Organic Process Research & Development **2000**, *4*, 567–570

Modulation of Catalyst Reactivity for the Chemoselective Hydrogenation of a Functionalized Nitroarene: Preparation of a Key Intermediate in the Synthesis of (*R*,*R*)-Formoterol Tartrate

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Abstract:

In the synthesis of the β_2-adrenoceptor agonist (*R*,*R*)-formterol, a key step in the synthesis was the development of a highly chemoselective reduction of (1*R*)-2-bromo-1-[3-nitro-4-(phenylmethoxy)phenyl]ethan-1-ol to give (1*R*)-1-[3-amino-4-(phenylmethoxy)phenyl]-2-bromoethan-1-ol. The aniline product was isolated as the corresponding formamide. The reaction required reduction of the nitro moiety in the presence of a phenyl benzyl ether, a secondary benzylic hydroxyl group, and a primary bromide, and with no racemization at the stereogenic carbinol carbon atom. The development of a synthetic methodology using heterogeneous catalytic hydrogenation to perform the required reduction was successful when a sulfur-based poison was added. The chemistry of sulfur-based poisons to temper the reacitivty of catalyst was studied in depth. The data show that the type of hydrogenation catalyst, the oxidation state of the poison, and the substituents on the sulfur atom had a dramatic effect on the chemoselectivity of the reaction. Dimethyl sulfide was the poison of choice, possessing all of the required characteristics for providing a highly chemoselective and high yielding reaction. The practicality and robustness of the process was demonstrated by preparing the final formamide product with high chemoselectivity, chemical yield, and product purity on a multi-kilogram scale.

(*R*,*R*)-Formoterol (**1**) is an extremely potent and selective β_2-adrenoceptor agonist[1,2] having rapid onset (1−5 min) and long duration (12 h) and is 1000 times more active than the (*S*,*S*) isomer.[3] The synthesis of **1** was described earlier,[4] and is outlined in Scheme 1. Starting with the nitroarene **2**, chemoselective reduction of the nitro group provided **3** (observed by HPLC analysis), which was directly formylated to give the isolable intermediate formamide **4**. Compound **4** was converted in several steps (epoxide formation, epoxide ring-opening, and debenzylation) to the desired final product, formoterol (**1**). Although each step in the total synthesis contained unique synthetic challenges, of particular interest to this contribution is the investigation and development of the chemoselective hydrogenation of nitroarene **2** to the corresponding aniline **3** in the presence of three reactive and labile functional groups: the benzyl-protected phenol, the benzylic hydroxyl group, and the primary bromide.

The mechanism for the hydrogenation of a nitro group is shown in Scheme 2.[5] The first step is the reduction of the nitroarene to the corresponding nitroso intermediate. A typical value for the heat of reaction is −32 kcal/mol. The second step consists of conversion of the nitroso intermediate to the hydroxylamine, with a typical accompanying heat of reaction of −37 kcal/mol. The final step in the mechanism is reduction to the aniline, having a heat of reaction of −62 kcal/mol. The total heat of reaction for the hydrogenation of a nitroarene to an aniline is in the range of −131 kcal/mol. The rate of reaction for each step is different: the nitroso intermediate is extremely reactive, and the hydroxylamine reduces slowly and accumulates in the reaction. The order of reactivity of the various intermediates and starting material are ArNO > $ArNO_2$ > ArNHOH. As a result, the conversion of the hydroxylamine to the aniline becomes the rate-determining step, and the step of greatest chemoselective concern. For the hydrogenation of **2**, the hydroxylamine intermediate was observed during the reaction (HPLC analysis).

The chemoselective catalytic hydrogenation of various functional groups, especially in the presence of benzyl ethers, has been demonstrated in the literature.[6,7] However, few hydrogenation methods exist for the reduction of nitroarenes to anilines with hydrogenation-sensitive functionalities present. The most popular methods for effecting the selectivity was by the addition of a catalyst poison to the reaction mixture or by careful selection of the reaction solvent. For the chemoselective reduction of **2** to **3**, development of the proper catalyst system would require consideration of the other three functional groups.

Initially, platinum- and palladium-catalyzed hydrogenations were investigated for the transformation shown in eq

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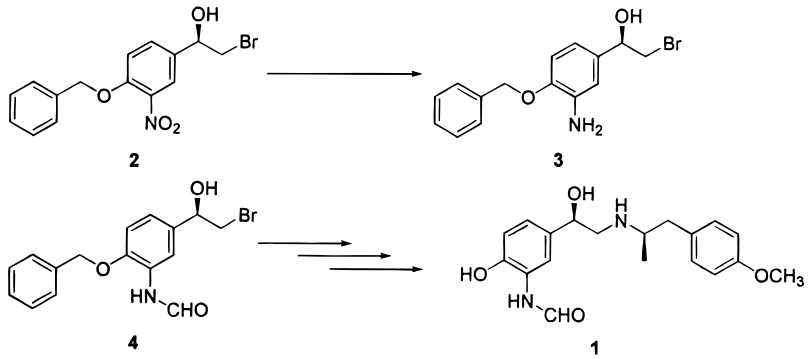
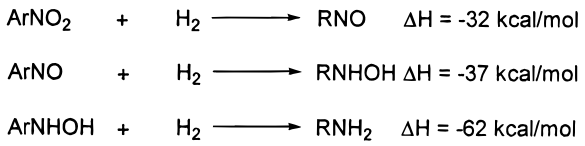
10.1021/op000287k CCC: $19.00
Published on Web 08/08/2000

Scheme 1



Scheme 2



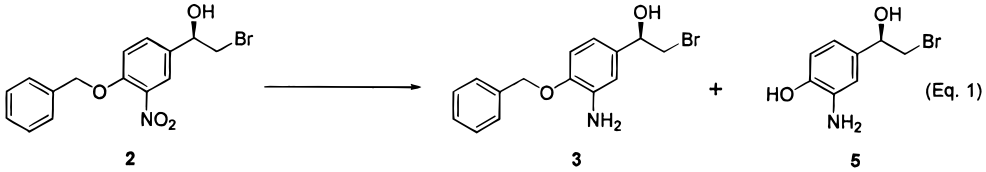


Table 1. **Hydrogenation of 2 with various platinum catalyst systems in THF**

entry	catalyst	Pt (mol %)	solvent	ratio of 3:5[a]	yield of 4 (%)[b]
1	PtO_2	1.5	THF	4:1	66
2	10% Pt/C	1.8	THF	4:1	−
3	10% Pd/C	1.8	THF	1:4	−
4	Pt−S/C	1.7	THF	33:1	72
5	Pt−S/C	1.8	THF/tol	70:1	72
6	10% Pt/C + Me_2S (2 mol %)	1.8	THF	181:1[c]	−

[a] Ratios were determined by HPLC analysis. [b] Yields are given for isolated product. [c] Does not include 7.5% hydroxylamine intermediate (after 3 days)

Table 2. **Investigation of various potential catalyst poisons[a]**

entry	additive	time	ratio of 3:5[b]
1	DMS	6	64:1
2	DMSO	30	>200:1
3	Ph_2SO	2	14:1
4	thioanisole	6	49:1

[a] Conditions: 1.1 mol % 10% Pt/C, 1.0% mol % additive, 50 psig H_2, THF, RT. [b] Ratios were determined by HPLC analysis.

1. The major side-reaction during the reaction was debenzylation to give phenol **5**; reductive debromination and hydrogenolysis of the carbinol moiety were not observed. As shown in Table 1, platinum oxide and platinum on carbon catalysts demonstrated poor chemoselectivity with no additive present, while the palladium catalyst gave **5** as the major product. When a pre-poisoned, sulfided Pt/C catalyst was used, the chemoselectivity was as high as 70:1, depending on the solvent system. When dimethyl sulfide was added to non-poisoned Pt/C, the chemoselectivity rose to 181:1, but with a longer reaction time: 7.5% of the hydroxylamine intermediate remained after 3 days of reaction. To generate a reactive and highly chemoselective Pt catalyst system, studies were directed toward the effect of catalyst poisons on the chemoselectivity and rate of the reduction.

Various coordinating additives were investigated for their potential as a poison possessing the required chemoselectivity and reactivity suitable for the synthesis. In particular, higher oxidation states of sulfur for in situ generation of sulfide poisons were studied. As shown in Table 2, DMSO as a poison gave a highly chemoselective reaction, but with a very long reaction time (30 h, entry 2). The use of a less nucleophilic sulfide, generated in situ from diphenyl sulfoxide (entry 3), allowed for faster reaction rates, but lower chemoselectivity (14:1 ratio of **3**:**5**). Thioanisole, more nucleophilic than diphenyl sulfide but less than dimethyl sulfide, gave an intermediate result: 6 h reaction time with a 49:1 ratio of **3**:**5**.

Table 3 lists the results of the effect of dimethylsulfide (DMS) poisoning on the rate and chemoselectivity of the hydrogenations. As discussed previously, without a poison present, a 4:1 ratio of **3**:**5** was obtained with PtO_2 and Pt/C systems. Poisoning PtO_2 with 0.2−1.4 mol % DMS resulted in very high chemoselectivities but with much longer reaction times (entries 1 and 2). The addition of 1.4 mol % DMS resulted in a >200:1 ratio of **3**:**5**, but with only a 15% conversion of **2** after 18 h. Lowering the DMS content to

Table 3. **Effect of DMS[a] on the chemoselectivity for the hydrogenation of 2[b]**

entry	catalyst	loading (mol %)	Me_2S (mol %)	time	ratio of 3:5[c]
1	PtO_2	1.6	1.4	18[d]	>200:1
2	PtO_2	1.6	0.2	50	27:1
3	Pt/C (10%)	1.8	1.9	18	166:1
4	Pd/C (10%)	1.0	2.0	2	1:1.5

[a] Dimethyl sulfide. [b] Other conditions: 50 psig H_2, THF, rt. [c] Ratios were determined by HPLC analysis. [d] 85% of **2** remaining after 18h.

Table 4. **Effect of DMS level on chemoselectivity[a]**

entry	Me_2S (mol %)	time (h)	ratio of 3:5[b]
1	100	20[c]	>500:1
2	2.0	9	67:1
3	1.0	6	64:1
4	0.5	3	106:1
5	0.25	5	>200:1
6	0	4	6.5:1

[a] Conditions: Pt/C (10%, 1.1 mol mol %), 1.4 M **2** in the THF, 50 psig H_2, rt. Ratios were determined by HPLC analysis. [b] Ratios were determined by HPLC analysis. [c] After 20 h, the reaction stopped at 57% hydroxylamine and 33% aniline.

0.2 mol % gave a lower selectivity, 27:1, with a reaction rate comparable to entry 1. However, a platinum on carbon catalyst system poisoned with 2 mol % DMS gave a very high chemoselectivity and faster reaction rates (entry 3). In contrast, a palladium on carbon catalyst system poisoned with 2 mol % DMS gave a very high reaction rate, 2 h, but with **5** being the major product (entry 4).

The encouraging results with the Pt/C catalyst system prompted further investigations. Table 4 shows the results of the chemoselectivity as a function of the amount of DMS present. When a stoichiometric amount of DMS was added (entry 1), the chemoselectivity was very high, >500:1, but the reaction rate was extremely slow; 57% hydroxylamine and only 33% aniline were present after 20 h. As the amount of DMS was lowered from 2.0 to 0.5 mol %, the reaction rate increased and the chemoselectivity ranged from 106:1 to 64:1 (entries 2−4). However, with 0.25 mol % DMS present, the reaction rate and the chemoselectivity were excellent. For comparison, performing the reduction with no DMS present, and using the Pt/C system, the reaction rate was comparable to the values observed with 0.25−2.0 mol % DMS, but the chemoselectivity was modest, giving 6.5:1 of **3**:**5** (entry 6).

Having established the synthetic utility of the DMS-poisoned Pt/C catalyst system, we directed studies toward the development of a pre-poisoned system, which should allow for preparation of large quantities of a ready-to-use reactive and chemoselective catalyst. The Pt/C catalyst was slurried in THF, treated with 0.5 mol % DMS, and stirred for 2 h at room temperature. After filtration and air-drying, the catalyst was used for the hydrogenation and showed good reactivity and excellent chemoselectivity, providing complete reduction in 6 h with a >165:1 ratio of **3**:**5**. When the catalyst was dried in vacuo, the reaction was complete in 3 h with a >165:1 ratio of **3**:**5**. For each example, the catalyst was recovered by filtration and reused. The reactivity and selectivity were not compromised. Preparation of a pre-poisoned catalyst by this method, therefore, provided an easily recovered and reusable chemoselective catalyst.

In conclusion, the use of sulfide poisons to temper the reactivity of a Pt/C catalyst system in the hydrogenation of the densely functionalized bromohydrin **2** has resulted in the demonstration of a highly chemoselective process for rapid production of the desired aniline **3**. The source of the sulfide poison and the level present in the reaction mixture were shown to have a direct effect on the reaction rate and chemoselectivity. In the presence of a benyzlic hydroxyl group, a primary bromide, and a phenolic benzyl ether, an aromatic nitro group was chemoselectively reduced to the aniline with less than 0.5% debenzylation, no observable hydrogenolysis or debromination, and with an excellent reaction rate. This process has been demonstrated several times on multi-kilogram scale and has consistently afforded the desired product in high yield and with high chemoselectivity. The process has been applied to the synthesis of the highly potent β-agonist (*R*,*R*)-formoterol tartrate in large-scale operations.

Experimental Section

General Procedures. All reactions were carried out under a nitrogen or an argon atmosphere. The extent of reaction and product purities were determined by reverse-phase HPLC analysis. ^{1}H NMR spectra were measured at 300 MHz, and ^{13}C NMR at 75.4 MHz. For ^{1}H NMR, chemical shifts are referenced to TMS, and for ^{13}C NMR to the center peak of the triplet corresponding to $CDCl_3$. Microanalyses were performed by Onieda Research Services, Inc.

Materials. Solvents and reagents were obtained from commercial sources and used without further treatment or purification. The Pt/C and sulfided Pt/C catalysts were obtained from Johnson Matthey Inc. and Aldrich, respectively, (1*R*)-2-Bromo-1-[3-nitro-4-(phenylmethoxy)phenyl]-ethan-1-ol was prepared in-house according to previous procedures.[8]

Preparation of Formic−Acetic Anhydride. To acetic anhydride (363 g, 353 mL, 3.56 mol) at ambient temperature was added 96% formic acid (330 g, 270 mL, 7.2 mol) over 30 min, maintaining the reaction temperature between 20 and 30 °C. The solution was stirred for 30 min and used directly for the formylation of **2**.

Preparation of *N*-[5-((1*R*)-2-bromo-1-hydroxyethyl)-2-(phenylmethoxy)phenyl]carboxamide (3). To 5% Pt/C (75 g, 50% wet) was added (1*R*)-2-bromo-1-[3-nitro-4-(phenylmethoxy)phenyl]ethan-1-ol (**1**) (1.1 kg, 3.1 mol), THF (2.2 L) and dimethyl sulfide (970 mg, 15.6 mmol). The mixture was stirred for 30 min under argon, then hydrogenated at 45−50 psig H_2 gas at 20−40 °C for 3.5 h. Then the mixture was filtered, and the catalyst was rinsed with THF (1 L) to give the intermediate aniline **2**.

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To the solution of **2** in THF was added formic−acetic anhydride over 30 min, maintaining the reaction temperature between 10 and 20 °C. The solution was warmed to room temperature and stirred for 30 min. The reaction mixture was concentrated to 2.2 L under vacuum. Toluene (3.5 L) was added, the mixture was concentrated to 2.2 L, and toluene (2.28 L) was added. The slurry was stirred at 20 °C for 30 min, filtered, and rinsed with toluene (1.0 L) to give 980 g (81% yield) of the desired product **3** as an off-white solid. ^{1}H NMR (300 MHz, $CDCl_3$) mixture of rotamers δ (ppm) 8.77 (d), 8.40 (dd), 8.35 (d), 8.19 (br s), 7.90 (m), 7.40 (m), 7.13 (m), 6.96 (m), 5.11 (m), 4.85 (m), 4.70 (m), 4.30 (d), 4.23 (d), 3.56 (m); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 158.9, 147.0, 135.9, 133.5, 128.9, 128.7, 128.0, 127.8, 127.2, 121.7, 118.4, 111.5, 73.5, 71.1, 40.3. Anal. Calcd for $C_{16}H_{16}BrNO_3$: C, 54.87; H, 4.60; N, 4.00. Found: C, 54.82; H, 4.60; N, 3.96.

Received for review May 26, 2000.

OP000287K