An Improved Method for the Preparation of N-Unsubstituted 1,4,5,6-Tetrahydrocyclopent[a][b]pyrroles: Synthesis of an Azaprostacyclin Analogue and Its 7-Cyano Derivative

Brigitte Rousseau, Fredy Nydegger, Albert Gossauer, Bärbel Bennu-Skalmowski, Helmut Vorbrüggen

Institut für Organische Chemie der Universität, Ch. du Musée 9, CH-1700 Fribourg, Switzerland
Fax + 41(31)299739; E-mail Albert. Gossauer@unifr.ch.
Research Laboratories of Schering AG, D-13342 Berlin, Germany

Received 13 May 1996

Paal-Knorr cyclization of 2-acetonylecyclopentanone derivatives can be carried out most efficiently by reaction with hexamethyldisilazane (HMDS) when the reagents are previously adsorbed on alumina. By this procedure, the unstable pyrrolprostaglandin derivative rac-

6a has been synthesized in 66% yield from racemic 6-oxoprostag-

landin E1 (rac)-5b. In order to obtain less sensitive pyrrolprostag-

landin derivatives, rac-6a has been transformed into the stable nitriles rac-7a and rac-7b by cyanation of the pyrrole ring with chlorosulfonyl isocyanate in the presence of triethylamine and sub-

sequent cleavage of the protecting groups, respectively.

Cyclopenta[b]pyrroles (1,4,5,6-Tetrahydrocyclopenta[b]-

pyrroles) are of interest not only as partial structures of the phorbine chromophore present in all types of chlorophylls, but also as intermediates in the synthesis of physiologically active cyclopenta[b][c]indoles and as precursors of the 2-azabicyclo[3.3.0]octane skeleton of some potential inhibitors of dipeptidyl carboxypeptidase and of the angiotensin converting enzyme (ACE). However, although diverse single cyclopenta[b]pyrrole derivatives have been reported in the literature, appropriate general methods for their synthesis are scarce. Most of the procedures described so far are associated with two obvious strategies: i) intramolecular cyclization of a side chain situated at the α- or β-position of a pyrrole derivative by electrophilic attack at the vicinal β- or α-position, respectively, and ii) construction of the condensed pyrrole ring starting from an appropriate cyclopentane derivative. Owing to the high versatility of the Paal-Knorr synthesis, the latter approach has been successfully employed in most cases, using 2-acetonylecyclopentanone derivatives and primary amines or hydrazines as reagents. However, although a N-unsubstituted cyclopenta[b]pyrrole have also been prepared by this method, attempted cyclization of diketone 3 in the presence of ammonia failed in our hands to yield the corresponding pyrrole derivative under standard conditions. Even in the presence of CO2 or substituting formamide for ammonia, diketone 3 could not be converted into 4 in appreciable amounts. Recently Rigo et al. reported the formation of 2,5-dimethylpyrrole in 81% yield by the reaction of hexane-2,5-dione with hexamethyldisilazane (HMDS) in the presence of trifluoromethanesulfonic acid. This modification of the Paal-Knorr reaction was carried out with 3 as the substrate, resulting in a moderate yield of the desired cyclopenta[b]pyrrole 4.

Among the different variants of the Paal-Knorr reaction, the cyclization of hexane-2,5-dione, heterogeneously catalyzed with alumina or clay, seemed to be particularly attractive because of the high yields (90–99%) of N-substituted 2,5-dimethylpyrroles obtained with primary amines at room temperature. Therefore, we tried to re-place the primary amine with HMDS in the heterogeneous medium, thus avoiding the use of trifluoromethanesulfonic acid as a catalyst. Under these conditions, hexane-2,5-dione (1) was converted in 60% yield into 2,5-dimethylpyrrole (2) within 2 hours at room temperature. After 24 hours a maximum conversion rate of 80% was attained, which could not be improved either by prolonging the reaction time (up to 5 days) or increasing the molar ratio of HMDS. A considerable reduction of the reaction time could be achieved, however, when the reaction mixture was heated to 100–110 °C, so that the hexamethyldisiloxane formed evaporated during the reaction (see Table). By this procedure, 4 could be obtained from diketone 3 in 78% yield.

After appropriate reaction conditions had been found to obtain the cyclopenta[b]pyrrole 4 as a model compound, we tackled the actual goal of the present work, namely the synthesis of the azaprostacyclin derivative 6c, the N-unsubstituted analogue of Prostacyclin (U-60, 257: 6d). The latter is a selective inhibitor of the leukotrienes LTA4, D4, and E4 biosynthesis in rat peritoneal cells, which attracts attention as a repressor of anaphylaxis in astmatic patients. Actually, a systematic study of synthetic analogues of prostaclin (PGI2) is worth carrying out, owing to the interesting properties of the latter as the most efficient natural inhibitor of platelet aggregation, as well as a potent vasodilator, the biological evaluation
Table. Dependence on the Reaction Conditions of the Heterogeneously Catalyzed Paal-Knorr Cyclization of Hexane-2,5-dione with HMDS

<table>
<thead>
<tr>
<th>HMDS (M)</th>
<th>Time</th>
<th>Temp. (°C)</th>
<th>% Conversion to 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.1</td>
<td>2 h</td>
<td>20</td>
<td>60</td>
</tr>
<tr>
<td>1.1</td>
<td>24 h</td>
<td>20</td>
<td>80</td>
</tr>
<tr>
<td>2.0</td>
<td>24 h</td>
<td>20</td>
<td>80</td>
</tr>
<tr>
<td>1.5</td>
<td>20 min</td>
<td>105 ± 5</td>
<td>quant.</td>
</tr>
</tbody>
</table>

* Monitored by 1H NMR spectroscopy.
| Isolated yield: 80%.

of which is severely complicated by the instability of this substance in aqueous solution under physiological conditions. Although derivative 6a is mentioned both in patents and in the literature details concerning its synthesis, which proved to be irreproducible via Paal–Knorr cyclization of 6-oxoprostaglandin E1 (5a), have not yet been published. Nevertheless, this route remained particularly attractive because of the ready accessibility of 5a, both from commercially available prostaglandin F2α (PGF2α) in five steps (53% overall yield) and by total synthesis. In any event, reaction of 5a with hydrazine yields the corresponding dihydropyridazine derivative, whereas its attempted transformation into the furan analogue of 6a failed. From this background, the Paal–Knorr cyclisation of 6-oxoprostaglandin E1 was attempted using the method described above for the synthesis of 4. For practical reasons, however, 6-oxoprostaglandin E1 was prepared by the three-component coupling method starting from racemic precursors, so that a racemic mixture of two epimers at C-15 (rac-5b) was obtained. Although, after cleavage of the silyl ether protecting groups, a chromatographic separation of the two epimers on silica gel using ethyl acetate/hexane (3:1) as eluent proved to be feasible, it was advantageous to carry out the separation of the diastereomeric products following the Paal–Knorr cyclization of rac-5b. As a result, after desilylation of the bis(silyl) ether rac-6a and chromatographic separation, one single diastereomer of rac-6b, the relative configuration of which at C-15 remains to be determined, was obtained as pale yellow crystals (mp 70–73 °C) in 55% overall yield (cf. Experimental Part). Unfortunately, however, rac-6b proved to be an extremely labile compound, which darkens visibly in the air, unless it is stored in the refrigerator at -18 °C, hence its hydrolysis to rac-6c was not attempted.

The extreme instability of the prostacyclin analogue rac-6b thwarted the evaluation of its potential pharmacological applications. However, as it is well known that electron-withdrawing substituents decrease both the nucleophilicity and the oxidisability of the pyrrole nucleus, the introduction of a cyano group in the pyrrole ring was investigated next. A particularly mild and efficient reagent for this purpose proved to be chlorosulfonyl isocyanate, which has been already used successfully by Anderson et al. to synthesize some pyrrole nitriles. Thus, reaction of rac-6b with chlorosulfonyl isocyanate in the presence of triethylamine afforded the cyano derivative rac-7a, which after cleavage of the silyl ether protecting groups could be transformed, albeit under considerable loss of material, into the corresponding carboxylic acid rac-7b by alkaline hydrolysis.

Since 5a is readily accessible, as mentioned before, from natural prostaglandin F2α, enantiomeric pure 6b and 7b were obtained by the same procedure outlined above. A study of the biological properties of the latter is, at present, in progress.

All air- and water-sensitive reactions were carried out under argon. Hexamethyldisilazane, hexane-2,5-dione, chlorosulfonyl isocyanate and other reagents were purchased from Fluka. Bu₄NF · 3H₂O (TBAF) was purchased from Aldrich. Solvents for chemical reactions and chromatography were generally dried and distilled prior to use. Paal–Knorr cyclizations were carried out on Al₂O₃ 90
(70–230 mesh) of activity II–III from E. Merck. Reactions were monitored by TLC on E. Merck silica gel 60 F254 (0.2 mm) precoated aluminium foils, developed with an aq solution of KMnO4 (1 %) and NaOH (2 %) or with Ehrlich’s reagent. Column chromatography (CC): E. Merck silica gel 60 (230–400 mesh). Mp’s: Koller hot stage apparatus (Thermovar, C. Reichert AG, Vienna); uncorrected. IR: Perkin-Elmer-IR-599. NMR (CDCl3): Varian Gemini 200 (1H: 50.30 MHz), Bruker-AM-360 (1H: 360.14 MHz; 13C: 90.56 MHz) equipped with a data system Aspect 3000 or Bruker Avance DRX500 (1H: 500.13 MHz; 13C: 125.76 MHz; chemical shifts (δ) in ppm, relative to MeSi as internal standard. J values in Hz; assignments based on homonuclear COSY-45. 1H/13C NOE difference correlations, and/or δ values. MS: Vacuum Generators Micromass 7070 E equipped with a data system DS 11–250. EI-MS were measured at an acceleration voltage of 70 eV, FAB-MS (at 6 kV) in 3-nitrobenzyl alcohol (NNOA) with argon at 8 kV; m/z and relative intensities (%) in parentheses.

2.5-Dimethylpyrrole (2); Typical Procedure:
Hexane-2,5-dione (342 mg, 3 mmol) was thoroughly mixed with alumina (1 g) before HMDS (1 mL, 4.8 mmol) was added, and the mixture was heated at 100–110°C until the hexamethyldisiloxane formed was completely evaporated (about 20 min). Once the mixture cooled down to r.t., the product was eluted with CHCl3 and the oil obtained after evaporation of the solvent was purified by distillation; yield: 231 mg (81 %); bp 68°C/18 Torr (Lit. 31 bp 78–80°C/25 Torr)

Methyl 6-Oxo-7-(2-oxocyclohexyl)heptanoate (3):
A solution of methyl 6-nitro-6-enoate (0.93 g, 5 mmol) in CH2Cl2 (10 mL) was cooled to –78°C before TICl3 (0.93 g, 5 mmol) was added. The mixture was stirred for 20 min and, thereafter, 1-trimethylsilyloxy-cyclopentene (0.67 g, 4.3 mmol) was added within 15 min. Stirring was continued for 1 h at –78°C before the mixture was allowed to warm up to r.t. Thereafter, H2O (7 mL) was added and the mixture was heated for 2 h at 100°C. The organic layer was separated, the aq phase extracted with CH2Cl2 (3 × 10 mL) and the combined organic extracts were evaporated to dryness. The residue was dissolved in MeOH (20 mL) and the solution was refluxed for 6 h, after addition of conc. H2SO4 (1 mL). The solvent was evaporated and the residue dissolved in Et2O (20 mL). The solution was washed successively with H2O and brine, and dried (MgSO4) before the solvent was evaporated. Finally, the residue was chromatographed (EtOAc/hexane, 1:2) to yield 580 mg (56 %) of 3 as an oil.

1H NMR (360.14 MHz): δ = 1.4–1.7 (m, 5H), 1.8 (m, 1H), 2.05 (m, 1H), 2.1–2.6 (m, 2H), 2.86 (m, 1H), 3.66 (s, OCH3). 13C NMR (50.30 MHz): δ = 20.71 (t), 23.12 (t), 24.34 (t), 29.44 (t), 33.71 (t), 37.13 (t), 42.26 (t), 42.76 (t), 44.01 (dd), 51.41 (q), 173.68 (s, CO2). EI-MS: m/z = 240 (M +), 208 (9), 143 (32), 140 (32), 140 (35), 125 (68), 115 (18), 111 (100), 97 (63), 83 (31), 73 (18), 69 (25), 55 (35). Anal. calc. For C13H22O4: C 64.98, H 8.39; found: C 64.92, H 8.55.

Methyl 5-(1,4,5,6-Tetrahydroyclopentyl)pyrrolo-2(1H)-pyranoate (4):
Diketone 3 (100 mg, 0.5 mmol) was reacted with HMDS (160 mg, 1 mmol), as described for 2, and the product obtained was purified by column chromatography on alumina (EtOAc/CH2Cl2/hexane, 1:2:2) to afford 87 mg (78 %) of 4 as white crystals; mp 66–68°C (hexane).

1H NMR (360.14 MHz): δ = 1.5–1.75 (m, 4H, H-3,4), 2.3–2.4 (m, 4H, H-2,5), 2.58 (t, J = 7.3, 4H, H-5), 2.65 (t, J = 7.0, H-4), 3.67 (s, OCH3), 5.60 (s, H-3), 7.63 (s, NH). 13C NMR (90.56 MHz): δ = 24.54 (t), 25.38 (t), 25.56 (t), 28.12 (t), 29.00 (t), 29.25 (t), 33.84 (t), 51.50 (q), 100.89 (d), 126.43 (s), 134.62 (s), 153.23 (s), 170.94 (s, CO2). EI-MS: m/z = 222 (14, [M + 1]t), 221 (91, M+), 190 (24), 134 (12), 133 (12), 132 (11), 121 (46), 120 (100), 118 (19), 106 (12), 77 (11). Anal. calc. For C13H15NO2: C 70.55, H 8.65, N 6.33; found: C 70.55, H 8.54, N 6.07.
(±)-(13E)-7-Cyano-6,9-iminoprosta-6,8,13-trien-1-oic Acid (rac-7b):
A solution of rac-7a (240 mg, 0.39 mmol) and TBAF (840 mg, 0.44 mmol) in anhyd THF (15 mL) was stirred for 24 h at r.t. and, thereafter, kept for 5 d at +40°C. After evaporation of the solvent, the residue was redissolved in CH₂Cl₂ and shaken with sat. NaHCO₃. The organic phase was separated, dried (Na₂SO₄), and the solvent evaporated yielding 350 mg of crude (±)-(13E)-7-cyano-6,9-iminoprosta-6,8,13-trien-1-oic acid methyl ester, which was purified by column chromatography on silica gel (5 g) using EtOAc as eluent. To a solution of the thus obtained methyl ester (52 mg) in MeOH (2 mL) was added a 5% aq solution of LiOH (1 mL), and the mixture was allowed to stand for 3 h at 24°C before an ice-cooled solution of citric acid was added, until pH 3–4 was attained. Extraction with EtOAc afforded, after evaporation of the solvent, 8 mg (24%) of crude rac-7b as an oil.

1H NMR (CDCl₃, 400 MHz): δ = 0.89 (t, J = 6.9, CH₃), 1.30–1.80 (m, 12H, H-3, 4, 16 to 19), 2.42 (t, J = 6.9, 2H, H-2), 2.63 (dd, J = 14.9, 4.0, 1H, H-10), 2.76 (t, J = 6.5, 2H, H-5), 3.10 (dd, J = 14.8, 6.8, 1H, H-9), 3.52 (dd, J = 6.4, 3.9, 2H, H-12), 4.08–4.15 (m, H-11), 4.51–4.60 (m, H-15), 5.64–5.75 (m, 2H, H-13,14), 8.62 (br s, NH).

Cl-Ms (NH₃): m/z = 392 (100, [M + NH₄⁺]), 374 (6.5, M⁺), 357 (5.7).

HR-FAB-MS: m/z = 397.2076 ([M + Na⁺]); calc. for [C₂₁H₃₀N₂O₄Na⁺]: 397.2103

Financial support of this work by the Schering A. G. (Berlin) is gratefully acknowledged. NMR and mass spectra were recorded at Fribourg by F. Fehr and F. Nyadeger, as well as at Schering A. G. by G. Michl, G. Baude and G. Bös. Elemental analyses were carried out at Ciba Geigy AG, Forschungszentrum, CH-1723 Marly, Switzerland.

(8) Cookson, G. H.; Rimington, C. Biochim. J. 1954, 57, 476.
(20) Meunier, A.; Neiter, R. Synthesis 1988, 381.