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Solid Phase Synthesis of Cyclopropenes

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Abstract: Cyclopropene derivatives of high purity were prepared by reaction of acetylenes with a rhodium carbenoid bound to a polystyrene resin. This solid phase method avoids the formation of undesired byproducts obtained in the corresponding solution reaction and an eventual extension to combinatorial synthesis of cyclopropene derivatives could be achieved.

Among the synthetic procedures for preparation of cyclopropene derivatives, the reaction of acetylenes with carbenoids generated by Rh(II) carboxylate catalyzed decomposition of diazoacetamides or esters is one of the most useful ones.[1] However, the experimental conditions used in this procedure must be carefully adjusted to avoid unwanted side reactions of the rhodium carbenoid with its own precursor, the diazo compound, or the cyclopropene product.

Our ongoing interest in cyclopropene derivatives as putative desaturase inhibitors in insect pheromone biosynthesis [2] prompted us to carry out the above reaction on a polymeric support. We anticipated that side reactions could be avoided in this way and an eventual extension to combinatorial synthesis of cyclopropene derivatives could be achieved.

A literature search revealed a few procedures using rhodium carbenoids bound to polystyrene supports for insertion in the hydroxyl group of alcohols,[3] for the synthesis of furans *via* 1,3-dipolar cycloaddition reactions [4] and for encoding of combinatorial libraries;[5] however, to the best of our knowledge the synthesis of cyclopropene derivatives using polymer bound carbenoids was unprecedented.

Our synthetic strategy is depicted in Scheme 1. Wang resin **1**,[6] a polystyrene polymer with *p*-alkoxybenzyl linker, was used as solid support. A commercial Fmoc glycine ester of this resin **2** was treated at room temperature with a solution of piperidine in DMF to give amino resin **3**. The next reaction, diazotisation of this resin, was the crucial step in this sequence because it was observed that the diazo derivative **4** decomposed in acidic media to give a product with a strong IR absorption at 1750 cm^{-1}.[7] Thus, the diazotisation of resin **3** was optimised by reaction in CH_2Cl_2 at room temperature with 4 eq. of $NaNO_2$/HCl for 2 hours to give the diazo derivative **4** wherein the IR absorption at 1750 cm^{-1} was the minimum obtained (similar to an aromatic combination band between 1600 and 2000 cm^{-1}), the 2108 cm^{-1}

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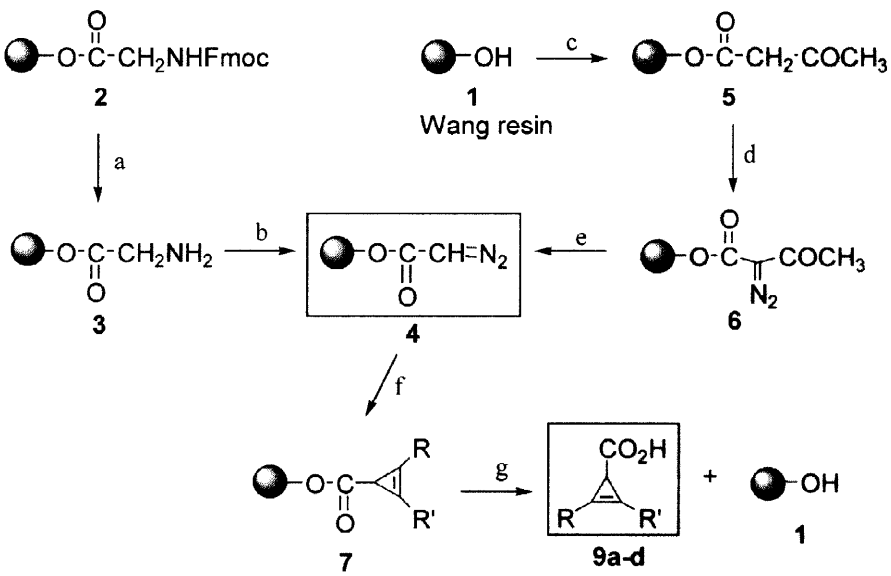
absorption was the most intense and the highest N content (≈2%) was obtained.

When the resin **4** was treated with catalytic amounts of Rh(II) acetate in the presence of acetylenes R-C≡C-R_1 **8a-d** (**a**: R=C_4H_9, R_1=C_5H_{11}; **b**: R=C_6H_{13}, R_1=$C_5H_{10}CO_2Me$; **c**: R=C_6H_5, R_1=C_4H_9; **d**: R=C_4H_9, R_1=$C_9H_{18}CO_2Me$) cyclopropenation occurs giving, after final cleavage from the support with trifluoroacetic acid, cyclopropene derivatives **9a-d** in 10-30% overall yields [8] (these yields, obtained for the four step sequence of reactions, were estimated from resin **2** loading and are comparable to those reached in our laboratories for the solution reaction to synthesise similar derivatives from the corresponding acetylenes, ethyl diazoacetate and rhodium acetate). The crude product was free of undesired side-products (diethyl fumarate, diethyl maleate and bicyclo[1.1.0]butane derivatives) obtained in the corresponding solution reaction.

Scheme 1



a) 20% Piperidine/DMF, 25°C; b) CH_2Cl_2/H_2O, $NaNO_2$/HCl (4 eq), 25°C, 4h; c) THF, $CH_3COCH_2CO_2H$, PPh_3, DEAD, 25°C, 24h; d) DMF/*i*Pr_2EtN, $TosN_3$; e) Pyrrolidine/DMF, 25°C, 2h; f) CH_2Cl_2/**8a-d** (20 eq), $Rh_2(OAc)_4$ (0.08 eq), 25°C, 4h; g) 50% CF_3CO_2H/CH_2Cl_2, 25°C, 2h.

As shown in Scheme 1, to circumvent the shortcomings indicated in the diazotisation step, diazo resin **4** was also prepared by an alternative route. Esterification of the Wang resin under Mitsunobu conditions [10] with acetoacetic acid, freshly prepared by hydrolysis of the corresponding commercial ethyl ester, afforded resin **5** (IR: 1741, 1720 cm^{-1}). Quantitative diazo-transfer was effected by reaction of **5** with tosyl azide in DMF/*i*-Pr_2EtN to give resin **6** (IR: 2138, 1716 cm^{-1}), that was easily deacetylated by suspension in pyrrolidine/DMF to the diazoester **4** [3]. Subsequent cyclopropenation with acetylenes **8** affords the corresponding cyclopropenic acid derivatives **9** with global yields over 30%. Further work is currently in progress in order to scale up and

optimise this new synthetic approach.

To conclude, we have shown that solid supported diazoesters react in a straightforward manner with acetylenes in the presence of Rh(II) carboxylate catalysts to give cyclopropenyl derivatives avoiding the formation of side products usually occurring in the corresponding solution reaction.

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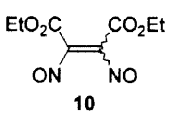
7. To gain insight of this reaction, a solution of ethyl diazoacetate in CH_2Cl_2 was treated with an excess of $NaNO_2$/HCl (10 eq.) at room temperature. After 3 hours a complete disappearance of the IR diazo absorption at 2110 cm^{-1} occurred and from the crude reaction mixture a definite product was isolated with spectral and analytical features in plausible agreement with isomeric structure **10**:



10

All new compounds have been characterised by elemental analysis and/or spectroscopic procedures. Selected analytical data for the mixture **10**: IR (film): 2989, 1755-1749, 1625, 1481, 1373, 1334, 1247, 1199, 1066, 1026, 856, 757 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 4.47 (q, 2H), 4.42 (q, 2H), 1.41 (t, 3H), 1.36 (t, 3H) ppm; ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 156.6, 155.0, 148.3, 63.6, 13.9, 13.8 ppm. GC-MS (*m/z*): 231, 200, 185, 158, 130, 100, 84, 69, 53.
8. A typical experimental procedure was as follows: 250 mg of commercial Fmoc-Gly-Wang resin **2** (Novabiochem, loading 0.51 mmol/g) was sequentially washed with 2 x 2 mL of Et_2O, CH_2Cl_2 and DMF. A suspension of this resin in 2 mL of a 20% solution of piperidine in DMF was shaken at 20 °C

for 20 min., then the polymer was filtered, successively washed with DMF, Et_2O and DMF; the above hydrolysis treatment repeated, then the polymer was filtered, sequentially washed three times with DMF, Et_2O, CH_2Cl_2, Et_2O and CH_2Cl_2 to give the amino resin **3** that gave a deep blue colour in the Kaiser test [9] (IR: 1741 cm^{-1}; N: 1.4%). This resin **3** was suspended, under nitrogen atmosphere, in a mixture of CH_2Cl_2 (5 mL) and H_2O (2.5 mL), concentrated HCl (42 mL, $5.08 \cdot 10^{-4}$ mol, 4 eq.) and $NaNO_2$ ($5.08 \cdot 10^{-4}$ mol, 4 eq) were successively added. The mixture was stirred for 2 hours when a negative Kaiser test was obtained. The polymer was filtered and subsequently washed with CH_2Cl_2, saturated aqueous solution of $NaHCO_3$, CH_2Cl_2, MeOH and CH_2Cl_2 and was dried overnight under high vacuum in the presence of P_2O_5 to give diazoacetoester resin **3** (200 mg, IR: 2108, 1699 cm^{-1}; N: 2.0%). To a mixture of this resin **3** (200 mg) in CH_2Cl_2 and one of the acetylenes **8a-d** (20 eq.) was added under nitrogen $Rh_2(OAc)_4$ (4.6 mg, 0.082 eq.). After stirring this mixture for 4 h, the polymer was filtered and sequentially washed with CH_2Cl_2, Et_2O and CH_2Cl_2 to give resin **4** (IR: 1730 cm^{-1}, N≈0%). This resin was suspended in a 1:1 mixture of CF_3COOH:CH_2Cl_2 and the mixture stirred for 2 hours at room temperature. The polymer was filtered, washed with CH_2Cl_2 and the filtrate concentrated at reduced pressure to give cyclopropenic acids **9a-d**

Selected analytical data for compounds **9**. Compound **9a**: IR(film): 3200, 2958, 1687, 1465, 1236 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 2.41 (m, 4H), 2.02 (s, 1H), 1.54 (m, 4H), 1.35 (m, 6H), 0.89 (m, 6H) ppm; ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 183.3, 105.45, 105.4, 31.4, 29.0, 26.6, 24.5, 24.2, 22.3, 22.0, 13.9, 13.7 ppm; GC-MS (*m/z*): 210, 181, 167, 165, 153, 111. Anal. Cald. for $C_{13}H_{22}O_2$: C, 74.24, H, 10.54, O, 15.21. Found: C, 74.39; H, 10.65%. Compound **9b**: ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 2.36 (m, 6H), 2.03 (s, 1H), 1.56 (m, 6H), 1.27 (br. s, 8H), 0.86 (t, 3H) ppm; GC-MS (*m/z*): 251, 239, 195, 125, 91, 79. Compound **9c**: IR(film): 4000-3000, 1884, 1691, 759, 690 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.4 (m, 5H), 2.69 (td, 2H), 2.44 (s, 1H), 1.73 (m, 2H), 1.46 (m, 2H), 0.96 (t, 3H) ppm; ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 180.3, 129.3, 128.8, 128.7, 126.6, 110.1, 29.4, 25.2, 22.5, 21.6, 13.8 ppm; GC-MS (*m/z*): 216, 173, 129, 115, 105, 91, 77. Compound **9d**: IR(film): 4000-3000, 2931, 1741, 1687, 1436, 1236 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 3.66 (s, 3H), 2.40 (m, 4H), 2.30 (t, 2H), 2.02 (s, 1H), 1.56 (m, 6H), 1.28 (br. s, 12H), 0.91 (t, 3H) ppm; ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 182.4, 174.4, 105.4, 105.3, 51.5, 34.1, 29.3, 29.2, 29.1, 28.9, 26.9, 24.9, 24.5, 24.2, 22.3, 21.9, 13.7 ppm; GC-MS (*m/z*): 293, 292, 251, 207, 179, 153, 111, 97, 69, 59, 55.

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