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INTRAMOLECULAR CONDENSATION OF N-HOMOPIPERONYL-N-DIALKYL-PHOSPHORYL GLYCINE UNDER THE CATALYSIS OF LEWIS ACID

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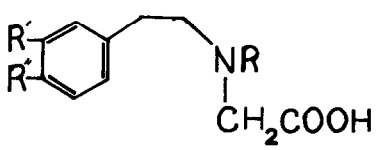
Summary: The synthesis of N-homopiperonyl-N-dialkylphosphorylglycine and a number of its analogues, and their intramolecular Lewis acid catalyzed Friedel-Crafts acylation to the stable N-dialkylphosphoryl tetrahydro-3-benzazepin-1-ones, is described.

The major interest in amine protection stems from its importance in peptide synthesis. The urethane-type, acyl, sulfonyl and phosphoryl amino protecting groups constitute by far the most important classes of amino protecting groups. However, the phosphoryl amino protecting reagents have hardly been applied to the organic synthesis. In this communication, we report a successful use of the phosphoryl as an amino protecting group in a Friedel-Crafts intramolecular acylation reaction.

It has been reported that the unprotected N-homopiperonyl glycine and the related compounds,(1a: R=H), fail to give Friedel-Crafts acylation products[1,2]. Only the compounds with non-basic nitrogen atoms, such as N-tosyl glycine derivatives (1b: R=tosyl), could be cyclized[2,3]. For synthesis of the corresponding N-phosphoryl glycine derivatives (1c: R=dialkylphosphoryl), there is no available method. Although of course, simple alkylated compounds such as N-methyl-N-diphenylphosphinyl glycine can be prepared by alkylation of N-diphenylphosphinyl glycine with excess of methyl iodide and sodium hydride[4].



a: R= H
b: R= tosyl
c: R= dialkylphosphoryl

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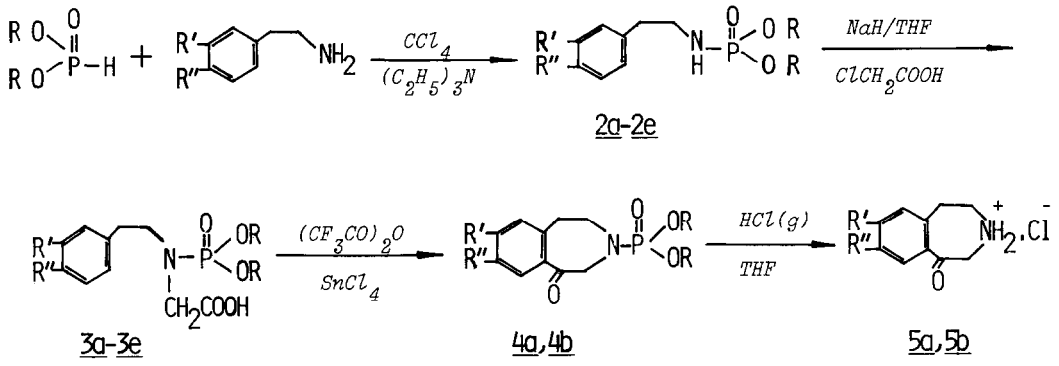
However, for synthesis of the compounds 3a-3e (table), these literature methods[4-6] were not applicable, due to β-elimination of the alkylation reagents, β-phenylethyl halides and the related compounds, in basic media. Therefore we developed a new synthetic approach, outlined in the Scheme, which involves an efficient and novel strategy for the achievement of this goal.

By reaction of the N-alkyl-N-dialkylphosphoramidates[7,8] (2a-2e) with chloroacetic acid under standard conditions (1.0 equiv 2a-2e, 6.0 equiv *NaH*, 2.0 equiv $ClCH_2COOH$ in *THF* at 20°) for 24 hr. followed by quenching (3N *HCl*), good yields of isolated 3a-3e[9] were obtained. Then, the Friedel-Crafts reaction of 3a and 3b were catalyzed by $SnCl_4$ (1.0 equiv 3a or 3b, 4.0 equiv $(CF_3CO)_2O$, 5.0 equiv $SnCl_4$ at 15°), for 4 hr. After destruction of the $SnCl_4$- products complex by addition of acetate buffer pH=3.0, chloroform extraction and recrystallization, 4a and 4b were obtained, (see table and note[9]). For compounds 3d and 3e, after the same treatment there were no ketone can be isolated.



SCHEME

The products (4a, 4b) of the present cyclization possess the N-diisopropylphosphoryl tetrahydro-3-benzazepine skeleton with a *ketonic* functional group, and are promising intermediates not only for the synthesis of the natural alkaloid cephalotaxine[1], but also possible precursors for agonists of central and peripheral dopamine receptors[10].

Thus we have shown that diisopropyl phosphite can be used as an economical amino protection reagent, and that the *P-N* bond persists during Lewis acid catalyzed reactions. This stbility extends its potential as a general amino protecting group in organic synthesis. In addition, the deprotection of the dialkylphosphoryl amino group is very simple. The compounds 4a and 4b can be quantitatively transformed into the amine-*HCl* salts 5a and 5b under very mild conditions[11], which can not be achieved for the corresponding N-tosyl derivatives[2]. The chemistry of these compounds is under further study.

Table : Physical and spectral data of the glycine derivatives and their cyclization products.

compound	R	R'	R''	IR(νC=O) cm^{-1}	δ(ppm)[a] J(Hz)	m.p. C^o	yield %
3a	iPr	CH_3O	C_2H_5O	1730	3.76(12.0)	83-85	81
3b	iPr	O-CH_2-O		1730	3.80(13.0)	93-94	85
3c	CH_3	O-CH_2-O		1735	3.85(13.0)	b	21
3d	iPr	H	CH_3O	1730	3.80(12.5)	80-82	85
3e	iPr	H	H	1730	3.83(13.0)	94-95	90
4a	iPr	CH_3O	C_2H_5O	1670	3.92(10.5)	92-94	60
4b	iPr	O-CH_2-O		1670	3.91(11.0)	154-156	73

(a). Chemical shifts of the -CH_2- in *P-N-CH_2-COOH or P-N-CH_2-C=O* in *$CDCl_3$ TMS* as the internal standard. J= coupling canstants $C\underline{H}_2$-N-$\underline{P}$. Spectra were measured on RMN-250 MHz NMR spectrometer.

(b). Semi-solid, purified by reversed phase column chromatography.

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9. Spectral and elemental analysis of 3a-3e and 4a, 4b. All ^{1}H-nmr were measured in $CDCL_3$, TMS as standard on 250 MHz NMR. MS were measured on MS-50.

3a 1.29(12H,m), 1.41(3H,t), 2.72(2H,t), 3.17(2H,m), 3.76(2H,d,J=12Hz), 3.83 (3H,s), 4.01(2H,q), 4.61(2H,m), 6.60-6.74(3H,m), 10.46(1H,br.). Anal. Calcd. for $C_{19}H_{32}NO_7P$: C, 54.68; H, 7.67; N, 3.36. Found: C, 54.47; H, 7.72; N, 3.33.

3b 1.28(12H,m), 2.70(2H,t), 3.12(2H,m), 3.80(2H,d,J=13Hz), 4.62(2H,m), 5.87 (2H,s), 6.50-6.70(3H,m), 10.04(1H,br.) Anal. Calcd. for $C_{17}H_{26}NO_7P$: C, 52.71; H, 6.77; N, 3.62. Found: C, 52.91; H, 6.80;N, 3.60.

3c 2.72(2H,t), 3.24(2H,m), 3.72(6H, d,J=11.5Hz), 3.85(2H,d,J=13Hz), 5.88 (2H,s), 6.66(3H,m), 10.60(1H,br.) Anal. Calcd. for $C_{13}H_{18}NO_7P$: C, 47.13; H, 5.44; N, 4.23. Found: C, 47.09, H. 5.46; N, 4.15.

3d 1.29(12H,m), 2.72(2H,t), 3.14(2H,q), 3.74(3H,s), 3.80(2H,d), 4.64(2H,m), 6.72(2H,d,J=8Hz), 7.01(2H,d,J=8Hz), 11.26(1H,br.) Anal. Calcd. for $C_{17}H_{28}NO_6P$: C, 54.69; H, 7.51;N, 3.75. Found: C, 54.87, H,7.73; N,3.92.

3e 1.28(12H,m), 2.70(2H,t), 3.19(2H,m), 3.83(2H,d,J=13Hz), 4.62(2H,m),7.10 (5H,m), 10.40(1H,br.), Anal. Calcd. for $C_{16}H_{26}NO_5P$: C, 55.92;H 7.63; N,4.08. Found: C, 55.80; H, 7.45; N, 4.01.

4a 1.08(6H,d), 1.22(6H,d), 1.46(3H,t), 2.97(2H,t), 3.46(2H,m), 3.92(5H,d) 4.10(2H,q), 4.24(2H,m), 6.64(1H,s), 7.27(1H,s).Anal. Calcd. for $C_{19}H_{30}NO_6P$ C, 57.16; H, 7.57; N. 3.51. Found: C, 57.51; H, 8.06;N, 3.35. MS, m/z (rel. intensity) M^+ 399(48.9), 357(24.4), 315(100), 300(5.4), 286(23.3) 218(26.4), 206(41.2), 190(7.5), 178(29.5).

4b 1.10(6H,d), 1.23(6H,d), 2.93(2H,t), 3.42(2H,m), 3.91(2H,d,J=10Hz), 4.28 (2H,m), 5.98(2H,s), 6.64(1H,s), 7.18(1H,s). Anal. Calcd. for $C_{17}H_{24}NO_6P$ C, 55.28; H, 6.55;N, 3.79. Found: C, 55.14; H, 6.40; N, 3.61. MS, m/z (rel intensity) M^+ 369(46.6), 327(18.5), 286(12.0), 285(100), 257(21.6) 240(11.4), 188(29.9), 148(37.4), 110(13.8).

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11. Compounds 4a and 4b can be hydrolyzed in *HCl* saturated *THF* solution at 20° for 24 hr. After recrystallization 5a and 5b were isolated in 88% and 85% yield respectively. Their ^{1}H-nmr were measured in *CF_3COOD*, *TMS* as standard,

5a 1.52(3H,t), 3.40(2H,t), 3.87(2H,t), 4.06(3H,s), 4.28(2H,q), 4.52(2H,s), 6.96(1H,s), 7.46(1H,s). Anal. calcd. for $C_{13}H_{18}ClNO_3$: C, 57.46;H, 6.68; N, 5.16. Found: C, 57.12; H, 6.77; N,5.23. IR: 1655, 1590, 2350-2380.

5b 4.03(2H,t), 4.52(2H,t), 5.18(2H,s), 6.81(2H,s), 7.53(1H,s), 7.98(1H,s), IR: 1650, 1560, 2350-2800 cm^{-1}. Anal. Calcd. for $C_{11}H_{12}ClNO_3$: C, 54.66 H, 5.01; N, 5.80. Found: C, 54.09; H, 5.07: N, 5.51.

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