Catalytic diastereoselective hydrogenation of (*S*)-proline-modified anthranilic acid

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The hydrogenation of (*S*)-proline-modified anthranilic acid was studied on Rh and Ru catalysts. The hydrogenation occurred with a very high diastereoselectivity but a moderate chemoselectivity. In general, the carbon-supported catalysts exhibited a higher activity but a lower diastereoselectivity than the alumina-supported catalysts. The use of water as the solvent instead of ethanol resulted in higher activities but lower diastereoselectivities. Rh- and Ru-based homogeneous catalysts gave a comparable selectivity but a lower activity than their heterogeneous counterparts.

Keywords: hydrogenation, diastereoselective, anthranilic acid, proline, noble metal catalysts

1. Introduction

Reduction of substituted aromatic substrates provides a convenient, short route to substituted alicyclics. Although asymmetric homogeneous catalysts have been employed with astounding success in the hydrogenation of a wide variety of substrates [1], reduction of substituted aromatic compounds has been relatively unexplored [2–5]. A large number of biologically active molecules contain enantiopure alicyclic component(s); hence, stereospecific hydrogenation of substituted aromatics to such compounds is of interest. Diastereoselective Birch reduction has been successfully employed for the total synthesis of many natural products [6–8]. To the best of our knowledge nothing has been published on the diastereoselective hydrogenation of benzenoid aromatic compounds using homogeneous catalysts; the use of heterogeneous catalysts for diastereoselective hydrogenation of aromatics has, however, attracted some attention in recent years [9–13]. This route is attractive, because it avoids meeting the demanding conditions of the Birch reduction and enjoys the traditional easy work-up advantage of heterogeneous catalysts. Here we report the use of heterogeneous catalysts in the reduction of anthranilic acid using (*S*)-proline as the chiral auxiliary with high diastereoselectivity (upto 96% *d.e.*), albeit with a moderate yield.

2. Experimental

The commercially available anthranilic acid–(*S*)-proline adduct, **1** ((11a*S*)-2,3-dihydro-1*H*-pyrrolo[2,1c][1,4]benzodiazepine-5,11-dione, Aldrich), was used without further purification. The catalysts investigated were Rh/C (Aldrich), Rh/Al_2O_3, Ru/charcoal and Ru/Al_2O_3 (all Fluka). Reactions were conducted in a 60 ml stainless steel autoclave equipped with a sampling tube at 50 °C and 50 bar hydrogen pressure. In a typical experiment, 100 mg of substrate was dissolved/suspended in 30 ml solvent and 50 mg of the supported catalyst was added. The slurry was transferred to the autoclave and flushed successively with nitrogen and hydrogen. The autoclave was pressurised to 50 bar with hydrogen and stirring at 1100 rpm using a gas inducing impeller was started. The conversion was determined by GC using a 5 m γ-DEX capillary column and the diastereoselectivity was determined with a 30 m RTX capillary column. Hydrogenation of **1** led to the simultaneous formation of the *cis*-cyclohexanedi-1,2-yl products (**3a** and **3b**) and of a cyclohexenedi-1,2-yl product **2** (figure 1). The *trans*-cyclohexanedi-1,2-yl products (**3c** and **3d**) were

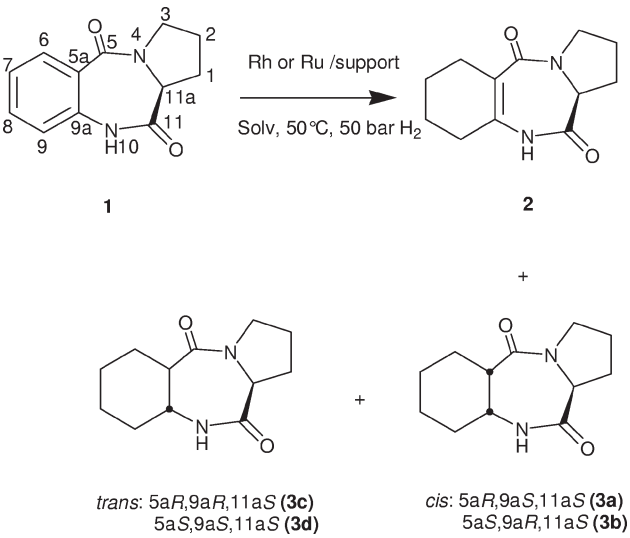

Figure 1. Hydrogenation of **1**.

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also obtained in very small amounts. Typically the yield of **3** was 30–40% and that of **2** was 60–70%. Samples were taken during the reaction to monitor the selectivity and the activity of the catalyst. Accurate determination of the concentration of one of the two *trans* isomers was not possible and, therefore, a good estimation of the *d.e.* between the two *trans* isomers cannot be given. However, a very high *cis* to *trans* ratio was obtained (typically 15–30). The activity of the catalysts is reported as the integral turnover frequency (TOF) at 50% conversion of the substrate. The **3a** diastereomer was always obtained in excess upon direct hydrogenation of **1**. The chemoselectivity is reported as the selectivity to the *cis* products (**3a** + **3b**), while the diastereoselectivity is reported as the diastereomeric excess between the *cis* diastereomers and is given by the formula $d.e. = (\mathbf{3a} - \mathbf{3b})/(\mathbf{3a} + \mathbf{3b})$. The chemoselectivity and the diastereoselectivity varied only slightly with the conversion of **1** for the Al_2O_3-supported catalysts. For the carbon-supported catalysts, the chemoselectivity increased but the diastereoselectivity decreased with the conversion of **1**. The identity of the products was established by GC-MS and by ^{13}C and ^{1}H NMR spectroscopy. The position of the double bond in **2** was verified using DEPT ^{13}C NMR spectroscopy. The relevant analyses data for **2** are given in the appendix. The absolute configuration of products was determined by preparing *cis* (**3a** and **3b**) and *trans* (**3c** and **3d**) reference compounds. Details of preparation and analyses can be found in the appendix. All the NMR spectra were recorded at 27 °C in $CDCl_3$ using a Bruker AMX 500 instrument.

3. Results and discussion

Preliminary experiments with Pt/Al_2O_3 and Pd/C catalysts revealed that they were not effective and, hence, they were excluded from further studies. Results of the hydrogenation reaction with the Rh and Ru catalysts are reported in table 1. The activity and selectivity of the catalysts vary widely depending on the catalyst and the solvent. In general, all the catalysts exhibit a low activity. The carbon-supported catalysts are more active than those supported on Al_2O_3. The activity is higher when water is used as the solvent and increases as expected with increasing hydrogen pressure and temperature. Ru-based catalysts give a higher yield of *cis* products than Rh catalysts but exhibit a lower diastereoselectivity. When water is used as the solvent with carbon-supported catalysts, the chemoselectivity increases, but the diastereoselectivity decreases. The Al_2O_3-supported Rh catalysts yield more *cis* products than the carbon-supported ones. In the case of Ru catalysts, it is difficult to draw any conclusions about the dependence of chemoselectivity on the nature of the support because of the subsequent reduction of **2**, as will be discussed later. Use of Al_2O_3 as the support results in a high diastereoselectivity with both Rh and Ru catalysts, as observed for other aromatic substrates with Rh catalysts [14,15]. As reported earlier by Besson et al. for the hydrogenation of

Table 1
Hydrogenation of **1** using Rh and Ru heterogeneous catalysts.

Catalyst	Solvent[a]	TOF at 50% conv. (h^{-1})	Selectivity[b], *cis* isomers (%)	*d.e.*[b], *cis* isomers (%)
Rh/Al_2O_3	EtOH	8.6	31	94
Rh/Al_2O_3[c]	EtOH	11.2	30	96
Rh/Al_2O_3[d]	EtOH	14.0	26	91
Rh/C	EtOH	14.0	22	76
Ru/Al_2O_3[e]	EtOH	1.9	26	83
Ru/charcoal	EtOH	18.7	36	73
Rh/Al_2O_3	H_2O	46.8	38	94
Rh/C	H_2O	62.3	32	50
Ru/Al_2O_3[d]	H_2O	11.2	33	82
Ru/charcoal	H_2O	56.1	53	52

[a] **1** is partially soluble in EtOH and H_2O.
[b] Chemoselectivity and *d.e.* reported at 98–100% conversion of **1**.
[c] Reaction conducted under 80 bar hydrogen pressure.
[d] Reaction conducted at 80 °C.
[e] Due to low reactivity of the catalyst, reaction was conducted at 80 °C and stopped at a conversion of 59%.

Table 2
Hydrogenation of **1** using Rh and Ru homogeneous catalysts

Catalyst	Solvent	TOF at 50% conv. (h^{-1})	Selectivity[a], *cis* isomers (%)	*d.e.*[a], *cis* isomers (%)
$[Rh(C_5Me_5)Cl_2]_2$[b]	*i*-PrOH	7.0	26	92
$[Ru(C_6H_6)Cl]_2$[c]	EtOH–H_2O	4.7	32	74

[a] Chemoselectivity and *d.e.* reported at 98–100% conversion of **1**.
[b] Reaction conditions: 70 °C and 50 bar hydrogen pressure with 200 mg substrate (substrate to metal molar ratio of 41) in 20 ml IPA and 20 equivalents of triethylamine.
[c] Reaction conditions: 90 °C and 60 bar hydrogen pressure with 430 mg substrate (substrate to metal molar ratio of 21) in 30 ml 1 : 1 EtOH–H_2O mixture.

N-(2-methylbenzoyl)-(*S*)-proline esters [13], we also found that the addition of five equivalents of triethylamine to the present reaction mixture, with Rh/C as the catalyst, resulted in an improved diastereoselectivity but in a concomitant reduction in the rate.

To compare the performance of heterogeneous and homogeneous catalysts, we hydrogenated the substrate using two homogeneous catalysts viz. $[Rh(C_5Me_5)Cl_2]_2$ [5] and $[(\eta^6\text{-}C_6H_6)RuCl]_2$ [4,16] which have been used successfully in the hydrogenation of a wide variety of substituted aromatic compounds. The reaction conditions and the results of hydrogenation with homogeneous catalysts are reported in table 2. In the case of the homogeneous Ru catalyst, colloidal metal particles were detected in the solution at the end of the reaction. The two homogeneous catalysts used in our investigation hydrogenate the substrate with a lower activity but a comparable selectivity to their heterogeneous counterparts.

The cyclohexenedi-1,2-yl product **2** could be isolated with more than 96% purity and was further hydrogenated with the Rh/C, Rh/Al_2O_3 and Ru/charcoal catalysts under the same reaction conditions as those for the hydrogenation of **1** but with a lower substrate to catalyst ratio of 9. The

hydrogenation of **2** occurred at a much slower rate than that of **1** on all catalysts. In the case of the Rh/Al_2O_3 catalyst, the activity was negligible, while in the case of the Ru/charcoal catalyst, hydrogenation proceeded at a moderate rate but not to completion, probably because of deactivation. The activity of Rh/C was low but detectable. Hydrogenation of **2** yielded predominantly *cis* diastereomers with carbon-supported catalysts. However, there was an inversion in the diastereoselectivity, and the **3b** *cis* diastereomer was obtained as the major product with a *d.e.* of about 30% for Ru/charcoal and about 40% for the Rh/C catalyst. Thus, the subsequent hydrogenation of **2** on carbon-supported catalysts accounts for their low overall *d.e.* Hydrogenation of **2** was facilitated when water was used as the solvent. This explains the low overall *d.e.* and the high yield of *cis* products obtained when water is used as the solvent as opposed to ethanol, especially with carbon-supported catalysts. The reason for the very slow hydrogenation of **2**, even when a powerful hydrogenating catalyst such as Rh is employed, is unclear. Hydrogenation of **2** may be difficult because of the inability of the olefinic carbons to coordinate with the metal surface, due to either electronic or steric reasons. In the case of Al_2O_3-supported catalysts, preferential adsorption of **2** on the Al_2O_3 surface via the polar amide groups can account for their inactivity. The Al_2O_3-supported catalysts exhibit a lower activity than the carbon-supported catalysts in the hydrogenation of **1**, probably due to a similar preferential adsorption of **1** on the Al_2O_3 support. We also attempted the hydrogenation of **2** using $[Ir(cod)py(PCy_3)]PF_6$ in CH_2Cl_2 [17]. Under the typical reaction conditions employed, no activity was detected.

The diastereoselectivity obtained in the hydrogenation of **1** is a result of the preferential reactivity of one of its two diastereotopic faces, on the surface of the catalyst. Surprisingly, if only steric factors are considered to be important in determining the face with which **1** adsorbs on the surface of the catalyst, the molecular model of **1** (as optimized using the molecular modeling program Cerius^2) suggests that the **3b** diastereomer is likely to be the major product. The NMR spectrum of **1** remains unchanged between -100 and 120 °C, suggesting conformational homogeneity of **1** in the $CDCl_3$ solution. The diasteroselectivity in the hydrogenation of **1** then should be a result of electronic interactions of the amide bonds in **1** with the surface of the catalyst. These electronic interactions with Ru are probably weaker than those with Rh, causing Ru catalysts to be less selective. The diastereoselectivity obtained in the hydrogenation of **1** is very high as compared to those obtained in the hydrogenation of other substrates [11]. The better performance of this system is attributed to the greater rigidity with which the chiral auxiliary is bound to the aromatic compound. This facilitates good differentiation between the two diastereotopic faces of the aromatic compound on the metal surface of a heterogeneous catalyst or at a homogeneous catalyst. The amino acid (S)-proline also imparts additional rigidity to the chiral auxiliary–aromatic compound adduct, favoring high stereocontrol during hydrogenation. In their recent publication [18], Besson et al. report a high diastereoselectivity in the hydrogenation of *o*-toluic acid using (S)-pyroglutamic acid as the chiral auxiliary. Also in their case, the high stereoinduction obtained is probably due to the rigidity of their aromatic compound–auxiliary system because of hindered rotation around the C(O)–N amide bonds.

4. Summary

Hydrogenation of (S)-proline modified anthranilic acid occurs with a high diastereoselectivity on Rh and Ru catalysts. The high diastereoselectivity is probably due to the rigidity of the anthranilic acid–proline moiety. The carbon-supported catalysts hydrogenate with a lower diastereoselectivity than the alumina-supported catalysts. The lower diastereoselectivity is due to the ability of the carbon-supported catalysts, especially when water is used as the solvent, to hydrogenate the cyclohexenedi-1,2-yl intermediate. All the catalysts exhibit a higher activity when water is used as the solvent. Rh- and Ru-based homogeneous catalysts are as selective but less active than their heterogeneous counterparts.

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Appendix

Reference *cis* (**3a** and **3b**) and *trans* (**3c** and **3d**) samples of the hydrogenated product were synthesized starting from *cis*-hexahydrophthalic anhydride (Fluka) and *trans*-hexahydrophthalic anhydride (Aldrich) (**4**), respectively. Figure 2 indicates the overall preparation procedure. **4** is converted to the corresponding hexahydro-benzo-oxazine-2,4-dione **5** [19], which is then reacted with (S)-proline [6] to give a mixture of *cis* or a mixture of *trans* diastereomers, depending on the starting anhydride. The relative and absolute configuration of the two diastereomeric *cis* products was determined by a NOESY experiment; only for diastereomer **3a**, was a nuclear Overhauser effect observed between the proton at 11a with those at the 5a and 9a positions on the ring. On this basis, the (5aR, 9aS, 11aS) absolute configuration was assigned to this diastereomer. The NMR, GC-MS and elemental analysis data for **2** and the reference compounds (**3a**–**3d**) follows.

(11aS)-1,2,3,6,7,8,9,10,11,11a-decahydro-5H-pyrrolo[2,1-c][1,4]benzodiazepine-5,11-dione (2): Repeated crystallisation of a mixture of **2** and **3** from hexane dichloromethane mixture yielded 96% pure **2**. Flash chromatography on

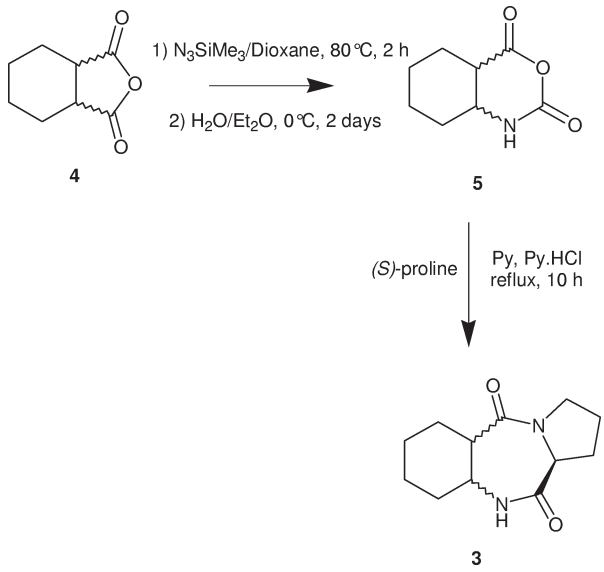

Figure 2. Preparation of reference compounds (**3a**–**3d**).

silica gel (EtOAc : MeOH, 19 : 1) yielded 98% pure **2**. ^{1}H NMR δ 7.57 (br, 1 H), 4.05 (dd, 1 H, $J = 2.3$, 8.0 Hz), 3.64 (m, 1 H), 3.49 (m, 1 H), 2.67–2.76 (m, 2 H), 2.17–2.31 (m, 3 H), 1.91–2.04 (m, 3 H), 1.79–1.90 (m, 2 H), 1.64 (m, 1 H), 1.47–1.60 (m, 1 H); ^{13}C NMR δ 170.1, 166.7, 135.8, 119.1, 57.2, 46.5, 30.2, 25.8, 25.4, 23.3, 22.1, 21.8; ^{13}C DEPT NMR δ: 57.2 (CH), 46.5, 30.2, 25.8, 25.4, 23.3, 22.1, 21.8 (all CH_2). Anal. Calcd for $C_{12}H_{16}N_2O_2$: C, 65.43; H, 7.32; N, 12.72. Found: C, 65.15; H, 7.26; N, 12.48. EI-MS: 220 (M^+, 78), 191 (21), 164 (20), 150 (7), 123 (13), 95 (35), 70 (100), 41 (17).

*Cis reference mixture (**3a** and **3b**):* Preparation as reported in text and subsequent purification by chromatography on silica gel (EtOAc : MeOH, 19 : 1) gave a 99% pure mixture of the **3a** and **3b** diastereomers in a ratio 1.8 : 1. Anal. Calcd for $C_{12}H_{18}N_2O_2$: C, 64.84; H, 8.16; N, 12.60. Found: C, 63.75; H, 7.75; N, 12.27. EI-MS: 222 (M^+, 33), 194 (11), 167 (6), 126 (7), 82 (12), 70 (100), 55 (9), 41 (15).

*(5aR,9aS,11aS)-perhydro-5H-pyrrolo[2,1-c][1,4]benzodiazepine-5,11-dione (**3a**):* ^{1}H NMR δ 5.80 (br, 1 H), 4.49 (t, 1 H, $J = 7$ Hz), 4.09 (br, 1 H), 3.67 (m, 1 H), 3.54 (m, 1 H), 2.71 (m, 1 H), 2.71 (m, 1 H), 2.59–2.66 (m, 1 H), 2.05–2.11 (m, 1 H), 1.38–2.00 (m, 10 H); ^{13}C NMR δ 171.1, 170.9, 57.4, 48.5, 48.4, 46.8, 30.1, 28.5, 25.7, 24.7, 22.4, 20.9.

*(5aS,9aR,11aS)-perhydro-5H-pyrrolo[2,1-c][1,4]benzodiazepine-5,11-dione (**3b**):* ^{1}H NMR δ 5.62 (br, 1 H), 4.46 (t, 1 H, $J = 7.8$ Hz), 3.92 (br, 1 H), 3.78 (m, 1 H), 3.49 (m, 1 H), 2.85 (m, 1 H), 2.37–2.50 (m, 2 H), 1.38–2.00 (m, 10 H); ^{13}C NMR δ 172.5, 171.3, 59.4, 50.1, 49.8, 48.9, 33.1, 31.5, 25.3, 22.2, 21.8, 19.8.

*Trans reference mixture (**3c** and **3d**):* Preparation and purification as reported for the *cis* reference yielded a 99% pure mixture of **3c** and **3d** diastereomers in a ratio 1.4 : 1. Anal. Calcd for $C_{12}H_{18}N_2O_2$: C, 64.84; H, 8.16; N, 12.60. Found: C, 63.74; H, 7.79; N, 12.26. EI-MS: 222 (M^+, 23), 194 (18), 166 (5), 126 (13), 82 (9), 70 (100), 55 (7), 41 (13). The absolute configuration of the *trans* diastereomers was identified by comparing the NMR spectra of the mixture to the NMR spectra reported by Schultz and Alva [20] for the **3d** diastereomer.

*(5aS,9aR,11aS)-perhydro-5H-pyrrolo[2,1-c][1,4]benzodiazepine-5,11-dione (**3c**):* ^{1}H NMR δ 5.50 (br, 1 H), 4.50 (dd,1 H, $J = 8.3$, 3.4 Hz), 3.53–3.62 (m, 1 H), 3.47–3.53 (m, 1 H), 3.28 (dt, 1 H, $J = 11.5$, 3.7 Hz), 2.7–2.77 (m, 2 H), 1.2–2.1 (m, 11 H); ^{13}C NMR δ 171.2, 171.0, 56.2, 52.5, 51.7, 48.8, 32.4, 29.7, 28.0, 25.7, 25.1, 22.3.

*(5aS,9aS,11aS)-perhydro-5H-pyrrolo[2,1-c][1,4]benzodiazepine-5,11-dione (**3d**):* ^{1}H NMR δ 5.63 (br, 1 H), 4.57 (t, 1 H, $J = 6.8$ Hz), 3.64–3.69 (m, 1 H), 3.53–3.62 (m, 2 H), 2.60–2.67 (m, 1 H), 2.52 (m, 1 H), 2.20 (dt, 1 H, $J = 11.5$, 3.0 Hz), 1.2–2.1 (m, 10 H); ^{13}C NMR δ 171.0, 169.9, 58.6, 56.1, 46.6, 45.2, 36.8, 28.3, 26.7, 24.2, 24.2, 23.2.

References

[1] R. Noyori, *Asymmetric Catalysis in Organic Synthesis* (Wiley, New York, 1994).
[2] M. Bennet, CHEMTECH (1980) 444.
[3] P.A. Chaloner, *Handbook of Coordination Catalysis in Organic Chemistry* (Butterworths, London, 1986).
[4] E.G. Fidalgo, L. Plasseraud and G. Süss-Fink, J. Mol. Catal. A 132 (1998) 5.
[5] M.J. Russell, C. White and P.M. Maitlis, J. Chem. Soc. Chem. Commun. (1977) 427.
[6] A.G. Schultz, P.J. McCloskey and J.J. Court, J. Am. Chem. Soc. 109 (1987) 6493.
[7] J.M. Hook and L.N. Mander, Nat. Prod. Rep. 3 (1986) 35.
[8] A.G. Schultz, Acc. Chem. Res. 23 (1990) 207.
[9] K. Nasar, M. Besson, P. Gallezot, F. Fache and M. Lemaire, in: *Chiral Reactions in Heterogeneous Catalysis*, eds. G. Jannes and V. Dubois (Plenum Press, New York, 1995) p. 141.
[10] H. Hönig, R. Rogi and H. Weber, in: *Chiral Reactions in Heterogeneous Catalysis*, eds. G. Jannes and V. Dubois (Plenum Press, New York, 1995) p. 135.
[11] M. Besson and C. Pinel, Topics Catal. 5 (1998) 25.
[12] M. Besson, B. Blanc, M. Champelet, P. Gallezot, K. Nasar and C. Pinel, J. Catal. 170 (1997) 254.
[13] M. Besson, B. Blanc, P. Gallezot, K. Nasar and C. Pinel, in: *Catalysis of Organic Reactions*, ed. R.E. Malz, Jr. (Dekker, New York, 1996) p. 177.
[14] M. Besson, P. Gallezot, C. Pinel and S. Neto, Stud. Surf. Sci. Catal. 108 (1997) 215.
[15] V.S. Ranade and R. Prins (1999), submitted.
[16] L. Plasseraud and G. Süss-Fink, J. Organomet. Chem. 539 (1997) 163.
[17] A.G. Schultz and P.J. McCloskey, J. Org. Chem. 50 (1985) 5905.
[18] M. Besson, P. Gallezot, S. Neto and C. Pinel, J. Chem. Soc. Chem. Commun. 14 (1998) 1432.
[19] H.R. Kircheldorf, Makromol. Chem. 173 (1973) 13.
[20] A.G. Schultz and C.W. Alva, Org. Synth. 73 (1996) 174.