Pergamon

Tetrahedron Letters, Vol. 36, No. 42, pp. 7749-7752, 1995
Elsevier Science Ltd
Printed in Great Britain
0040-4039/95 $9.50+0.00

0040-4039(95)01616-3

Palladium(II)-Catalyzed Cyclization Using Molecular Oxygen as Reoxidant

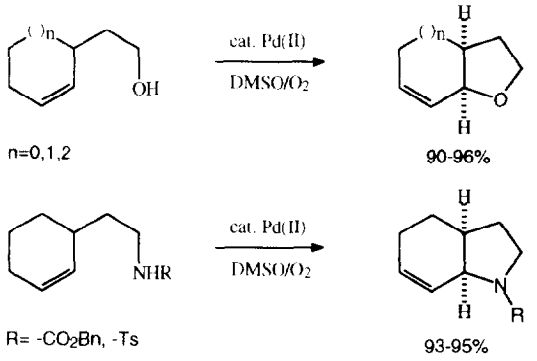
Magnus Rönn, Jan-E. Bäckvall and Pher G. Andersson*

Department of Organic Chemistry, University of Uppsala

Box 531, S-751 21 Uppsala, Sweden

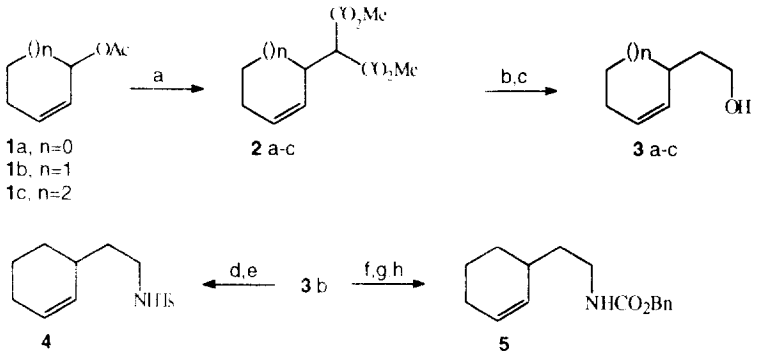
Abstract: A Palladium(II)-catalyzed intramolecular allylic oxidation using nitrogen and oxygen nucleophiles and molecular oxygen as reoxidant has been developed.

We have earlier reported a number of Pd(II)-catalyzed cyclization reactions using dienes as starting materials.[1-3] In this communication we report on an intramolecular oxidation of olefins which opens new avenues for the stereoselective synthesis of a variety of oxygen- or nitrogen-containing heterocycles. The cyclization makes use of alkenes with an internal nucleophile consisting of either an amino or alcohol functionality which makes the reaction versatile (Scheme 1). Furthermore, this process takes place with a high degree of stereo- and regioselectivity and furnish the products in high yield. We were also able to avoid the use of reoxidants for the palladium such as 1,4-benzoquinone or Cu(II) by performing the reactions in DMSO under an atmosphere of oxygen.[4]



Scheme 1

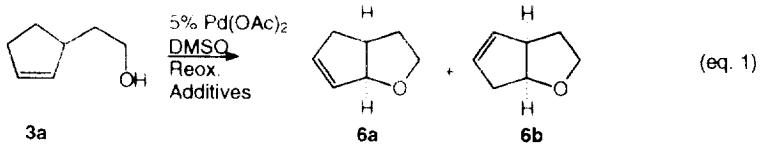
The starting materials chosen for the study were prepared following known literature procedures and the routes are outlined in Scheme 2. The allylic acetates **1a-c**[5] were alkylated via a palladium(0)-catalyzed allylic substitution with sodium malonate. The resulting malonates were then subjected to a decarbalkoxylation using the Krapcho conditions[6] to yield the monoesters. Subsequent reduction with $LiAlH_4$ gave the olefinic alcohols **3a-c**. The cyclic olefins with nitrogen as internal nucleophile were both prepared from alcohol **3a**. Mesylation and subsequent nucleophilic displacement of mesylate with sodium tosylate in DMF gave tosylamide **6**. A Mitsunobu[7] reaction of alcohol **3a** with phthalimide followed by deprotection with hydrazine hydrate[8] resulted in the corresponding amino-hydrochloride. The aminohydrochloride was then alkylated by benzyl chloroformate in a two-phase system[9] to give the corresponding carbamate **7**.



Scheme 2

a) $NaCH(CO_2Me)_2$, Pd(0), THF (83-88%). b) NaCN, wet DMSO (70-90%). c) $LiAlH_4$, ether (83-93%). d) MsCl, NEt_3, CH_2Cl_2 (99%) e) NaNHTs, DMF (56%). f) $P(Ph)_3$, phthalimide, DEAD, THF (99%). g) hydrazine hydrate, EtOH then HCl (85%). h) $NaHCO_3$, BnOCOCl, $CHCl_3$ (93%).

A number of different reaction parameters such as solvents, reoxidants and additives were evaluated in order to optimize the reaction. The first attempts to perform the cyclization were made using 1,4-benzoquinone as reoxidant and acetic acid as solvent. This resulted in a fast consumption of the starting material but led to a inseparable mixture of products. Use of other solvents such as DMF or EtOH did not result in any reaction at all. However DMSO has recently been reported to be an excellent solvent for Pd(II)-catalyzed reactions and also allows for the direct reoxidation of the palladium by molecular oxygen.[4b,10] DMSO was therefore examined more closely using the substrate **3a** as a model (eq. 1).



(eq. 1)

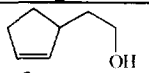
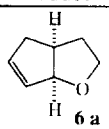
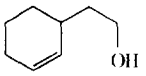
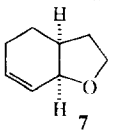
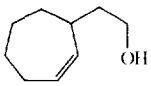
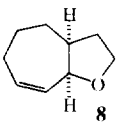
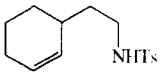
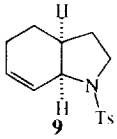
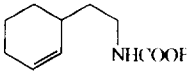
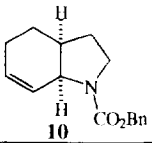
Table 1

Entry	Reoxidant	Additives	Conversion(%)[1]	Time (hrs.)	6a:6b[a]
1	*p*-BQ	-	> 95	24	76:24
2	*p*-BQ	10 mol% $MeSO_3H$	>95	0.5	66:34
3	*p*-BQ	2 equiv. NaOAc	10	24	>95:5
4	*p*-BQ	10 equiv. K_2CO_3	<5	24	-
5	*p*-BQ	2 equiv. LiCl	<5	24	-
6	*p*-BQ	2 equiv. LiCl + 10 mol% MeO_3H	<5	24	-
7	O_2	10 mol% $Cu(OAc)_2$ + 2equiv. NaOAc	52	24	>95:5
8	O_2	2 equiv. $Cu(OAc)_2$ + 2 equiv. NaOAc	67	24	>95:5
9	O_2	2 equiv. $CuCl_2$ + 2 equiv. NaOAc	<5	24	-
10	O_2	10 mol% $Cu(OAc)_2$	>95	5	>95:5
11	O_2	2 equiv. $Cu(OAc)_2$	>95	2	>95:5
12	O_2		>95	7	>95:5

[a]Determined by GLC

The reaction using DMSO/1,4-benzoquinone as solvent/reoxidant was found to give the cyclized product together with large amounts of the homoallylic isomer (Table 1 entry 1). It was possible to control the regioselectivity of the reaction by changing the acidity of the reaction medium. When a small amount of methanesulfonic acid (twice the molar amount of palladium) was added to the reaction the rate increased tremendously but with a concomitant decrease in selectivity (Table 1 entry 2). On the other hand, the addition of a stoichiometric amount of NaOAc not only completely inhibited the formation of the homoallylic isomer but also decreased the rate to such an extent that the reaction no longer was synthetically useful. Further increase of the basicity (10 equiv. K_2CO_3) totally stopped the reaction. The addition of LiCl was also found to inhibit the reaction (Table 1 entry 5 and 6). More promising results were obtained when the 1,4-benzoquinone was replaced by Cu(II)/O_2 as reoxidant. This system resulted in a reaction which smoothly furnished the cyclized product without any traces of the homoallylic isomer. The NaOAc could be omitted from the DMSO/O_2 system which increased the rate by a factor of 10 but with no loss in selectivity. If $CuCl_2$ was used instead of $Cu(OAc)_2$ no reaction took place, (Table 1 entry 9) again suggesting that Cl^- inhibits the catalysis. The dependence of the amount of added Cu(II) on the rate for the catalysis was also studied. It is interesting to note that the rate of the "direct" redox process between oxygen and Pd in DMSO is comparable to that of the Cu(II) mediated process. Even though the reaction using 2 equiv. of Cu(II) was slightly faster than the reaction using DMSO/oxygen the latter was considered superior as it avoids the use of $Cu(OAc)_2$. Using these conditions[11], it was possible to isolate the cyclic ethers **6-8** (Table 2) in excellent yields within 24 hours and with no formation of the homoallylic isomers. The cyclizations using nitrogen as intramolecular nucleophiles functionalities required a slightly elevated temperature and 10 mol% Pd(II) to be completed within 24 hours (Table 2).

Table 2

Starting material	Product	Yield (%)	Reaction conditions[1]
 **3 a**	 **6 a**	90	A
 **3 b**	 **7**	96	A
 **3 c**	 **8**	91	A
 **4**	 **9**	93	B
 **5**	 **10**	95	B

[1]A: 5 mol% $Pd(OAc)_2$ in DMSO/O_2 at 23° C for 24 hrs. B: 10 mol% $Pd(OAc)_2$ in DMSO/O_2 at 55° C for 24 hrs

In conclusion, the methodology presented in this paper describes a simple and effective method to synthesize cyclic ethers and amine derivatives in high yields under mild conditions. This extremely convenient and selective method should be useful in e.g. natural product synthesis.

Acknowledgments. We thank Mr. S. Gohil for performing HRMS and Prof. D. Tanner for fruitful discussions. We are also grateful to the Swedish Natural Science Research Council and to the Swedish Research Council for Engineering Science for financial support.

References and Notes

1. (a) Bäckvall, J. E.; Andersson, P. G.; Vågberg, J. O. *Tetrahedron Lett.* **1989**, *30*, 137. (b) Bäckvall, J. E.; Granberg, K. L.; Andersson, P. G.; Gatti, R.; Gogoll, A. *J. Org. Chem.* **1993**, *58*, 5445
2. Bäckvall, J. E.; Andersson, P. G. *J. Am. Chem. Soc.* **1992**, *114*, 6374
3. Bäckvall, J. E.; Andersson, P. G. *J. Am. Chem. Soc.* **1990**, *112*, 3683
4. (a) Recently Larock[4b] described a related procedure for lactonization employing DMSO and molecular oxygen. (b) Larock, R. C.; Hightower, T. R. *J. Org. Chem.* **1993**, *58*, 5298
5. Hansson, S.; Heumann, A.; Rein, T.; Åkermark, B. *J. Org. Chem.* **1990**, *55*, 975
6. (a) Krapcho, A. P. *Synthesis* **1982**,805. (b) Pearson, A. J.; Ray, T. *Tetrahedron* **1985**, *41*, 5765.
7. Mitsunobu, O. *Synthesis* **1981**, 1
8. Ing, H. R.; Manske, R. H. F. *J. Chem. Soc.* **1926**, 2348
9. Moeller, O.; Steinberg, E. M; Torsell, K. *Acta Chem. Scand.* **1978**, *B 32*, 98.
10. (a) van Benthem, R. A. T. M.; Hiemstra, H.; Speckamp, W. N. *J. Org. Chem.* **1992**, *57*, 6083. (b) van Benthem, R. A. T. M.; Hiemstra, H.; Michels, J. J.; Speckamp, W. N. *J. Chem. Soc., Chem. Commun.* **1994**, 357. (c) van Benthem, R. A. T. M.; Hiemstra, H.; van Leeuwen, P. W. N. M.; Geus, J. W.; Speckamp, W. N. J. *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 457.
11. **General procedure for alcohol substrates:** The alkene (1 mmole) was dissolved in DMSO (4 mL) and the vessel was purged with O_2. 5 mol% of $Pd(OAc)_2$ was added and the vessel was sealed, evacuated and filled with oxygen twice. The reaction mixture was stirred at room temperature. After 24 hours the reaction was stopped by adding 40 mL of water. The aqueous phase was extracted four times with pentane:ether 1:1. The organic layer was dried over $MgSO_4$ and the solvent was carefully distilled off. The crude mixture was purified by flash chromatography using pentane:ether 7:3 as eluent. This solvent was carefully removed by distillation and the remaining product was examined by NMR spectroscopy.

    General procedure for nitrogen substrates: The same procedure as above was used but 10 mol% of $Pd(OAc)_2$ was added and the reaction temperature was 55° C. When the reaction was complete the aqueous phase was extracted with ether. The organic layer was then washed twice with water to get rid of traces of DMSO, dried over $MgSO_4$ and evaporated to dryness. The products were purified by flash chromatography using pentane:ether 1:1 as eluent.

    Spectral data for compound 7: ^1H NMR (300 MHz, $CDCl_3$) δ 5.95 (dm, J=9.9 Hz, 1H), 5.83 (app dq, J=1.8, 9.9 Hz, 1H), 4.07 (br, 1H), 3.95 (ddd, J=6.1, 8.3, 14.1 Hz, 1H), 3.75 (ddd, J=6.1, 8.3, 14.1 Hz, 1H), 2.3-1.8 (m, 4H), 1.75-1.60 (m, 2H), 1.40 (m, 1H); ^{13}C NMR δ 131.5, 126.0, 74.3, 66.3, 36.1, 31.5, 24.6, 23.8; HRMS, *m/z* calcd. for $C_8H_{12}O$ 124.0888, found 124.0896.

    Spectral data for compound **9** ^1H NMR (300 MHz, $CDCl_3$) δ 7.73 (d, J=8.3 Hz, 2H), 7.31 (d, J=8.3 Hz, 2H), 5.80 (m, 2H), 3.99 (m, 1H), 3.48 (ddd, J=4.2, 7.4, 9.8 Hz, 1H), 3.16 (ddd, J=7.3, 8.2, 9.8 Hz, 1H), 2.42 (s, 3H), 2.1-1.5 (m, 7H); ^{13}C NMR δ 143.2, 134.9, 129.6, 128.2, 127.6, 127.4, 57.4, 47.3, 35.6, 27.7, 22.8, 21.5, 20.8; HRMS, *m/z* calcd. for $C_{15}H_{19}O_2NS$ 277.1137, found 277.1139.

(*Received in UK* 16 *May* 1995; *revised* 21 *August* 1995; *accepted* 25 *August* 1995)