Tetrahedron Letters,Vol.27,No.33,pp 3899-3902,1986 0040-4039/86 $3.00 + .00
Printed in Great Britain Pergamon Journals Ltd.

# REACTIONS OF PYRIDYL AND QUINOLYL SULFOXIDES WITH GRIGNARD REAGENT : A CONVENIENT PREPARATION OF PYRIDYL AND QUINOLYL GRIGNARD REAGENTS

Naomichi Furukawa*, Tadao Shibutani, Kazunori Matsumura, and
Hisashi Fujihara
Department of Chemistry, Tsukuba University, Sakura-mura,
Niihari-gun, Ibaraki 305, Japan
Shigeru Oae
Department of Chemistry, Okayama University of Science, Ridai-cho,
Okayama 700, Japan

Abstract: 3-,4-Pyridyl and 4-quinolyl Grignard reagents were generated by the reaction of the corresponding phenyl sulfoxides with PhMgBr and give the adducts upon treatment with various aldehydes and ketones. The stereochemistry for the reaction was investigated.

A few reports on the preparation of the Grignard reagents of heterocycles have been published in the literatures.1) However, the procedures require somewhat special technique. Recently, we found that 2-methylsulfinyl pyridine reacts with Grignard reagents to give 2-pyridyl Grignard reagent as an intermediate, since when the reaction was carried out in the presence of benzaldehyde, (2-pyridyl-phenylmethyl)alcohol was obtained though poor yield.2) We tried to find a convenient preparative method for heteroaromatic Grignard reagent and found that 3-,4-pyridyl and 4-quinolyl Grignard reagents could be generated and upon treatment in situ with various aldehydes or ketones, the corresponding addition products were obtained in moderate to good yields. This communication describes the results of the preparation of the heteroaromatic Grignard reagents and scope and limitations of their utilizations in organic synthesis.

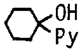
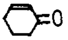
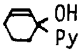
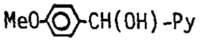
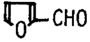
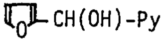
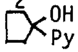
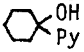
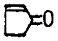
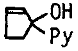
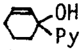
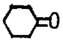
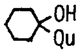
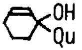
A typical reaction was carried out as follows. To a THF solution of the sulfoxide was added an equimolar amount of PhMgBr in THF and the solution was stirred for 15 min at -10°C to room temperature under $N_2$ stream. To this solution was added an equimolar amount of an appropriate aldehyde or ketone in THF at room temperature. After usual work-up process, the products were separated and identified their structures by $^1$H-nmr, IR, mass spectrosoopies and elemental analyses. Alkyl or benzyl pyridyl or quinolyl sulfoxides were not recommended as a starting material since these gave the corresponding $\alpha$-sulfinyl carbanions which resulted in formation of complex mixtures of the products. Hence pyridyl or quinolyl phenyl sulfoxides were employed in the reactions in order to avoid such disadvantages. Furthermore, neither 2-pyridyl(1) nor 2-quinolyl phenyl sulfoxide(2) did give the corresponding desired addition compounds by this procedure, but give the coupling product such as 2,2'-bipyridine or 2,2'-biquinoline in substantial yield together with several others.$^{2)}$ The results are summarized in Table 1.

Inspection of these results demonstrates the following aspects for these reactions. Phenyl pyridyl or quinolyl sulfoxides(3),(4) and (5) react nicely with PhMgBr to generate the corresponding Grignard reagents which may react in situ with the added aldehyde, ketone or some other reactants to afford the desired products in good to moderate yields together with diphenyl sulfoxide. However, the Grignard reagents did not react at all with esters, thus this suggests that the heteroaromatic Grignard reagents should be a weaker nucleophile than typical alkyl or aryl Grignard reagents On the other hand, the reaction of the pyridyl Grignard reagent with acid anhydride, for example, with benzoic anhydride, gave pyridyl phenyl ketone as a sole product in good yield. Thus, this procedure may become a convenient procedure to prepare heteroaromatic ketones. The reactions of the Grignard reagents generated from the sulfoxides,(3),(4),(5) with 2,3-cyclopentenone or -cyclohexenone afforded the 1,2-adducts while with chalcone gave 1,4-adduct. Apparently, these results tell us that the whole reaction proceeds via an initial nucleophilic attack by PhMgBr on the sulfinyl sulfur atom to displace the heteroaryl group directly. However, the formation of a $\sigma$-sulfurane as a discrete or an incipient intermediate could not be ruled out at this moment since in our previous report, the formation of $\sigma$-sulfurane has been rationalized already.$^{3)}$

In order to know the sterochemical process and to elucidate the rational mechanism for these reactions, we prepared optically active 3- and 4-pyridyl p-tolyl sulfoxides(6) and (7) by treating $\ell$-menthyl-p-tolylsulfinate with either 3- or 4-pyridyl Grignard reagent generated by the present experimental procedure. Then, the sulfoxides(6) and (7), after determining their optical purity by using $^1$H-nmr shift reagent Eu(tfc)$_3$ were treated again with PhMgBr then with $\alpha$-naphthylaldehyde or chalcone to give p-tolyl phenyl sulfoxide and the addition products. The optical purities and absolute configurations of the sulfoxides (6), (7) and phenyl p-tolyl sulfoxides are shown in Table 2. and 3. Both the optical active sulfoxide (6) and (7) are unknown compounds and their absolute configurations have not been determined. The absolute configurations of the starting sulfinate(to be S) and phenyl p-tolyl sulfoxide have been determined from their optical rotations and signs.$^{4)}$ Therefore, one can estimate the absolute configurations of (6) and (7) to be S, if the reaction of Eq.1 would proceed via an inversion process as is generally accepted Andersen's mechanism in the reaction of $\ell$-menthyl-p-tolylsulfinate with Grignard reagents.5) The optical purities of (6) and (7) could be determined to be 100% by using shift reagent. Thus, if one started the

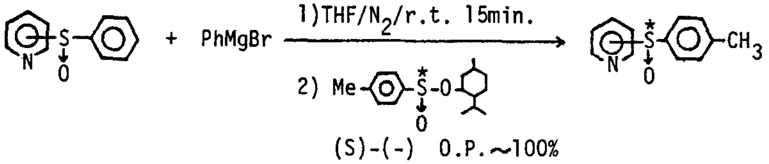
$$\begin{matrix}\text{3-PySOPh}\\ \text{4-PySOPh}\\ \text{4-QuSOTol-}\rho\end{matrix} + \text{PhMgBr} \xrightarrow[\text{2) Add.}]{\text{1)THF/N}_2\text{/r.t. 15min.}} \text{Product}$$

Table 1 Reactions of Pyridyl and Quinolyl Grignard Reagents with Aldehydes and Ketones

| Sulfoxide | Add. | Product a) | Yield,% |
|---|---|---|---|
| 3-PySOPh (3) | PhCHO | Py-CH(OH)-Ph | 88 |
| " | PhCOMe | PyPhMeCOH | 47 |
| " |  |  | 54 |
| " |  |  | 61 |
| " | PhCH=CHCOPh | PyPhCH-$CH_2$COPh | 64 |
| " | $(PhCO)_2O$ | PyCOPh | 75 |
| " | $PhCO_2Et$ (60°C) | no reaction | |
| 4-PySOPh (4) | PhCHO | Py-CH(OH)-Ph | 64 |
| " | PhMeCHCHO | PhMeCH-CH(OH)-Py | 63 |
| " |  |  | 73 |
| " |  |  | 81 |
| " | PhCOMe (60°C) | PyPhMeCOH | 26 |
| " | PhCOPh (60°C) | $PyPh_2COH$ | 7 |
| " |  |  | 55 |
| " |  |  | 38 |
| " |  |  | 64 |
| " |  |  | 66 |
| " | PhCH=CHCOPh | PyPhCH-$CH_2$COPh | 60 |
| " | PhCOCl | PyCOPh | 24 |
| " | $(PhCO)_2O$ | PyCOPh | 70 |
| " | $PhCO_2Et$ (60°C) | no reaction | |
| 4-QuSOTol-ρ (5) | PhCHO | Qu-CH(OH)-Ph | 80 |
| " | PhCH=CHCHO | PhCH=CHCH(OH)-Qu | 53 |
| " |  |  | 16 |
| " |  |  | 20 |
| " | PhCH=CHCOPh | QuPhCH-$CH_2$COPh | 72 |

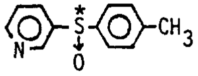
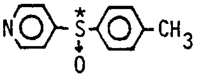
a) All products gave the satisfactory elemental analyses.

reaction of Eq.2 with sulfoxides (6) or (7) with 100% optical purity and Eq.2 might be 100% inversion process, phenyl p-tolyl sulfoxide obtained in this experiments is consistent with S-configuration and the four reactions shown in Table 3 gave all S-phenyl p-tolyl sulfoxide with 100% optical purity. Thus, these reactions of pyridyl phenyl sulfoxides with PhMgBr proceed at least via an $S_n2$-like process at the sulfinyl sulfur atom to give the free



-Eq.1-

Table 2 Preparation of Optically Active Pyridyl Sulfoxides

| Sulfoxide | | Yield,% | $[\alpha]_D^{25}$(c=2,$CHCl_3$) | e.e.% a) |
|---|---|---|---|---|
|  | (6) | 80 | +85° | 100 |
|  | (7) | 77 | +134° | 100 |

a) The enantiomeric excesses were determined by $^1$H-NMR using $Eu(tfc)_3$ as a chiral shift reagent.

$$\begin{array}{l} 3\text{-Py}\overset{*}{S}\text{OTol-}p \\ 4\text{-Py}\overset{*}{S}\text{OTol-}p \end{array} + \text{PhMgBr} \xrightarrow[\text{2) Add.}]{\text{1)THF/}N_2\text{/-10°C 15min.}} \text{Product}$$

-Eq.2-

Table 3 The Reactions of Optically Active Sulfoxides with PhMgBr

| | | Product | | | |
|---|---|---|---|---|---|
| | | Yield , $[\alpha]_D^{25}$ ($CHCl_3$) | | | |
| Sulfoxide | Add. | (-)-Ph$\overset{*}{S}$OTol-p a) | | Adduct B or C | |
| 3-Py$\overset{*}{S}$OTol-p | α-napht.CHO | 91% | -23° | B: 80% | 0° |
| 4-Py$\overset{*}{S}$OTol-p | " | 87% | -23° | B: 63% | 0° |
| 3-Py$\overset{*}{S}$OTol-p | PhCH=CHCOPh | 90% | -23° | C: 64% | 0° |
| 4-Py$\overset{*}{S}$OTol-p | " | 88% | -24° | C: 57% | 0° |

a) (R)-(+)-Ph$\overset{*}{S}$OTol-p $[\alpha]_D$= +22°

B: Py-CH(OH)-napht.-α

C: PyPhCH-$CH_2$COPh

pyridyl Grignard reagents which then react with various added reagents to the adducts. We are now undergoing to extend the present method to other systems.

References

1) H.H.Paradies, M.Görbing, Angew. Chem. Internation.Ed., 8, 279(1969)
H. H. Paradies, Naturwissenshaften, 61, 168 (1974).
2) T. Kawai, N. Furukawa, and S. Oae, Tetrahedron Lett., 25, 2549 (1984).
3) S. Oae, T. Kawai, and N. Furukawa, Tetrahedron Lett., 25, 69 (1984).
4) K. Mislow, M. M. Green, P. Laur, J. T. Mellilo, T. Simmons, and A. L.Ternay Jr., J. Am. Chem. Soc., 87, 1958 (1965).
5) K. K. Andersen, Tetrahedron Lett., 93 (1962).
K. K. Andersen, W. Gaffield, N. E. Papanikolaou, J. W. Foley, and R. I. Perkins, J. Am. Chem. Soc., 86, 5637 (1964).

(Received in Japan 20 May 1986)