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A MILD METHOD FOR THE SYNTHESIS OF 2-KETOPYRROLES FROM CARBOXYLIC ACIDS

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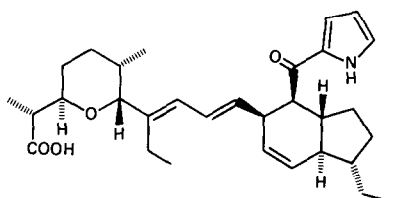
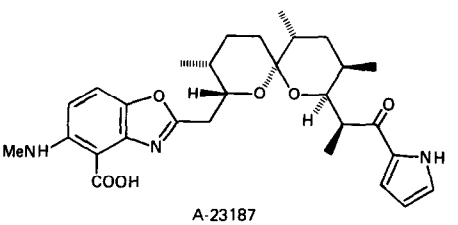
Summary: A mild method for the synthesis of 2-ketopyrroles from carboxylic acids via 2-pyridylthiolesters and pyrrylmagnesium chloride is described.

The 2-ketopyrrole grouping, although rarely reported is apparently biologically important as evidenced by its presence in naturally occurring molecules such as X-14547A[2] and A-23187 (calcimycin)[3]. In conjunction with our program directed towards the total synthesis of the ionophore antibiotic X-14547A[4] we were faced with the introduction of a 2-ketopyrrole system into a complex polyfunctional molecule a problem requiring a mild and chemoselective method for a successful solution.

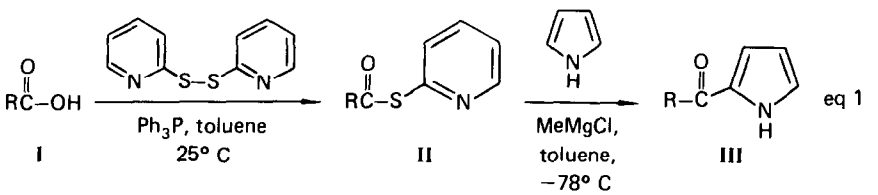


X 14547A



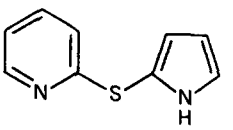
A-23187

In this paper we wish to describe a convenient, mild and highly efficient method for the construction of this functionality from carboxylic acids. Equation (1) outlines the one-pot sequence for this conversion. The carboxylic acid (I) is first converted to the 2-pyridylthiolester (II) with 2,2'-dipyridyldisulfide (1.5 equiv.) and triphenylphosphine (1.5 equiv.)[5] in toluene at 25°C under an argon atmosphere and then pyrrylmagnesium chloride (3 equiv. or more,



I II III eq 1

depending on the number of free hydroxyl groups present in the substrate) is added at -78°C. The reaction is usually complete in a few minutes (typically 10-15 min. at 0.1M concentrations). After quenching at -78°C with saturated ammonium chloride solution the 2-ketopyrrole (III) is isolated in excellent yield either by preparative layer chromatography or flash column chromatography. A common byproduct derived from excess 2,2'-dipyridyldisulfide was also isolated and assigned structure IV on the basis of its spectral data. This material was obtained in 95% yield by reaction of pyrrylmagnesium chloride (2 equiv.) on 2,2'-dipyridyldisulfide in toluene at -78°C (15 min).



IV

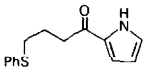
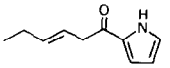
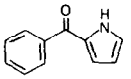
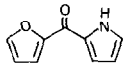
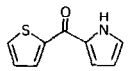
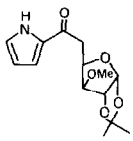
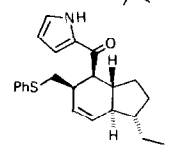
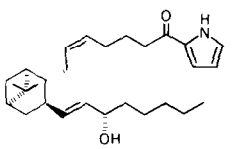
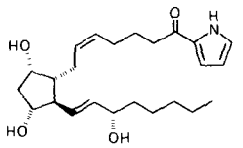
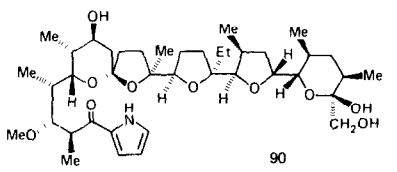
To demonstrate the versatility and mildness of this new methodology, a series of carboxylic acids were utilized as substrates to produce a number of ketopyrroles presented in the Table together with some of their characteristic properties. Among these are included three novel and complex 2-ketopyrrole products derived from biologically active molecules, namely pinanethromboxane A_2 (PTA_2)[6], prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$)[7] and monensin.[8] The biology of these molecules is currently under investigation.

Regarding 2-ketopyrrole synthesis in general, the following comments should be made. Acid chlorides[9] also react with pyrrylmagnesium chloride at -78°C to afford 2-ketopyrroles as the major products but often contamination with 3-ketopyrroles is observed (e.g. n-octanoyl chloride→85% 2-ketopyrrole, 6% 3-ketopyrrole). Methyl esters[10] are inert towards the pyrrylmagnesium chloride at -78°C but react at 25-50°C to afford initially pyrroleamides (C-N bond formation) which are slowly converted to 2-ketopyrroles (e.g. n-methyl-10-undecenoate→amide→2-ketopyrrole, 80%). Lactones also react with the above reagent at elevated temperatures to afford initially hydroxypyrroleamides which also undergo further conversion to hydroxyketopyrroles as final products.[11] Finally a phenylselenoester has been shown to produce a 2-ketopyrrole on exposure to pyrrole and cuprous triflate at 25°C.[12] Clearly, however, the described methodology involving 2-pyridylthiolesters has several advantages over the other methods in terms of mildness, selectivity, efficiency and convenience. The experimental procedure is exemplified below by the preparation of monensin 2-ketopyrrole (10).

Experimental Procedure. Preparation of Monensin 2-Ketopyrrole (10).

Monensic acid (200mg, 0.30 mmole), 2,2'-dipyridyldisulfide (132mg, 0.60 mmole) and triphenylphosphine (156mg, 0.60 mmole) were stirred in toluene (0.60ml, distilled from CaH_2) at 25°C under argon for 24h (TLC indicated complete conversion to thiolester, R_f= 0.30, silica-ether). This reaction mixture was then cooled to -78°C and dropwise treated with pyrrylmagnesium-chloride (5.30ml, 0.34M, 6.0 equiv.; prepared from 0.89ml 2.8M methylmagnesium-chloride in THF diluted with 6.5ml toluene and 0.25ml pyrrole, -40→-10°C, 10 min.). TLC analysis indicated complete reaction in 20 min. at which time the reaction was quenched at -78°C with saturated aqueous ammonium chloride solution (10ml) and the products extracted with ether (3 x 50ml). The combined organic phase was washed with 5% aqueous potassium carbonate solution (3 x 10ml), water (10ml) and brine (10ml) dried (anhydrous $MgSO_4$) and concentrated. The product 2-ketopyrrole monensin (10) was purified by flash column chromatography (silica, 70% ether in hexane, R_f= 0.25) (200mg, 90%). ^1H NMR (250MHz, $CDCl_3$) δ: 11.18 (bs, 1H), 7.03, 6.93, 6.19 (m, 1H, each), 5.90 (s, 1H), 4.65 (d, J = 8.0Hz, 1H) 4.34 (m, 1H), 4.02-3.22 (m, 10H), 3.40 (s, 3H), 2.35-0.75 (m, 45H).

Table Synthesized 2 Ketopyrroles and Selected Properties

Entry	Compound	Yield (percent)	^1H 250-MHz NMR (ketopyrrole) ($CDCl_3$, δ)	IR (ketopyrrole) (ν_{max}, cm^{-1})	RF (silica)[a]
1		95	10 09 (bs, 1H, NH), 7 03, 6 92 and 6 27 (m, 1H each, pyrrole C H)	3440 (s, NH), 1635 (vs, C=O)	0 40, 50EP
2		90	10 12 (bs,1H, NH), 7 04, 6 96 and 6 26 (m, 1H each, pyrrole C H)	3215 (s, NH), 1640 (vs, C=O)	0 45, 50EP
3		92	10 03 (bs, 1H, NH), 7 18, 6 90, and 6 35 (m, 1H each, pyrrole C H)	3280 (vs, NH), 1620 (s, C=O)	0 35, 50EP
4		90	10 65 (bs, 1H, NH), 7 42, 7 15 and 6 35 (m, 1H each, pyrrole C H)	3280 (s, NH), 1600 (s, C=O)	0 23, 50EP
5		89	9 70 (bs, 1H, NH), 7 15 (m, 2H, pyrrole C H), 6 16 (m, 1H pyrrole C H)	3275 (s, NH), 1570, 1580 (s, C=O)	0 48, 50EP
6		89	10 22 (bs, 1H, NH), 7 07, 7 00 and 6 26 (m, 1H each, pyrrole C H)	3290 (s, NH) 1640 (vs, C=O)	0 50, 50EP
7		95	9 63 (bs, 1H, NH), 7 20–6 98 (m, 6H, aromatic and pyrrole C H), 6 85 and 6 29 (m, 1H each, pyrrole C H)	3270 (s, NH), 1640, 1628 (s, C=O)	0 63, 50EP
8		80	9 72 (bs, 1H, NH), 7 01, 6 90 and 6 25 (m, 1H each, pyrrole C H)	3280 (s, NH) 1640 (s, C=O)	0 37, 50EP
9		95	10 02 (bs, 1H, NH), 7 01, 6 91 and 6 24 (m, 1H each, pyrrole C H)	3350 (s, NH), 1640 (s C=O)	0 29 10 MM
10		90	11 18 (bs, 1H, NH), 7 03, 6 93 and 6 19 (m, 1H each pyrrole C H)	3280 (s NH), 1635 1645 (s, C=O)	0 48, E

[a] Key 50EP = 50% ether in petroleum ether 10MM = 10% methanol in methylene chloride E = ether

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