Tetrahedron Letters,Vol.23,No.44,pp 4547-4550,1982 0040-4039/82/444547-04$03.00/0
Printed in Great Britain 

# A CONVENIENT PREPARATION OF AN OPTICALLY ACTIVE TRIALKYLPHOSPHINE, (+)-(S)-n-PROPYLMETHYLBENZYLPHOSPHINE, FROM (-)-(S)-S METHYL O-ISOPROPYL METHYLPHOSPHONOTHIOATE

Masaru Moriyama and Wesley G. Bentrude*
Department of Chemistry, University of Utah, Salt Lake City, Utah 84112

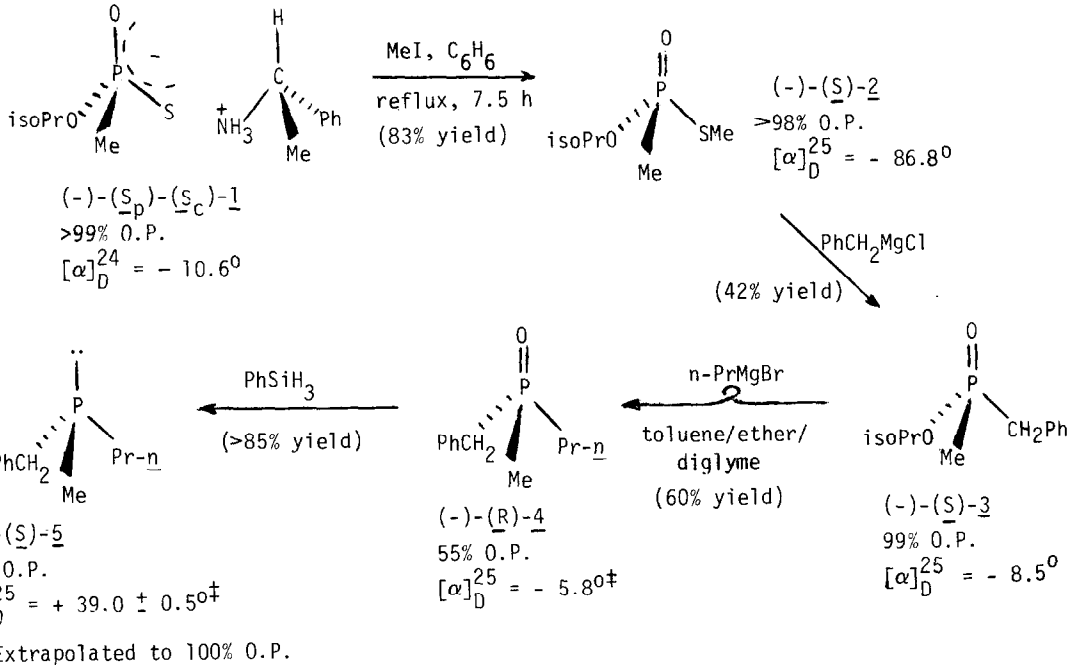
Abstract: Details are presented for the first convenient, reasonable-yield preparation of a chiral trialkylphosphine. The material is of optical purity suitable for stereochemical studies involving the phosphorus atom.

Optically active tertiary phosphines continue to be valuable substrates for the study of the stereochemistry of reactions at phosphorus.[1] Nonetheless, even the more recent synthetic routes[2] to such compounds either have not been applied to the preparation of optically active trialkylphosphines[2d-j] or have met with very limited success.[2c] This is unfortunate since the absence of aryl substituents can be a requisite condition in a particular stereochemical study.

We report here a facile preparation of n-propylmethylbenzylphosphine in reasonable overall yield and optical purity sufficient for stereochemical studies. The only previous reference to this phosphine concerns material[3] we now know to be only about 19% optically pure and for which the method of preparation was not published. Our method is based on the easy availability of S-methyl O-isopropyl methylphosphonothioate, 2,[4] of high optical purity. Moreover, this new approach potentially is applicable to the synthesis of a variety of optically active phosphines including other trialkylphosphines.

The preparation of optically active n-propylmethylbenzylphosphine oxide, 4, from which the target phosphine, 5, is derived is presented in Scheme 1. O-isopropyl methylphosphonothioic acid[5], 1, is readily resolved as the diasteomerically and enantiomerically pure 1-phenylethylammonium salt, (-)-($S_p$)-($S_c$)-1, in just two recrystallizations using a literature method.[6] By using both (R)-and (S)-amines, (-)-($S_p$)-($S_c$)-1 as well as its mirror image are isolated in high yields. Therefore, both (+)-(S)- and (-)-(R)-5 are easily accessible. (This synthetic flexibility is not generally true of synthetic methods for chiral phosphines.) Methylation of 1 by MeI in refluxing benzene yields the known[4,7] S-methyl O-isopropyl methylphosphonothioate, (-)-(S)-2, shown to be 98% O.P. by comparison of its rotation [$[\alpha]_D^{25}$ = -86.8° (c 1.48, $C_6H_6$)] with the literature value for optically pure material, $[\alpha]_D^{25}$ = -87.8°.[4] The high optical purity of (-)-S-2 was confirmed by $^1$H NMR using the chiral shift reagent (-)-t-BuPhP(S)OH[8] (MeP resonance, $C_6D_6$ $\Delta\delta$ = 4.8 Hz, 90 MHz).

SCHEME 1




‡Extrapolated to 100% O.P.

Conversion of (-)-(S)-2 to (-)-(S)-isopropyl methylbenzylphosphinate, 3, of close to 100% optical purity, was readily accomplished in 42% yield on reaction with $PhCH_2MgCl$. Thus, to (-)-(S)-2 (5.0 g, 30 mmol) in 450 mL of dry toluene was added 150 mL of a 1-M ether solution of $PhCH_2MgCl$. After 8 h at reflux, the reaction mixture was cooled in ice and hydrolyzed with 100 mL of saturated $NH_4Cl$. The separated aqueous layer was extracted several times with toluene, and the combined organic phases were washed with saturated aqueous NaCl and dried over $MgSO_4$. Solvent removal and chromatography of the residue on $SiO_2$ with $CHCl_3$ as eluant yielded 2.7 g (42% yield) of (-)-(S)-3, an oil, 94% pure by GLC. Product from another reaction was further purified to analytical purity (C,H,P), mp 50-51°, $[\alpha]_D^{25}$ = -8.5° (c 1.96, $C_6H_6$), optical purity >99% [(-)-t-BuPhP(S)OH, $CCl_4$, 90 MHz, MeP doublet].

The subsequent reaction of (-)-(S)-3 with n-PrMgBr affords (-)-(R)-4 in 50-60% yield, 55-60% optical purity. E.g., (-)-(S)-3 (4.1 g, 19 mmol), optical purity 85%, was dissolved in a solvent mixture composed of 300 mL of toluene and 7.3 mL of diglyme. A quantity of 1-M ether solution of n-PrMgBr was added such that the Grignard/ester ratio was 5/1. After a 6.5 h reflux, the reaction mixture was quenched by the addition, with ice cooling, of about 250 mL of saturated $NH_4Cl$ and worked up in the same manner as the Grignard reaction giving 3. Column chromatography on $SiO_2$ (with successively, $CHCl_3$ and 50/1 $CHCl_3$/MeOH as eluants) followed by sublimation gave (-)-(R)-4, 2.2 g (60%), mp 54-59°, $[\alpha]_D^{25}$ = -3.2°(c 4.4 MeOH), optical purity 55% [based on $^1H$ NMR with (-)-t-BuPhP(S)OH added ($C_6D_6$ at 300 MHz, $\Delta\delta$= 10.6 Hz, MeP)], analytically pure (C,H.P,).

The absolute configuration of (-)-(R)-4 was assigned on the basis of that known for (-)-(S)-2,[4,7] the retention of configuration normally accompanying reactions of Grignard reagents with phosphonothioates like 2[7,9,10] [hence the assignment of $S_p$ configuration to (-)-3], and the well-proven inversion of configuration at phosphorus which occurs in reactions of Grignards with phosphinates.[2b,c,7] The assignment of the $R_p$ configuration to (-)-4 is consistent as well with that established in the earlier report.[3] To increase the reaction rate and optimize the stereochemistry of the conversion of 3 → 4, it is absolutely necessary to use diglyme in the amount specified.

Trialkylphosphine (+)-(S)-5 is obtained in a completely straightforward manner on stereospecific reduction of (-)-(R)-4 by $PhSiH_3$.[11] The assignment of the $S_p$ configuration to (+)-5 also is consistent with that made earlier by Horner et al.[3] The yield of isolated, pure (+)-(S)-5 from (-)-(R)-4 was 85% even on a 300 mg scale and higher with larger amounts of (-)-(R)-4. Thus reduction of (-)-(R)-4 of optical purity 55% [$^1$H NMR with added (-)-t-BuPhP(S)-OH] gave (+)-(S)-5, $[\alpha]_D^{25}$ = +21.5° (c 0.97, MeOH). The highest previously reported specific rotation for (+)-(S)-5 of +7.3°,[3] therefore, corresponds to an optical purity of only 19%. The stereospecific, retentive nature of the reduction is attested to by the fact that the t-BuOOH reoxidation of (+)-(S)-5, to (-)-(R)-4, which proceeds with retention,[11,12] generated phosphine oxide of the same optical rotation as that reduced.

The potential generality of this approach, which uses readily prepared optically active S-alkyl O-isopropyl methylphosphonothioates as the source of optical activity at phosphorus, is illustrated by the successful preparation of methylphenylbenzylphosphine oxide in 65-75% optical purity. The $SCH_2CH_2OCH_2CH_2OCH_2CH_3$ group is used in the place of the SMe in 2 of Scheme 1. On successive reactions with PhMgBr and $PhCH_2MgCl$, the requisite phosphine is prepared in 50% overall chemical yield. This method offers a great advantage in ease of preparation, yield and time compared to the classical method using menthyl methylphenylphosphinate.[2a-c] It also affords both enantiomers of the phosphine with equal ease. Details concerning these reactions will appear in a full paper. A variety of resolved O-alkyl alkylphosphonothioic acids are available[13] which means that a number of substituent combinations at phosphorus potentially can be realized. Moreover, the known stereospecific replacement of the benzyl substituent of optically active tertiary benzylphosphines on nucleophilic attack by alkyl lithium reagents[14] further adds to the potential scope of the method.

Acknowledgment. We thank the National Science Foundation and the NCI of the Public Health Service (CA 11045) for grants in support of this research.

References


1. See e.g. M. Mikolajczyk and J. Luczak, J. Org. Chem., 43, 2132 (1978).
2. a) K. Nauman, G. Zon and K. Mislow, J. Am. Chem. Soc. 91, 7012 (1969); b) O., Korpium, R.A. Lewis, J. Chickos and K. Mislow, ibid., 90, 4824 (1968); c) R.A. Lewis and K. Mislow, ibid., 91, 7009 (1969); d) K. Tani, L.D. Brown, J. Ahmed, J.I. Ibers, M. Yokota, A. Nakamura and S. Otsuka, ibid., 99, 7876 (1977); e) W. Chodkiewicz and D. Guillerm, Tetrahedron Letts., 3573 (1979); f) W. Chodkiewicz, D. Jore and W. Wodzki, ibid., 1069 (1979); g) W. Chodkiewicz, D. Jore, A. Peirrat and W.J. Wodzki, J Organomental. Chem., 174, c21 (1979); h) J. Omelanczuk, W. Perlikowska and M. Mikolajczyk, J. Chem. Soc., Chem. Commun., 24 (1980); i) M. Mikolajczyk and W. Perlikowska, Tetrahedron, 35, 1531 (1979); j) M. Mikolajczyk, Pure and Appl. Chem.,52, 959 (1980).
3. L. Horner, R. Luckenbach and W.D. Balzer, Tetrahedron Letts., 3157 (1968).
4. H.S. Aaron, R.T. Uyeda, H.G. Frak and J.I. Miller, J. Am. Chem. Soc., 81, 617 (1962).
5. Easily prepared from $MePCl_2$ by the method of Z. Pelchowicz and H. Leader, J. Chem. Soc., 3320 (1963).
6. H.L. Boter and D.H.J.M. Platenburg, Recl. Trav. Chim. Pays-Bas., 86, 399 (1967).
7. a) G.R. van den Berg, D.H.J.M. Platenburg and H.P. Benschop, Recl. Trav. Chim. Pays-Bas. 91, 929 (1972); b) H.P. Benschop, G.R. van den Berg and H. Boter, ibid., 87, 387 (1968).
8. M.J.P. Harger, J. Chem. Soc., Perkin Trans. 2, 1505 (1980); ibid., 326 (1978).
9. K.E. DeBruin and D.M. Johnson, J. Chem. Soc., Chem. Commun., 753 (1975).
10. J. Donohue, N. Mandel, W.B. Farnham, R.K. Murray, K. Mislow and J.P. Benschop, J. Am. Chem. Soc., 93, 3792 (1971).
11. K.L. Marsi, J. Org. Chem., 39, 265 (1974).
12. D.B. Denney and J.W. Hanifin, Jr., Tetrahedron Letts., 2177 (1963).
13. M. Mikolajczyk and M. Leitloff, Russ. Chem. Rev., 44, 670 (1975).
14. E.P. Kyba, J. Am. Chem. Soc., 97, 2554 (1975).


(Received in USA 5 August 1982)