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A Rapid Synthesis of 2,3,11,11a-Tetrahydro-6*H*-pyrazino[1,2-*b*]isoquinoline-1,4-diones Through an Amido Iminium Ion Cyclization

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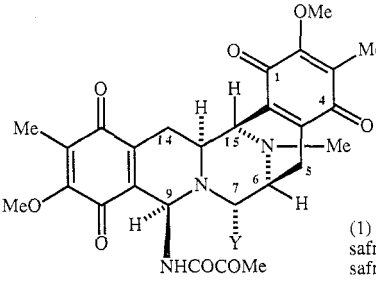
Abstract

7,10-Dimethoxy-6-methyl-2,3,11,11a-tetrahydro-6*H*-pyrazino[1,2-*b*]isoquinoline-1,4-diones (5) and (6) were synthesized from glycine anhydride and 2,5-dimethoxybenzaldehyde through an amido iminium ion cyclization reaction. This method for the construction of the tetrahydroisoquinoline ring will be useful for the synthesis of saframycins.

Saframycins (1)[1] are a class of antitumour antibiotics which possess a common dimeric isoquinoline quinone system. Previous approaches to saframycins have concentrated mainly on the synthesis of the 1,5-imino-3-benzazocine system[2] for subsequent transformations. We now describe a potentially useful new approach to saframycin by the synthesis of the tetrahydropyrazino[1,2-*b*]isoquinoline system, e.g. (5) and (6).

Monocondensation of 2,5-dimethoxybenzaldehyde (2) with *N*,*N*′-diacetyl glycine anhydride[3] could easily be controlled in dimethylfornamide, with potassium t-butoxide and t-butyl alcohol mixture as a base, to give 1-acetyl-3-(2,5-dimethoxybenzylidene)piperazine-2,5-dione (3), a yellowish solid. Hydrogenation of the arylmethylene group in (3), in the presence of palladium on carbon, in acetic acid gave 1-acetyl-3-(2,5-dimethoxybenzyl)piperazine-2,5-dione (4) as a white solid in near quantitative yield.



(1)
saframycin A Y = CN
saframycin S Y = OH

[1] Arai, T., and Kubo, A., in 'The Alkaloids' (Ed. A. Brossi) Vol. 21, pp. 55–100 (Academic Press: New York 1983.
[2] Kurihara, K., Mishima, H., and Arai, T., *Heterocycles*, 1986, **24**, 1549, and references therein.
[3] Shin, C., Yonezawa, Y., Sato, Y., Nakono, T., and Yoshimura, J., *Heterocycles*, 1983, **20**, 405.

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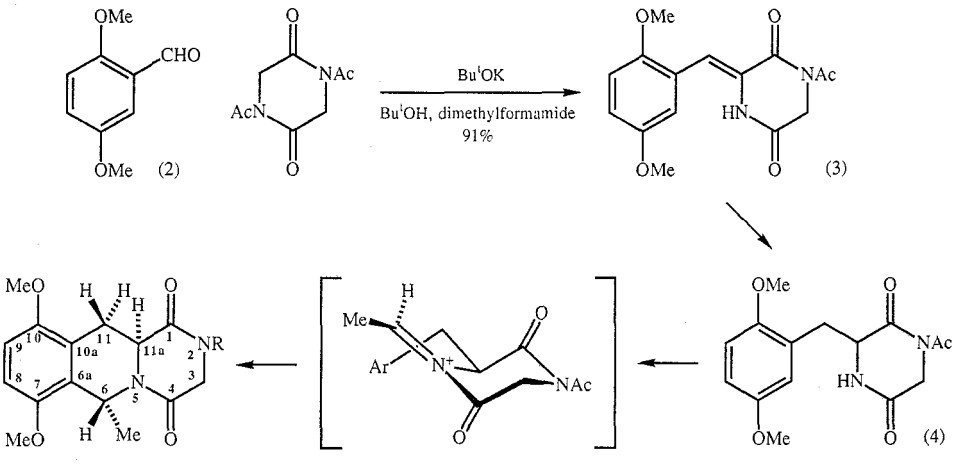
The next stage of this investigation was to establish a method to construct a 1-substituted tetrahydroisoquinoline from (4). The amide in the piperazine-2,5-dione ring of (4) was condensed with acetaldehyde in the presence of trifluoroacetic acid in acetic acid to give (5) and (6). The formation of compounds (5) and (6) must proceed through the reactive amido iminium intermediate (see Scheme 1), followed by an intramolecular Friedel–Crafts cyclization reaction. The amount of deacetylated product (6) obtained is reaction time-dependent, but (6) is normally obtained as the major product. The C4 oxo group in (5) or (6) has the potential of being transformed into the hydroxy or cyanide functional group at C7 of saframycin S or A. Previous construction of the tetrahydroisoquinoline system in saframycin required the reduction of the amide in the piperazine-2,5-dione ring into a secondary amine, followed by a modified Pictet–Spengler cyclization.[4] This method has the disadvantage of giving only unfunctionalized C7 saframycin B.[4]



Scheme 1

The ^{1}H n.m.r. spectrum of (6) displayed H11a as a doublet of doublets at δ 4·37 (J 5·5, 12 Hz), and the methylene protons H11 are both doublet of doublets at δ 3·48 (J 5·5, 17 Hz) and 2·67 (J 12, 17 Hz). The coupling constant of 17 Hz corresponds to the geminal coupling of the C11 methylene protons. The coupling constants of 5·5 Hz (equatorial–equatorial coupling or equatorial–axial coupling) and 12 Hz (axial–axial coupling) between the H11 methylene protons and H11a require H11a to occupy the axial position in the molecule, an arrangement which is also thermodynamically more stable. NOESY experiment allowed us to define the geometry of the C6 methyl group in (6). The C6 methyl group shows a cross-peak to H11a at the axial position. The methyl group at C6 therefore occupies the axial position. The cyclization reaction is thus stereospecific, and proceeds from the less hindered α-face, similar to the reaction reported by Kubo.[4] The stereochemistry of the methyl group is epimeric to that of saframycin A and S, and correct for renieramycins.[5]

[4] Kubo, A., Saito, N., Yamoto, H., Masubuchi, K., and Nakamura, M., *J. Org. Chem.*, 1988, **53**, 4295.

[5] Frincke, J. M., and Faulkner D. J., *J. Am. Chem. Soc.*, 1982, **104**, 265.

In summary, we have developed a new synthetic route towards saframycins, starting from piperazine-2,5-dione.

Experimental

Melting points were determined on a Fisher–Johns apparatus, and are uncorrected. Nuclear magnetic resonance spectra were determined on Varian 300-MHz n.m.r. spectrometer. Infrared spectra were recorded on a Perkin–Elmer 1300 instrument by using liquid cells, and microanalyses for C, H and N were carried out on a Heraeus CHNO rapid analyser. Mass spectra were measured on an A.E.S. MS-12 spectrometer (12 eV).

N,N'-Diacetyl glycine anhydride[3] and 1-acetyl-3-(2,5-dimethoxybenzylidene)piperazine-2,5-dione[3] were prepared according to the procedures described in the literature.

1-Acetyl-3-(2,5-dimethoxybenzyl)piperazine-2,5-dione (4)

1-Acetyl-3-(2,5-dimethoxybenzylidene)piperazine-2,5-dione (3) (2 g, 6·5 mmol) was dissolved in acetic acid (80 ml), and 10% Pd/C was added to the solution. The mixture was set up for hydrogenation in a Parr hydrogenator, and heated at 120° (6 h). The reaction mixture was filtered and on removal of acetic acid afforded (4) in near quantitative yield, m.p. 128–130° (Found: C, 58·6; H, 6·0; N, 9·2. $C_{15}H_{18}N_2O_5$ requires C, 58·8; H, 5·9; N, 9·2%). ν_{max} ($CHCl_3$) 1715, 1670 cm^{-1}. δ $CDCl_3$) 7·36, 1H, br, NH; 6·80, 2H, br s, ArH; 6·75, 1H, br s, ArH; 4·27, 1H, d, J_{gem} 18 Hz, $AcNCH_2CO$; 3·85, 1H, d, J_{gem} 18 Hz, $AcNCH_2CO$; 3·74 and 3·72, 6H, s, 2xOMe; 3·10, m, 3H, CH_2 and CH; 2·60, 3H, s, Ac. *m/z* 306 (M).

*7,10-Dimethoxy-6-methyl-2,3-11,11a-tetrahydro-6*H*-pyrazino[1,2-*b*]isoquinoline-1,4-dione (6), and* N*-Acetylated (5)*

A mixture of compound (4) (1 g, 3·27 mmol), acetaldehyde (0·25 ml), acetic acid (8 ml) and trifluoroacetic acid (2 ml) was refluxed for 5 h. It was left to cool and water added, followed by extraction with chloroform. The chloroform layer was washed several times with sodium bicarbonate solution; it was then dried over anhydrous sodium sulfate, and evaporated to give (5) and (6) (560 mg). Pure *compounds* were obtained after column chromatography [silica gel, with ethyl acetate/light petroleum (4 : 1) as eluent].

Physicochemical data for compound (5): m.p. 206–207° (Found: C, 61·5; H, 6·2; N, 8·6. $C_{17}H_{20}N_2O_5$ requires C, 61·4; H, 6·1; N, 8·4%). ν_{max} ($CHCl_3$) 1710, 1665, 1605 cm^{-1}. δ ($CDCl_3$) 6·90, 2H, s, ArH; 6·15, 1H, q, C**H**CH_3; 4·68, 1H, d, J_{gem} 18 Hz, $AcNCH_2CO$; 4·60, 1H, dd, J 5·5, 12 Hz, CH_2CHCO; 4·21, 1H, d, J_{gem} 18 Hz, $AcNCH_2CO$; 3·83 and 3·80, 6H, s, 2xOMe; 3·45, 1H, dd, J_{gem} 17, $J_{a,e}$ 5·5 Hz, Ar**H**$_2$CH; 2·80, 1H, dd, J_{gem} 17, $J_{a,a}$ 12 Hz, Ar**H**$_2$CH; 2·65, 3H, s, CH_3CO; 1·50, 3H, d, CH_3. Mass spectrum: *m/z* 332 (M), 317 (M−Me), 275 (M−[Me+Ac]), 190 (M−[$CONHCH_2CO$+Me+Ac]).

Physicochemical data for compound (6): m.p. 257–258° (Found: C, 62·0; H, 6·1; N, 4·7. $C_{15}H_{18}N_2O_4$ requires C, 62·0; H, 6·3; N, 4·8%). ν_{max} ($CHCl_3$) 1685, 1655 cm^{-1}. δ ($CDCl_3$) 7·15, 1H, br, NH, exchangeable with D_2O; 6·68, 2H, s, ArH; 5·92, 1H, q, C**H**CH_3, collapsed into a close doublet on decoupling of the methyl group; 4·37, 1H, dd, J 5·5, 12 Hz, $ArCH_2CHCO$; 4·00, 2H, s, $COCH_2NH$; 3·80 and 3·77, 6H, s, 2xOMe; 3·40, 1H, dd, J_{gem} 17, $J_{e,e}$ 5·5 Hz, Ar**H**$_2$CHCO; 2·62, 1H, dd, J_{gem} 17, $J_{a,a}$ 12 Hz, $ArCH_2CHCO$; 1·47, 3H, d, Me. Mass spectrum: *m/z* 290 (M), 275 (M−Me), 247 (M−CONH), 190 (M−[$CONHCH_2CO$+Me]).

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