Pergamon

Tetrahedron Letters 41 (2000) 1877–1881

TETRAHEDRON LETTERS

Rhodium-carbenoid-mediated intermolecular O–H insertion reactions: a dramatic additive effect. Application in the synthesis of an ascomycin derivative

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Received 6 January 2000

Abstract

A catalyst system of $Rh_2(oct)_4$/DIPEA or TMU allows for the rapid construction of α-alkoxyketones from the corresponding α-diazo ketone and alcohol. This methodology was applied to the synthesis of immunoregulant **1**.

The macrolides FK-506 and cyclosporin A exhibit immunosuppressive activity and are used in the treatment of organ transplant rejection. However, the narrow therapeutic index of these drugs renders it desirable to find a more potent and less toxic immunosuppressant.[1] Macrocycle **1** was one such possible candidate.[1b] The structure **1** can be divided into two parts: the macrolide ascomycin[2] and a naphthyl-containing side chain connected via an ether linkage on C32 of the macrocycle (Scheme 1). It was desirable to use the C32–OH as the nucleophilic partner in the reaction of an appropriate electrophilic naphthyl counterpart, since the absolute stereochemistry at this position is the same in both ascomycin and the target molecule. A subsequent diastereoselective reduction would afford the desired compound. Mild coupling conditions were investigated in order to minimize the potential for epimerization, nucleophilic addition, elimination, and rearrangement of the macrolide.

Silver-promoted (AgOTf, $AgClO_4$, $AgBF_4$) coupling[3] of the protected ascomycin (24-OTBS) with 2-bromoacetylnaphthalene **2** led to varying degrees of desilylation, decomposition and unreacted starting material. Bromide **2** was then converted to the allyl trichloroacetimidate **3** [(a) NaOAc/DMF; (b) $PPh_3{=}CH_2$; (c) NaOH; (d) Cl_3CCN/DBU]. Attempted coupling of this trichloroacetimidate **3** with unprotected ascomycin in the presence of TfOH[4] afforded only small amounts of the desired C32–allyl ether.

Initial rhodium octanoate [$Rh_2(oct)_4$] mediated insertion reactions between diazoketone **4**[5] and ascomycin resulted in low yields (25–30%) with numerous side products being observed by HPLC,

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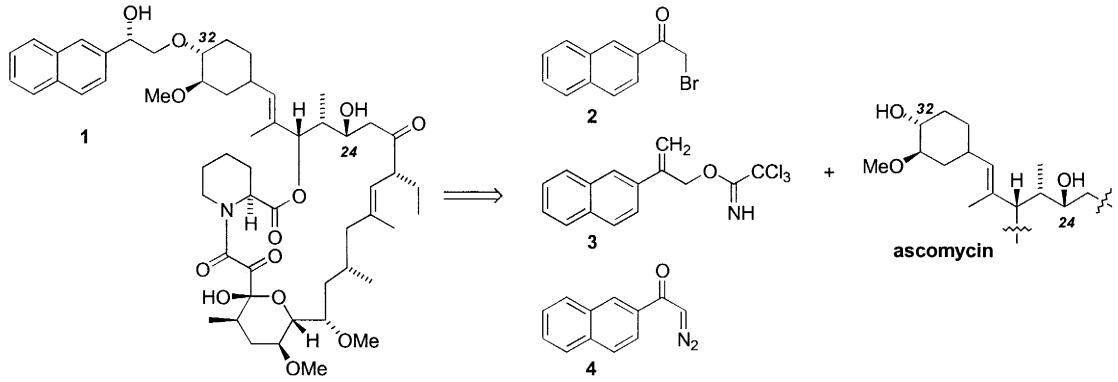
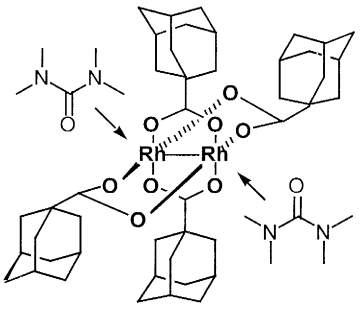
0040-4039/00/$ - see front matter
PII: S0040-4039(00)00069-1



Scheme 1.

presumably due to a host of alternate insertion products.[6] A modest yield increase (36%) was observed after typical parameter optimization was made. Those optimized parameters were: addition rate (30 min), mode of addition (diazoketone solution added to a solution of ascomycin), ascomycin concentration (0.1 M, 1.0 equiv.), catalyst charge (0.5 mol%), diazoketone charge (2.3 equiv.), temperature (ambient), and solvent (CH_2Cl_2). Modulation of the catalytic system by adjustment of the electronic and steric nature of the rhodium ligand was next attempted. Many ligands for rhodium were systematically screened. The use of $Rh_2(pfb)_4$ [pfb=perfluorobutyramide] gave a similar yield to that of $Rh_2(oct)_4$, with more side products being formed. Optimal results were obtained when moderately hindered rhodium catalyst ligands (e.g. 1-adamantanecarboxylic acid[7] and 1-methylcyclohexyl carboxylic acid) were employed. Conversely, extremely hindered carboxylates [e.g. $Rh_2(O_2CCPh_3)_4$] or those containing electron-withdrawing groups [e.g. $Rh_2(O_2CCF_3)_4$] functioned poorly as catalysts in the diazo insertion.

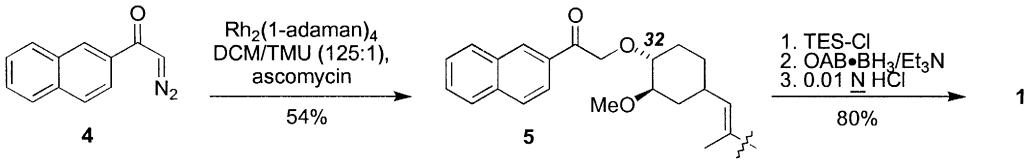
The ability of a co-solvent to modulate the reactivity and selectivity of the diazo insertion was also investigated. Weakly coordinating additives were found to make the reaction profile (HPLC) cleaner. Examples of these included tetramethyl urea (TMU), Hünig's base, *N*,*N*-diethylaniline, and 2,4,6-trimethylpyridine. The amount of necessary additive was dependent on the electron-donating efficiency of the system into rhodium. For example, a solvent system of 1:1 TMU:CH_2Cl_2 almost completely suppressed diazo insertion, whereas a solvent system of 1:1 Hünig's base:CH_2Cl_2 allowed for rapid diazo insertion. Rapid diazo insertion was also observed when the TMU additive ratio was decreased to 1:125 TMU:CH_2Cl_2. The proposed Rh_2(1-adaman)$_2$-TMU complex is shown below. A direct comparison of equimolar amounts of *N*,*N*-dimethylacetamide and of bulkier *N*,*N*-dimethylpivalamide showed that in the former case diazoketone decomposition did not occur, while in the latter case, diazoketone insertion was immediate.



Rh_2(1-adaman)$_4$-TMU complex

Thus, by adjustment (steric, electronic, and quantity) of an additive/co-solvent, the reactivity and selectivity of ether formation by a hydroxy diazo insertion can be modulated. To the best of our knowledge,

this phenomenon has not been reported in the literature and should prove to be of general utility in the optimization of other similar diazo insertion reactions. Surprisingly, when we incorporated both rhodium adamantane carboxylate dimer and TMU, the HPLC assay yield was higher (60–65%) than for either of the two changes made individually (55%). The unprotected ascomycin was reacted with diazoketone **4** on a 20 g scale and the amorphous ether **5** was isolated in a 54% yield (after resin chromatography followed by silica gel chromatography) (Scheme 2).[8] This represents a substantial increase over the yield obtained by traditional catalytic systems [e.g. $Rh_2(oct)_4$, $Rh_2(OAc)_4$] in dichloromethane as the sole solvent.



Scheme 2.

To complete the synthesis, the C-24 hydroxy of the ketone **5** was protected with a triethylsilyl (TES) group,[9] the carbonyl was reduced with (*S*)-OAB-BH_3[10] (*S:R* =98:2),[11] the silyl ether deblocked (0.01 M HCl), and purified by silica gel chromatography to afford macrocycle **1** in an 80% isolated yield as an amorphous foam.[12]

The generality of this methodology was next explored by using a solvent additive for rhodium-carbenoid mediated intermolecular O–H insertion reactions. A current drawback to the existing hydroxyl diazo insertion protocol (rhodium ester dimer with no additive) is that many of the reported examples require an excessive charge of alcohol (the alcohol commonly functions as solvent) or utilize relatively stabilized carbenoid species other than diazo ketones. The diazo insertions were more sensitive to the amount and nature of the additive as opposed to the steric bulk of the rhodium ligands. Simply changing the ligand (e.g. octanoate to adamantoate) did not significantly alter the insertion reaction.

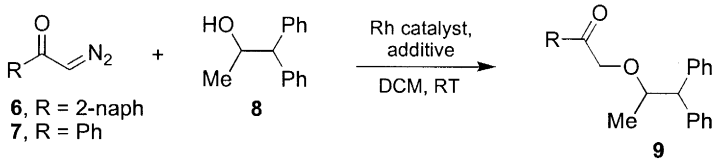
Initially, a 0.1 M solution of diazo **6** (1.1 equiv.) was added over 30 min to a 0.1 M solution (DCM) of the alcohol (1.0 equiv.) and 0.5 mol% of $Rh_2(OAc)_4$ at room temperature. HPLC analysis indicated that a non-chemoselective decomposition–insertion pathway was predominating. These conditions afforded the coupled product in 24% yield, while 49% of starting alcohol did not react (entry 1, Table 1). In addition, a number of other unidentified products were present, thus accounting for the low mass balance. When $Rh_2(OAc)_4$ was replaced with $Rh_2(oct)_4$, a similarly poor reaction profile was observed, albeit a somewhat better alcohol to alkoxy ether **9** conversion occurred (entry 2) (Scheme 3). When 10 mol% of diisopropylethylamine (to alcohol) was added to the rhodium solution followed by diazoketone addition, the reaction profile markedly improved and the product assay yield increased more than two-fold (69%). Similar results were obtained when phenyldiazoketone **7** (entries 4 and 5) was used. The reactions in which DIPEA was present (entries 3 and 5) were complete immediately after diazoketone addition. On the other hand, when DIPEA was not present (entry 4), the amount of alkoxy ether formed increased over time, while the amount of unconsumed alcohol remained constant. In this initial non-optimized work, generally 20–25% of starting alcohol remained unreacted. In addition to 2° alcohols, a similar enhanced yield and reaction cleanness was observed when phenacyl derivatives of a 3° alcohol [1-methylcyclohexanol, (1-MCH)] (entries 6 and 7) and 2,6-dimethylphenol [2,6-DMP] (entries 8 and 9) were prepared. The phenacyl derivative of ethyl (*S*)-(+)-mandelate could also be prepared without epimerization (SFC, ODH column, CO_2, 5% MeOH modifier).

In summary, we have found that a subtle modification of traditional diazo decomposition conditions greatly improves the coupling yield and reaction profile between diazoketones and alcohols. The synergistic effect between a solvent additive and rhodium catalyst was used to modulate the reactivity and

Table 1
Diazo insertion reactions

Entry	Diazo ketone	Alcohol	Rh Catalyst	Additive	Unreacted Alcohol[a]	Ether **9**[a]
1	6	8	$Rh_2(OAc)_4$	------	49%	24%
2	6	8	$Rh_2(oct)_4$	------	39%	31%
3	**6**	**8**	**$Rh_2(oct)_4$**	**DIPEA**	**24%**	**69%**
4	7	8	$Rh_2(oct)_4$	------	30%	48%
5	**7**	**8**	**$Rh_2(oct)_4$**	**DIPEA**	**21%**	**74% (65%)[b]**
6	7	1-MCH	$Rh_2(oct)_4$	------	NA	20%
7	**7**	**1-MCH**	**$Rh_2(oct)_4$**	**DIPEA**	**NA**	**60%**
8	7	2,6-DMP	$Rh_2(oct)_4$	------	28%	35%
9	**7**	**2,6-DMP**	**$Rh_2(oct)_4$**	**DIPEA**	**15%**	**68%**

[a]HPLC assay; [b]isolated yield; In all experiments, 1.0 eq of alcohol and 1.2 eq of diazoketone were used.



6, R = 2-naph
7, R = Ph
8
9

Scheme 3.

selectivity of a rhodium carbenoid insertion into the C32–OH of ascomycin as a key step in the synthesis of the immunoregulant **1**.

Acknowledgements

The authors thank Dr. F. Wong (Merck) for providing an authentic sample of macrocycle **1** and Edward Corley for the preparation of initial quantities of the diazoketone **4**.

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7. Rh_2(1-adaman)$_4$ preparation: To a flask charged with 20 ml chlorobenzene were added adamantanecarboxylic acid (10 g, 55 mmol) and rhodium acetate dimer (1.0 g, 2.26 mmol) and the mixture was heated to reflux for 2 h. Then 6 mL of the solvent was distilled off and the remaining residue was concentrated under vacuum to a green–blue solid. This solid was then stirred with acetonitrile (500 mL) and dichloromethane (50 mL) for 2 h. The solid turned purple and it was collected by filtration, washed with 10:1 acetonitrile:dichloromethane (200 mL). The solid was first dried in air on the funnel with suction which made it turn blue and then in an 80°C vacuum oven with nitrogen sweep overnight. The title compound was obtained as a blue powder (amorphous), wt 1.98 g (96%). ^{1}H NMR ($CDCl_3$, CD_3OD), δ 1.71 (br s, 3H), 1.45 (br s, 12H); ^{13}C NMR δ (ppm) ($CDCl_3$, CD_3OD), 183.5, 43.0, 39.2, 36.4, 28.0.
8. Procedure: 28.1 g of ascomycin (35.5 mmol, dried in a 50°C oven to <0.2 wt) was dissolved in 70 mL CH_2Cl_2 with 165 mg of rhodium adamantane carboxylate dimer (0.18 mmol) and 0.56 mL tetramethylurea (4.7 mmol) was added. A solution of the diazoketone 14.8 g (74.6 mmol) in 210 mL CH_2Cl_2 was added over 7 h. After 30 min, the reaction mixture was mixed with 500 mL acetonitrile and concentrated to an oil. Purification by Amberchrom CG-161cd resin chromatography (3:1, acetonitrile:water) and then by silica gel column chromatography (hexane:EtOAc:MeOH gradient) afforded 18.3 g (54%) of the product as an amorphous foam. A similar yield was obtained when 0.1–0.2 equiv. of Hünig's base or $PhNEt_2$ was substituted for TMU. Selected resonances: ^{1}H NMR of selected resonances (399.9 MHz, CD_3CN) δ 8.55 (br s, 1H), 8.03 (d, J=8.0, 1H), 7.96 (om, 3H), 7.64 (m, 1H), 7.58 (m, 1H), 5.18 (d, J=4.0, 1H), 5.14 (d, J=9.2, 1H), 5.04, 5.02 (AB pattern, J=16.9, 2H), 4.95 (d, J=10.0, 1H), 4.58 (d, J=5.2, 1H), 4.40 (br s, 1H), 4.30 (br d, J=~13, 1H), 3.59 (dd, J=9.6, 1.2, 1H), 3.33 (s, 3H), 3.28 (s, 3H), 3.27 (s, 3H), 2.74 (dd, J=14.5, 4.8, 1H), 1.61 (br d, J=1.2, 3H), 1.57 (d, J=1.2, 3H), 0.90 (d, J=6.4, 3H), 0.87 (d, J=6.4, 3H), 0.85 (d, J=6.8, 3H), 0.81 (t, J=7.2, 3H); ^{13}C NMR (100.5 MHz, CD_3CN) δ 212.8, 198.6, 197.9, 170.4, 166.5, 139.4, 136.5, 133.8, 133.5, 132.9, 132.3, 130.7, 130.5, 129.6, 129.3, 128.7, 127.9, 124.7, 124.6, 98.2, 84.3, 83.5, 79.7, 76.2, 74.7, 74.5, 73.9, 70.4, 57.5 (2 C), 57.2, 56.9, 55.8, 49.6, 46.1, 41.0, 39.9, 36.9, 35.5, 35.4, 34.1, 33.4, 31.5, 31.1, 28.5, 27.2, 25.5, 25.1, 21.9, 20.3, 16.5, 16.1, 13.7, 12.0, 10.1.
9. This protection was necessary so the competing reduction of C22 ketone is minimized.
10. The ketone reduction was done in the presence of 1.5 equiv. Et_3N in toluene at –60°C and quenched into MeOH. OAB–BH_3 triethylamine complex: Cai, D.; Tschaen, D.; Shi, Y.-J.; Verhoeven, T. R.; Reamer, R. A.; Douglas, A. W. *Tetrahedron Lett.* **1993**, *34*, 3243.
11. *R*/*S* ratios were determined by HPLC on a YMC PVA-sil column 96:4 (hex:EtOH); 1.5 mL/min; 215 nm. NMR data for macrocycle **1** matched the authentic sample. The (*R*) isomer was also provided by F. Wong (Merck).
12. Macrocycle **1**: ^{1}H NMR of selected resonances (399.9 MHz, CD_3CN) δ 7.85 (om, 4H), 7.49 (om, 3H), 5.17 (d, J=4.4, 1H), 5.14 (d, J=9.2, 1H), 4.95 (d, J=~10, 1H), 4.91 (dd, J=8.8, 3.6, 1H), 4.58 (d, J=4.8, 1H), 4.40 (d, J=0.8, 1H), 4.31 (br s, 1H), 3.88 (dd, J=10.6, 3.6, 1H), 3.59 (dd, J=9.6, 1.2, 1H), 3.48 (dd, J=10.6, 8.8, 1H), 3.38 (s, 3H), 3.33 (s, 3H), 3.28 (s, 3H), 2.74 (dd, J=14.5, 4.8, 1H), 1.61 (d, J=1.2, 3H), 1.57 (d, J=1.2, 3H), 0.90 (d, J=6.4, 3H), 0.88 (d, J=6.4, 3H), 0.85 (d, J=6.8, 3H), 0.82 (t, J=7.2, 3H); ^{13}C NMR (100.5 MHz, CD_3CN) δ 212.8, 198.6, 170.4, 166.5, 140.1, 139.4, 134.3, 133.9, 132.9, 132.3, 128.8, 128.6, 128.5, 127.1, 126.7, 125.8, 125.6, 124.7, 98.2, 84.6, 83.8, 79.7, 77.4, 76.2, 74.6, 74.5, 73.9, 70.4, 57.5 (2 C), 57.3, 56.7, 55.8, 49.6, 46.1, 41.0, 39.9, 36.8, 35.5, 35.3, 34.1, 33.4, 31.4, 31.2, 28.5, 27.2, 25.5, 25.1, 22.0, 20.3, 16.5, 16.1, 13.7, 12.0, 10.1