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Generation of Rhodium Carbenoids on a Polystyrene Support and their OH-Insertion Reaction with Alcohols

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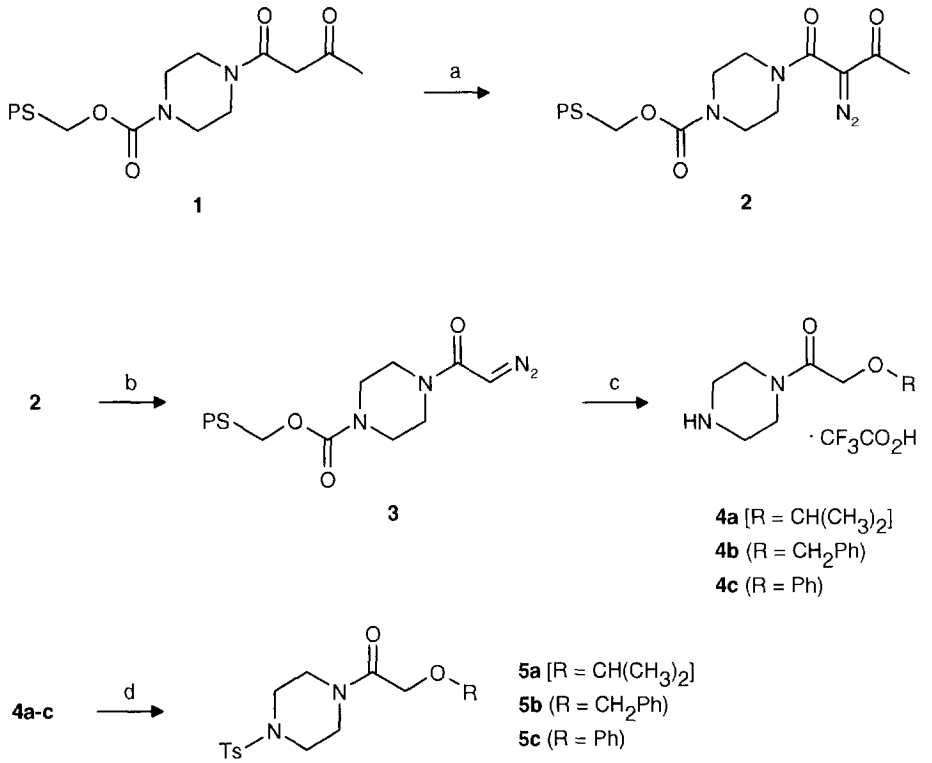
Abstract: A rhodium carbenoid attached to a polystyrene resin was generated by treatment of a resin-bound diazoacetamide with rhodium(II) acetate in dichloromethane. This immobilized reactive species underwent OH-insertion reactions with alcohols to yield ethers of high purity.

The rhodium(II) carboxylate catalyzed decomposition of diazoacetamides or -esters is one of the best methods for the generation of synthetically useful carbenoids.[1] Commonly, preparations with such rhodium carbenoids are carried out by slow addition of a solution of the diazoacetic acid derivative to a mixture of the rhodium carboxylate, an inert solvent and, in the case of intermolecular reactions, a suitable carbene acceptor. Slow addition of the carbene precursor is essential for keeping its concentration as low as possible. Otherwise, the olefin-yielding reaction of the rhodium carbenoid with its precursor, the diazo compound, might become the major reaction pathway.[2] Another way, by which high dilution can be mimicked, but which has not yet been applied to carbene precursors, consists in the attachment of a reacting species to a solid support. This technique has been successfully applied to the otherwise difficult preparation of monoacylated diamines[3] and macrocyclic compounds.[4]

In view of the latter results we reasoned, that the generation of a rhodium carbenoid on a solid support could be a practical alternative for suppressing the dimerization of the carbenoid. Additionally, the realization of carbene reactions on solid support would significantly broaden the range of synthetic procedures applicable to solid-phase synthesis and thus amenable to automatization.[5]

In order to check our hypothesis, we examined the reaction sequence shown in the scheme.



Scheme. PS = polystyrene-based support with p-alkoxybenzyl linker ("Wang resin"); a) tosyl azide, diisopropylethylamine, DMF; b) pyrrolidine, DMF; c) ROH, rhodium(II) acetate, dichloromethane, then trifluoroacetic acid, dichloromethane; d) tosyl chloride, pyridine, dichloromethane.

Treatment of the resin-bound 3-oxobutyramide **1**[13a] with tosyl azide yielded the diazoamide **2**, which could cleanly be deacetylated to give the diazoacetamide **3**.[6] The identity of the 3-oxobutyramide **1** and the diazoamides **2** and **3** was unequivocally established by characterization of the products resulting from the cleavage from the support.[7] When the immobilized diazoacetamide **3** was treated with catalytic amounts of rhodium(II) acetate in the presence of aliphatic or aromatic alcohols,[8] smooth etherification occurred, yielding, after cleavage from the support, the alkoxyacetamides **4a-c**.[9]

Despite the high purity of the crude products (^{1}H NMR), these proved difficult to be crystallized. Therefore they were converted for analytical purposes into the corresponding tosyl amides **5a-c**.

Other catalysts, which were examined for their ability to promote carbene OH-insertion were copper(I) cyanide[10] and palladium(II) acetate,[11] but none of these provided as pure ethers as those obtained with rhodium(II) acetate.

These results show, that rhodium(II) acetate is able to diffuse into dichloromethane-swollen polystyrene resins and to react efficiently and under very mild conditions with diazoamides to give resin-bound rhodium carbenoids. These species react with alcohols to give ethers by carbene OH-insertion. Further reactions of these

new, immobilized reactive intermediates are presently being investigated.

EXPERIMENTAL

Typical Procedure: Synthesis of 1-isopropoxyacetyl-4-tosylpiperazine (5a)

To a suspension of the resin-bound 3-oxobutyramide **1**[3a] (0.60 g, approx. 0.54 mmol) in DMF (6 mL) first tosyl azide (0.60 mL, 3.83 mmol) and then diisopropylethylamine (2 mL) were added. The mixture was shaken for 1 h, the resin was washed with DMF and then suspended in a mixture of DMF (6 mL) and pyrrolidine (2 mL). After shaking for 2 h the resin was washed extensively in the given order with DMF, dichloromethane (DCM), 5% acetic acid in DCM and then several times with DCM. The resin was then suspended in DCM (4 mL) and first isopropanol (2 mL) and then a suspension of rhodium(II) acetate (18 mg, 0.041 mmol, 7.5%) in DCM (8 mL) were added. After shaking for 20 h the resin was again washed (DMF, DCM, methanol), then mixed with DCM (4 mL) and trifluoroacetic acid (4 mL) and shaken for 3 h. Filtration and concentration of the filtrates yielded 318 mg of 1-isopropoxyacetylpiperazinium trifluoroacetate (**4a**) as an oil. The ^{1}H NMR spectrum of the crude trifluoroacetate **4a** indicated the presence of small amounts of DMF, diisopropylethylamine and 5-10% piperazine trifluoroacetate (resulting from crosslinking and/or incomplete formation of the acetoacetamide **1**), but no other major side-product. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 1.11 (d, J = 5.5 Hz, 6H), 3.03-3.15 (m, 4H), 3.56-3.65 (m, 5H), 4.12 (s, 2H), 8.85 (s, br, 2H). This crude ether **4a** was redissolved in DCM (10 mL), and triethylamine (1 mL), pyridine (1 mL) and a solution of tosyl chloride (0.53 g, 2.78 mmol) in DCM (2 mL) were added. The resulting mixture was stirred for 1.5 h at room temperature. Aqueous work-up and flash chromatography (17 g silicagel, gradient elution with heptane/ethyl acetate) yielded 73 mg (40%, based upon loading of initial Wang resin) of 1-isopropoxyacetyl-4-tosylpiperazine (**5a**) as a colorless solid. Recrystallization (ethyl acetate/heptane) gave colorless crystals, m.p. 97-98 °C ; ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 1.01 (d, J = 5.5 Hz, 6H), 2.41 (s, 3H), 2.80-2.92 (m, 4H), 3.44-3.56 (m, 5H), 4.01 (s, 2H), 7.47 (d, J = 8.6 Hz, 2H), 7.61 (d, J = 8.6 Hz, 2H); $C_{16}H_{24}N_2O_4S$ (340.4): calcd C 56.45, H 7.11, N 8.23; found C 56.46 H 7.34 N 8.19.

*Data for the crude trifluoroacetates **4b,c** and the tosylamides **5b,c**:*

1-Benzyloxyacetylpiperazinium trifluoroacetate (**4b**): ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 3.06-3.18 (m, 4H), 3.58-3.68 (m, 4H), 4.25 (s, 2H), 4.52 (s, 2H), 7.26-7.40 (m, 5H), 8.95 (s, br, 2H). 1-Phenoxyacetylpiperazinium trifluoroacetate (**4c**): ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 3.10 (s, br, 2H), 3.19 (s, br, 2H), 3.67 (s, br, 4H), 4.88 (s, 2H), 6.92-6.99 (m, 3H), 7.26-7.32 (m, 2H), 9.00 (s, br, 2H). The ether **4c** was identical (^{1}H NMR) to the product obtained by acylation of resin-bound piperazine[3a] with phenoxyacetic acid (diisopropylcarbodiimide, DMF, 2 x 2 h), followed by cleavage from the resin. 1-Benzyloxyacetyl-4-tosylpiperazine (**5b**): 10% yield. M.p. 143-145 °C (ethyl acetate); ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 2.41 (s, 3H), 2.84 (s, br, 4H), 3.45-3.58 (m, 4H), 4.13 (s, 2H), 4.42 (s, 2H), 7.24-7.35 (m, 5H), 7.45 (d, J = 8.6 Hz, 2H), 7.59 (d, J = 8.6 Hz, 2H); $C_{20}H_{24}N_2O_4S$ (388.5): calcd C 61.84, H 6.23, N 7.21; found C 61.85 H 6.36 N 7.05. 1-Phenoxyacetyl-4-tosylpiperazine (**5c**): 25% yield. M.p. 189-192 °C (ethyl acetate); ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 2.41 (s, 3H), 2.82 (s, br, 2H), 2.90 (s, br, 2H), 3.52 (s, br, 4H),

4.75 (s, 2H), 6.83 (d, br, J = 8.1 Hz, 2H), 6.89 (t, br, J = 8.1 Hz, 1H), 7.22 (t, br, J = 8.1 Hz, 2H), 7.43 (d, J = 8.5 Hz, 2H), 7.60 (d, J = 8.5 Hz, 2H); $C_{19}H_{22}N_2O_4S$ (374.5): calcd C 60.94, H 5.92, N 7.48; found C 60.64, H 6.03, N 7.15.

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