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Traceless Solid-Phase Synthesis of Heterosteroid Framework

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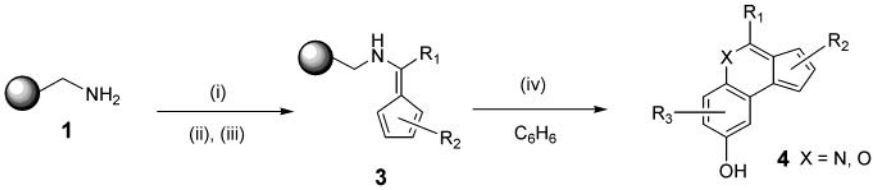
ABSTRACT



(i) R_1CO_2H, DCC, HOBt, DMAP, Et_3N, CH_2Cl_2; (ii) Et_3OBF_4/THF; (iii) Sodium cyclopentadienide/THF; (iv) Benzoquinones or indoanilines

A traceless solid-phase synthesis of cyclopenta[*c*]-4*H*-chromen-8-ol, benzo[*d*]cyclopenta[*e*]-3*H*-3-azin-8-ol, and other 11-heterosteroids via the fulvene hetero [6 + 3] cycloaddition is described.

The explosive development of combinatorial chemistry over the past few years has led to a renaissance in the development of solid-phase synthetic methodologies.[1,2] The development of efficient and reliable methods of forming carbon−carbon bonds remains an important issue in solid-phase synthesis. In conjunction with our continuing efforts in fulvene chemistry,[3] we recently reported the fulvene hetero [6 + 3] cycloaddition[4] and the facile synthesis of 11-oxosteroid derivatives.[5] The synthesis and physiological activity of heterosteroids have received a lot of attention over the years.[6] In light of the physiological significance of the 11-oxo-adenocortical hormones, heterosteroids in which the methylene group at position 11 has replaced by a heteroatom are of special interest.[7] Herein, we report the application of this technology to the solid-phase synthesis of cyclopenta[*c*]-4*H*-chromen-8-ol, benzo[*d*]cyclopenta[*e*]-3*H*-3-azin-8-ol and 11-heterosteroids libraries. To the best of our knowledge, this is the first example of a [6 + 3] cycloaddition as well as the first example of fulvene chemistry on solid support.

Scheme 1 outlines our traceless linker strategy using polystyrene amino resin (**1**).[8] Formic acid was coupled to **1**

(1) For recent reviews of solid-phase organic reactions, see: (a) Hermkens, P. H. H.; Ottenheijm, H. C. J.; Rees, D. C. *Tetrahedron* **1997**, *53*, 5643. (b) Brown, R. C. *J. Chem. Soc, Perkin Trans. 1* **1998**, 3293. (c) Früchtel, J. S.; Jung, G. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 17. (d) Obrecht, D.; Villalgordo, J. M. *Solid-Supported Combinatorial and Parallel Synths of Small-Molecular-Weight Compound Libraries*; Pergamon: Kidlington, UK, 1998; p 1131. (e) Booth, S.; Hermkens, P. H. H.; Ottenheijm, H. C. J.; Rees, D. C. *Tetrahedron* **1998**, *54*, 15385. (f) James, I. W. *Tetrahedron* **1999**, *55*, 4855. (g) Dolle, R. E.; Nelson, K. H. *J. Comb. Chem.* **1999**, *1*, 235.

(2) For an excellent example of a recent publication, see: Nicolaou, K. C.; Snyder, S. A.; Bigot, A.; Pfefferkorn, J. A. *Angew. Chem., Int. Ed.* **2000**, *39*, 1093.

(3) For previous papers in this series, see: (a) Hong, B.-C.; Chen, Z.-Y.; Kumar, E. S. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1135. (b) Hong, B.-C.; Hong, J.-H. *Tetrahedron Lett.* **1997**, *38*, 255. (c) Hong, B.-C.; Sun, S.-S. *Chem. Commun.* **1996**, 937. (d) Hong, B.-C.; Sun, S.-S. *Tetrahedron Lett.* **1996**, *37*, 659.

(4) For [6 + 3] cycloaddition, see: Hong, B.-C.; Sun, S.-S.; Tsai, Y.-C. *J. Org. Chem.* **1997**, *62*, 7717.

(5) For hetero [6 + 3] cycloaddition, see: Hong, B.-C.; Sun, H.-I.; Chen, Z.-Y. *Chem. Commun.* **1999**, 2125.

(6) Kutney, J. P.; Vlattas, I.; Rao, G. V. *Can. J. Chem.* **1963**, *41*, 958. Rastogi, R. C.; Chowdhury, M. N. R.; Engel, C. R. *Steroids* **1973**, *21*, 147.

(7) Engel, C. R.; Rastogi R. C.; Chowdhury, M. N. R. *Steroids* **1972**, *19*, 1. Engel, C. R.; Chowdhury, M. N. R. *Tetrahedron Lett.* **1968**, 2107. Suginome, H.; Wang, J. B.; Yamada, S. *Chem. Lett.* **1987**, 783. Suginome, H.; Yamada, S.; Wang, J. B. *J. Org. Chem.* **1990**, *55*, 2170. Hildebrandt, K.; Debaerdemaeker, T.; Friedrichsen, W. *Tetrahedron Lett.* **1988**, *29*, 2045.

(8) Purchased from Aldrich Chemical Co. (1.5 mmol/g) or Advanced ChemTech, Inc. (1.1 mmol/g, 100−200 mesh).

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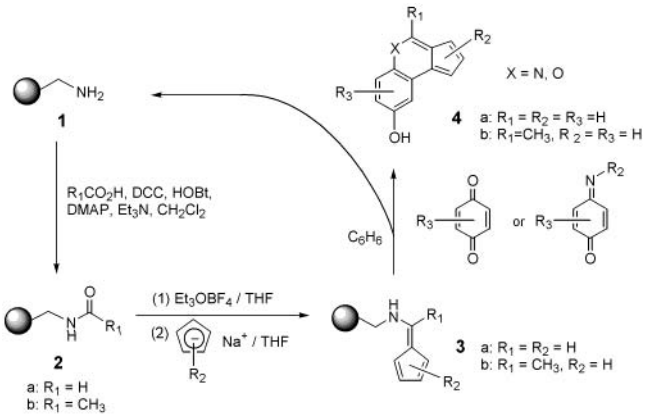
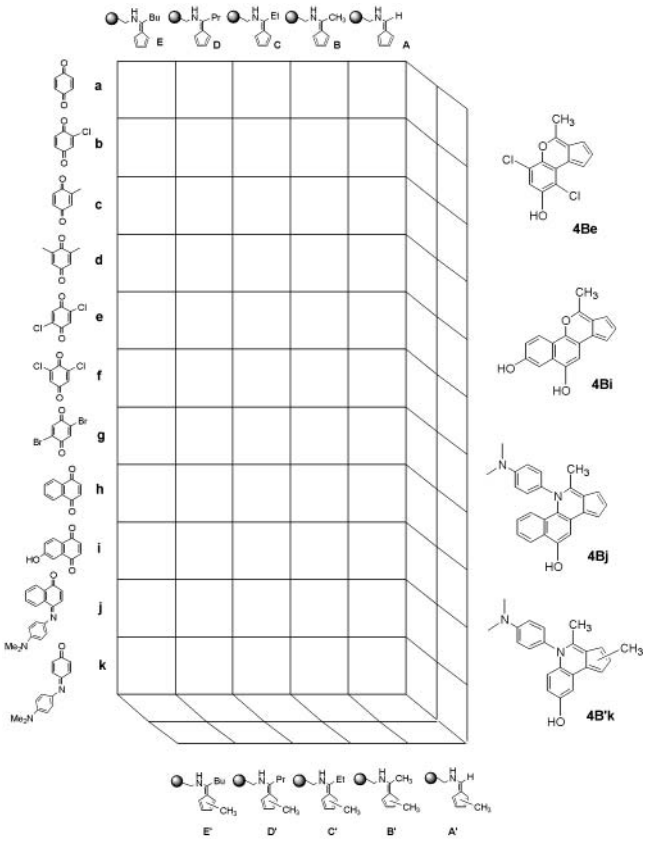
Scheme 1



under standard conditions (DCC, HOBt, DMAP, CH_2Cl_2).[9] Product **2a** was then treated with Et_3OBF_4[10] in THF at 0 °C for 1 h. Subsequently, a 3.0 M THF solution of sodium cyclopentadienide was added and the reaction was slowly warmed to room temperature and agitated for 12 h.[11] The resin was filtered, washed with CH_2Cl_2 (3×), and dried under high vacuum to afford **3a**. The fulvene resin **3a** (100 mg) was added to a solution of benzoquinone in C_6H_6 (0.8 mL, 0.1 M), and the mixture was placed on a rotary motor for 12 h at 25 °C.[12] The supernatant was filtered through a short pad of silica gel and eluted with 4 mL of C_6H_6. Product **4a** was isolated in greater than 95% purity, with no other observable side products.[13] The same reaction sequence was successfully carried out on a 10-fold larger scale without any loss of purity.[14] The methodology was then generalized to a 110-membered heterosteroid library. A selection of 5 carboxylic acids, 2 cyclopentadienyl anions, and 11 benzoquinones were reacted according to the process illustrated in Scheme 1. Following SiO_2 filtration, the final products were isolated in good yield[15] and >95% purity as determined by HPLC and/or GC-MS analysis (Table 1).[16]

Table 1. Traceless Solid-Phase Synthesis of **4** via Hetero [6 + 3] Cycloaddition



Preliminary in vitro assay revealed that **4Be** and **4Bj** possess moderate inhibitory activity against a variety of NCI cancer cell lines (average $GI_{50} = 2.4 \times 10^{-5}$ and 9.5×10^{-6} M, respectively).[17] It is noteworthy that **4Bj** exhibits high inhibitory activity against MCF7 and T-47D breast cancer cells ($GI_{50} = 3.9 \times 10^{-7}$ and 3.0×10^{-7} M, respectively).[18] We are currently following up on these results.

(9) The reactions were conducted in Bio-Rad Econo-Pac Disposable columns. Agitation was accomplished by rotating the column with a rotary motor unless otherwise indicated. The extent of the coupling reaction was monitored by IR.

(10) For preparation, see: Hafner, K.; Schulz, G.; Wagner, K. *Liebigs Ann. Chem.* **1964**, *678*, 39.

(11) The reaction was agitated in an ultrasonic bath.

(12) In solution phase, this reaction was completed in a few minutes.

(13) The purity of the products was determined by GC-MS and HPLC analysis.

(14) The product was conformed by its ^1H and ^{13}C NMR spectrum.

(15) The loading of the fulvene resin **3** was estimated to be ca. 0.4 mmol/g on the basis of the consumption amount of benzoquinones in the following hetero [6 + 3] reaction (assume 100% conversion in the reaction). On the basis of this loading number, we noticed that when slightly less than 1 equiv of benzoquinone was used in the last step, products **4** were isolated free of impurity as shown by HPLC. The following are selected overall yields of isolated products after four steps: **4Be** (40%), **4Bj** (42%), **4Bi** (38%), **4B′k** (32%). These yields are based on the initial loading of the amino polystyrene resin (1.1 mmol/g).

(16) Selected spectral data for **4Be**: ^1H NMR (acetone-d_6, 400 MHz) δ 7.64 (dd, J = 2.8, 1.2 Hz, 1H), 7.20 (s, 1 H), 7.07 (d, J = 2.8 Hz, 1 H), 7.02 (d, J = 1.2 Hz, 1 H), 2.79 (s, 3 H); ^{13}C NMR (acetone-d_6, 100 MHz) δ 158.56 (C), 151.97 (C), 140.02 (C), 133.03 (CH), 123.67 (C), 122.69 (C), 122.57 (C), 122.18 (C), 120.35 (CH), 116.02 (CH), 115.35 (CH), 18.57 (CH_3); MS (*m*/*z*, relative intensity) 270 ($M^+ + 4$, 13), 268 ($M^+ + 2$, 64), 266 (M, 100), 231 (8), 167 (10), 139 (33); exact mass calculated for $C_{13}H_8O_2Cl_2$ (M^+) 265.9902, found 265.9903. For **4Bi**: ^1H NMR (DMSO-d_6, 400 MHz) δ 8.29 (d, J = 8.8 Hz, 1 H), 7.47 (d, J = 2.4 Hz, 1 H), 7.22 (dd, J = 2.8, 9.2 Hz, 1 H), 7.20 (s, 1 H), 7.00 (d, J = 2.8 Hz, 1 H), 6.86 (dd, J = 4.8, 1.2 Hz, 1 H), 6.71 (dd, J = 2.4, 1.2 Hz, 1 H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 156.57 (C), 155.52 (C), 149.56 (C), 137.44 (C), 131.12 (CH), 126.04 (C), 124.65 (C), 122.56 (CH), 121.53 (C), 119.23 (C), 118.98 (CH), 114.14 (C), 111.37 (CH), 108.12 (CH), 105.29 (CH), 100.73 (CH), 17.94 (CH_3); MS (*m*/*z*, relative intensity) 264 (M^+, 100), 235 (12), 221 (8), 189 (9), 178 (10), 125 (15), 111 (22); exact mass calculated for $C_{17}H_{12}O_3$ (M^+) 264.0786, found 264.0781.

(17) The testing was performed by the Developmental Therapeutics Program, NCI, USA. The compounds were evaluated for their in vitro cytotoxicity against 60 human cell lines derived from seven clinically isolated cancer types (lung, colon, melanoma, renal, ovarian, brain, and leukemia) according to the NCI standard protocol, see: http://dtp.nci.nih.gov/.

(18) For a 3D QSAR study of the specific mitogenic response of MCF-7 cells by estradiol analogues, see: Wiese, T. E.; Polin, L. A.; Palomino, E.; Brooks, S. C. *J. Med. Chem.* **1997**, *40*, 3659. (b) For inhibition of glutathione S-transferase activity by the equilenin analogues, see: Chang, M.; Zhang, F.; Shen, L.; Pauss, N.; Alam, I, van Breemen, R. B.; Blond, S. Y.; Bolton, J. L. *Chem. Res. Toxicol.* **1998**, *11*, 758.

In conclusion, we have developed a novel example of the construction of steroid frameworks on solid supports. The mildness of the reaction and traceless cleavage conditions make this process well suited to automated synthesis for the construction of large array libraries. This strategy exploits a unique reaction for liberating the fully elaborated product from resin and offer a new approach toward combinatorial libraries of hereosteroids frameworks. An extension of this sequence to a more extensive library synthesis and the biological screening assay is currently underway.

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