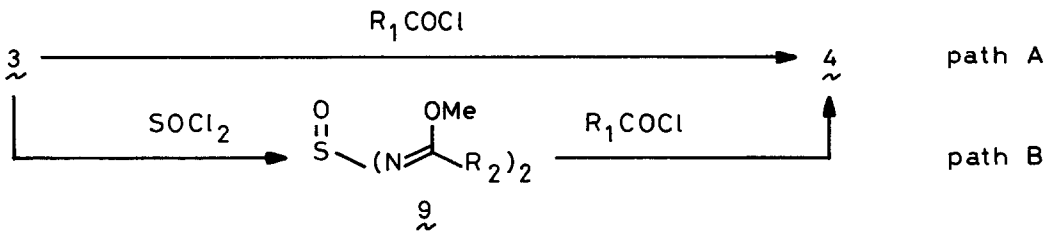
(a) Satisfactory spectral and analytical data were obtained for all new compounds.
(b) Isolated yield (silica gel chromatography) of the N-(1-methoxyalkyl)amide.
(c) Prepared from (±)-lactic acid.
(d) Prepared from (+)-(S)-mandelic acid.
(e) Prepared from the corresponding racemic amide[1a] by treatment with trimethyloxonium tetrafluoroborate[5,7].
(f) Based on methyl benzoimidate. A 1:1 diastereoisomeric mixture by nmr except entries 1 and 2.
(g) Based on the corresponding amide. A 1:1:1:1 diastereoisomeric mixture by nmr.

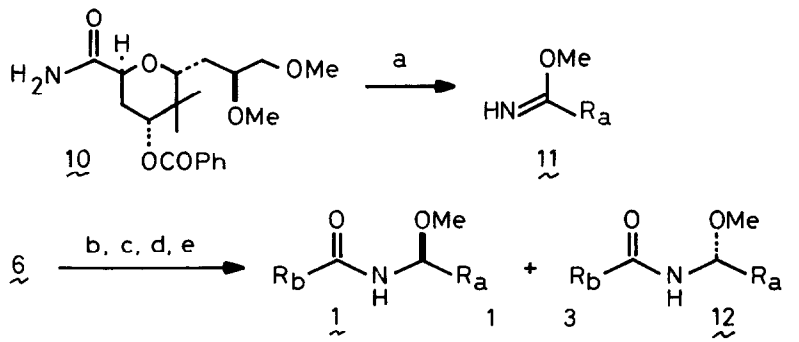
interrupting this acylation reaction after 1 - 3 h, dimethyl N,N'-sulfinyldibenzoimidate 8[8] was obtained along with 7. Compound 8 was formed also by the reaction of methyl benzoimidate with a half equiv. of thionyl chloride employing triethylamine as a base. Treatment of 8 with acetyl chloride or O-acetyllactoyl chloride in the presence of pyridine (r.t., 6 h) afforded the corresponding methyl N-acylbenzoimidates almost quantitatively. Therefore, it is likely that in the case of sterically hindered acetylpederic acid 6 bearing three substituents at the β-position, the rate of the acid chloride formation is slow and the abnormal acylation path via intermediate 9 (path B) proceeds concurrently with the normal acylation path (path A). In the cases of other less hindered acids in the table the acylation reaction takes place via seemingly only path A (Fig 1)[9].

Fig 1



Pederine 1 and acetylpederic acid 6 are extremely sensitive to acidic conditions. Therefore, an attempt was made to apply the new and mild method to the total synthesis of optically active pederine 1. Methyl pedimidate 11[10], obtained from (+)-benzoylpedamide 10[1a] by treatment with trimethyloxonium tetrafluoroborate[5,7], and (+)-acetylpederic acid 6 were connected together through the N-(1-methoxyalkyl)amide linkage by the sequence of reactions shown in Fig 2. After deprotection, a mixture of (+)-pederine 1 and (+)-10-epipederine 12[11] was obtained in 68% overall yield from 10. The mixture was separated by silica gel chromatography and the less polar compound was identical with natural pederine in all respects. The ratio of (+)-pederine 1 to (+)-10-epipederine 12 was 1 to 3.

Fig 2



(a) $Me_3O\ BF_4$ (7 equiv.), CH_2Cl_2, r.t., 14 h (b) $SOCl_2$ (1.4 equiv.), Py (1.9 equiv.), 5 min (c) 11 (0.67 equiv.), Et_3N (1.7 equiv.), 2 h (d) $NaBH_4$, EtOH, 0 °C, 30 min (e) 1N-LiOH, MeOH, r.t., 2 h.

References and Notes

(1) (a) T. Matsumoto et al., Tetrahedron Lett., preceding paper and references cited therein. (b) Optically pure (+)-acetylpederic acid 6 was synthesized through a similar route to that to the racemic one [K. Tsuzuki, T. Watanabe, M. Yanagiya, and T. Matsumoto, ibid., 4745 (1976)], from commercially available (-)-(2R,3R)-2,3-butanediol.

(2) Previously known synthetic methods for this class of compounds: R. P. Linstead, B. R. Shephard, and B. C. L. Weedon, J. Chem. Soc., 2854 (1951); J. E. Baldwin, F. J. Urban, R. D. G. Cooper, and F. L. Jose, J. Am. Chem. Soc., 95, 2401 (1973).

(3) For conventional procedure see for example: J. Cason and E. J. Reist, J. Org. Chem., 23, 1492 (1958).

(4) Almost quantitative formation of acid chlorides was confirmed by comparison of the ^{1}H and ^{13}C nmr spectra of the methylene chloride solution of a mixture of isobutyric acid, thionyl chloride (1.1 equiv.) and pyridine (1.3 equiv.) with (a) those of a methylene chloride solution of authentic isobutyryl chloride and (b) those of a mixture of these two solutions.

(5) General synthetic methods for imidates: R. Roger and D. G. Neilson, Chem. Rev., 61, 179 (1961): D. G. Neilson, in "The Chemistry of the Amidines and Imidates", S. Patai, Ed., John Wiley & Sons, New York, p 389 (1975).

(6) H. Bader, J. Org. Chem. 30, 707 (1965). All methyl N-acylimidates in this paper were obtained as single product. Lanthanide induced shift (LIS) nmr spectra of methyl N-acetylbenzoimidate 1 and methyl N-benzoylacetimidate 11 employing Eu(fod)$_3$ show that those compounds have the E-configuration about C,N-double bond: 1; S[$\Delta\delta$/(Substrate/Eu^{3+})]($CDCl_3$) 8.1 (Me), 4.9 (ortho H), 2.8 (OMe), 11; S($CDCl_3$) 5.9 (ortho H), 5.0 (Me), 1.7 (OMe).

(7) H. Meerwein, Org. Synth., 46, 120 (1966); T. J. Curphey, ibid., 51, 142 (1971).

(8) 8: δ($CDCl_3$) 3.96 (6H, s), 7.27 (10H, bs); m/z 316 (M^+). Anal. Calcd. for $C_{16}H_{16}O_3N_2S$: C, 60.74; H, 5.10; N, 8.85; S, 10.13%. Found: C, 60.64; H, 5.27; N, 8.82; S, 10.20%. In contrast to methyl N-acetylbenzoimidate 1[6], 8 showed in the LIS nmr spectra [$CDCl_3$, Eu(fod)$_3$] the very close S values, 2.5 and 2.3, for ortho protons and methoxy protons respectively. Since Eu^{3+} is expected to coordinate around the oxygen atom of C=O or S=O group, those contrasting results suggest that the configuration of the C,N-double bond of 8 is Z.

(9) This presumption was also supported by monitoring TLC in the course of these acylation reactions.

(10) Unstable. The crude product was used without purification.

(11) Satisfactory spectral and analytical data were obtained for this compound.

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