Regioselective Carbonyl Insertion Reactions with α-Substituted Heterocycles

Kanjai Khumtaveeporn and Howard Alper*

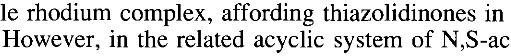
Department of Chemistry, University of Ottawa, 10 Marie Curie Priv., Ottawa, Ontario, Canada K1N 6N5

The rhodium(I) complex [Rh(cod)Cl]$_2$ catalyses the selective insertion of carbon monoxide into the ring carbon–heteroatom bond of a side chain ether or thioether functional group of a tetrahydrothiophene or tetrahydrofuran.

There has been considerable interest in recent years in metal catalysed reactions (*e.g.* ring expansion, net oxidation, rearrangement) of heterocyclic compounds.[1,2] Recently, we reported that the carbon–nitrogen bond of various thiazolidines can be readily carbonylated, using 1% of a commercially available rhodium complex, affording thiazolidinones in good yield.[3] However, in the related acyclic system of N,S-acetals, insertion of cabon monoxide occurs into the C–S instead of the C–N bond.[4] Most examples of insertion into carbon–heteroatom bonds utilize a cyclic system, and, to our knowledge, there are only two other reports on acyclic carbonylation reactions, both involving allylic substrates and palladium complexes as catalysts.[5,6] We now describe our studies on systems containing two heteroatoms, with one in the ring and the other in the side chain. The key question which we wished to address was whether carbon monoxide insertion occurred preferentially into the ring or the side chain.

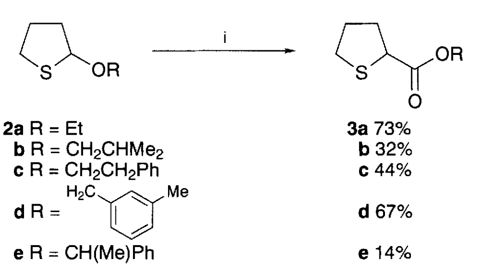
N,S-Heterocycles of structure type **1** were synthesized from tetrahydrothiophene by modification of the excellent procedure reported by Johnstone and Delaney (Scheme 1).[7] In our previous studies of cyclic and acyclic N,S-systems, we found that a 1,3-relationship was necessary for successful carbonylation.[3] Therefore, using **1**, we thought that we were in a position to determine whether the cyclic C–S bond or the acyclic C–N bond would undergo selective carbonylation.

No reaction occured on exposure of **1** to 1% [Rh(cod)Cl]$_2$ under 54 atm CO at 150 °C for 48 h. Under more vigorous conditions (170 °C, 67 atm), there was again no reaction and decomposition of the reactant occurred to some extent. We assumed at this point that compounds of type **1** are unstable at the high temperatures usually required for the carbonylation of 5-membered ring heterocycles.[2]



1a R^1 = Me, R^2 = CH$_2$Ph
b R^1 = R^2 = Et
c R^1, R^2 = CH$_2$CH$_2$CH$_2$CH$_2$
d R^1, R^2 = CH$_2$CH$_2$OCH$_2$CH$_2$

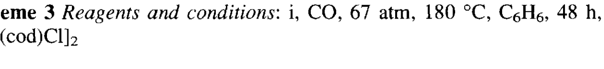
Scheme 1 *Reagents and conditions*: i, NCS, C$_6$H$_6$; ii, 2 equiv. HNR^{1}R^2



2a R = Et
b R = CH$_2$CHMe$_2$
c R = CH$_2$CH$_2$Ph
d R =
e R = CH(Me)Ph

3a 73%
b 32%
c 44%
d 67%
e 14%

Scheme 2 *Reagents and conditions*: i, CO, 67 atm, 180 °C, C$_6$H$_6$, 48 h, [Rh(cod)Cl]$_2$



4

5
20%

Scheme 3 *Reagents and conditions*: i, CO, 67 atm, 180 °C, C$_6$H$_6$, 48 h, [Rh(cod)Cl]$_2$

Our attention was then turned to the corresponding tetrahydrothiophene ethers which should be more stable than their amine analogues. Compounds of type **2** were easily prepared in one step from 2-chlorotetrahydrothiophene,[7] and subjected to carbonylation under 67 atm CO and 180 °C using 1% [Rh(cod)Cl]$_2$. We were gratified to observe preferential carbonylation of the ring carbon–ether oxygen bond of **2a–d** affording the tetrahydrothiophene-2-carboxylic esters **3a–d**, respectively, in moderate to good yields (Scheme 2). The structures of the products were determined by spectroscopic methods [IR, NMR (^{1}H, ^{13}C), HRMS—see data in Table 1] and supported by elemental analysis. The reaction proceeds using alkyl ethers (**2a–c**) or primary (**2d**) or secondary (**2e**) benzylic ethers. [Note that some starting material (32%) was recovered when using **2e** as the substrate].

Finally, to further compare the carbonylation of cyclic and acyclic carbon–heteroatom bonds, we prepared the tetrahydrofuran–thioether system **4**.[8] After reaction under identical conditions to those used for the conversion of **2** to **3**, a product **5** was isolated in 20% yield in which the acyclic C–S bond was carbonylated selectively (Scheme 3; **4** was recovered in 26% yield).

The following general procedure was used: a mixture of the heterocyclic substrate (2 mmol),[7–10] [Rh(cod)Cl]$_2$ (0.02 mmol) and dry benzene (10 cm^3) was reacted in a stainless steel autoclave having a glass liner at 67 atm of carbon monoxide for 48 h at 180 °C. The reaction mixture was then cooled to room temperature and filtered through acidic alumina with CH$_2$Cl$_2$. After evaporation of CH$_2$Cl$_2$, the crude mixture was purified by preparative silica gel thin layer chromatography using 25% EtOAc in hexane as eluent.

In conclusion, the results described herein clearly demonstrate complete regioselectivity for carbonyl insertion into a ring carbon–heteroatom (O,S) bond of a side chain, given the choice between such an insertion and that involving a heterocyclic carbon–heteroatom bond. Furthermore, this methodology compares favourably with existing routes for the syntheses of tetrahydrothiophene-2-carboxylic esters.[11]

We are grateful to the Natural Sciences and Engineering Research Council of Canada for support of this research. K. K. is appreciative of the award of a Chulabhorn Graduate Research Scholarship. We also thank Dr Y. Goldberg and Dr C. Crudden for helpful discussions.

Received, 11th January 1995; Com. 5/00193E

References

1 D. Tanner, *Angew. Chem., Int. Ed. Engl.*, 1994, **33**, 599 and references cited therein.
2 M. D. Wang and H. Alper, *J. Am. Chem. Soc.*, 1992, **114**, 7018.
3 K. Khumtaveeporn and H. Alper, *J. Am. Chem. Soc.*, 1994, **116**, 5662.
4 K. Khumtaveeporn and H. Alper, *J. Org. Chem.*, 1994, **59**, 1414.
5 S.-I. Murahashi, Y. Imada and K. Nishimura, *Tetrahedron*, 1994, **50**, 453.
6 M. Miyazawa, S.-Z. Wang, H. Takeda and K. Yamamoto, *Synlett*, 1992, 323.

7 R. A. W. Johnstone and P. A. Delaney, *Tetrahedron*, 1985, **41**, 3845.
8 E. L. Eliel, B. E. Nowak and R. A. Daignault, *J. Org. Chem.*, 1965, **30**, 2448.
9 V. Y. Mavrin and V. V. Moskva, *Zh. Obshch. Khim.*, 1988, **58**, 1667.
10 C. G. Kruse, E. K. Poels, F. L. Jonkers and A. van der Gen, *J. Org. Chem.*, 1978, **43**, 3548.
11 S. Ikegami, T. Asai, K. Tsuneoka, S. Matsumura and S. Akaboshi, *Tetrahedron*, 1974, **30**, 2087.