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DIPHENYLPHOSPHINAMIDES : SYNTHESIS OF SECONDARY AMINES AND N-METHYLAMINOACID DERIVATIVES

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Recently we have investigated[1] the use of phosphinamide protection of amino groups due to the facile acid hydrolysis of Dpp.NH.R (1) which is initiated by N-protonation.[2,3] Another aspect of the chemistry of phosphinamides is the cleavage of the N-H bond with subsequent alkylation to give Dpp.NMe.R (2) which may be compared with the well known alkylation of $Ph.SO_2.NH.R$ to $Ph.SO_2.NMe.R$. Further reaction of $PhSO_2.NMe.R$ to give the secondary amine is not an easy process due to the stability of aryl sulphonamides, however the corresponding phosphinamides (2) are acid labile and, therefore, may be transformed into the salt of the secondary amine (3) under relatively mild conditions. Hendrickson has investigated phenacylsulphonamides[4] and triflamides[5] as a means of circumventing the difficult deprotection of arylsulphonamides.

$Ph_2PO.NH.R$ (1) $\qquad$ $Ph_2PO.NMe.R$ (2) $\qquad$ $R.\overset{+}{N}H_2.Me\ X^-$ (3)

Earlier studies[6,7] on the preparation of Dpp derivatives of primary amines and the reactivity of the potassium salt of Dpp.NH.Ph encouraged us to employ phosphinamides as synthetic intermediates to secondary amines via crystalline intermediates of the type (1). These were prepared from $R.NH_2$ using $Ph_2PO.Cl$[8]/N-methylmorpholine or Et_3N in CH_2Cl_2. Table 1[9] gives some examples of the method in which the anion derived from (1) could be formed by NaH in THF or THF/HMPA (9/1) or DMF at room temperature followed by treatment with MeI. Deprotection of (2) to (3) may be accomplished by mild acid treatment using p-toluenesulphonic acid in MeOH, p-toluenesulphonic acid. H_2O in benzene/ether, HCl in 50% aqueous dioxan. 95% TFA produces rapid cleavage but TFA in the absence of water generates by-products which are probably due to the formation of $CF_3.CO.O.PO.Ph_2$. In the case of the

Table 1

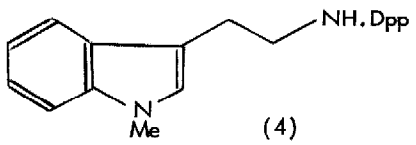
R	$Ph_2PO.NH.R$ (1) m.p.	(Yield)	$Ph_2PO.NMe.R$ (2) m.p.	(Yield)	$R.\overset{+}{N}H_2.Me\ \overset{-}{TosO}$ (3) m.p.	(Yield)
$PhCH_2.$	111-2°	(77%)	82-3°	(76%)	159-161°	(96%)
$PhCH_2.CH_2.$	140-2°	(70%)	63-5°	(60%)	82-3°	(96%)
	199-200°	(71%)	119-120°	(85%)	135-7°	(91%)
$n.C_6H_{13}.$	70-2°	(78%)	oil	(100%)	105°	(89%)

Table 2

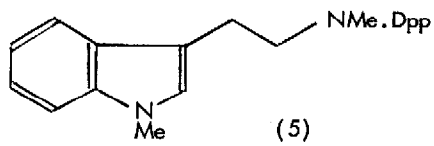
Dpp-Amino Acid (7)	Dpp-N-Me-Amino Acid (8) m.p.	(Yield)	$[\alpha]_D^{25}$ +	$[\alpha]_D^{25}$ of (8) in 6N HCl ‡	$[\alpha]_D^{25}$ of N-Me Amino Acid ‡ (literature)
Dpp-Gly-OH	147-9°	(71%)			
Dpp-Ala-OH	148-9°	(89%)	-29.6°	+11.0°	+11.5°
Dpp-Leu-OH	161-3°	(81%)	-14.3°	+28.5°	+31.8°
Dpp-Ile-OH	150-2°	(90%)	-12.3°	+42.0°	+47.7°
Dpp-Met-OH	145-155°	(52%)	-24.0°	+21.0°	-
Dpp-Phe-OH	182-4°	(69%)	-87.1°	+25.6°	+26.6°
Dpp-Val-OH	150-1°	(74%)	-26.1°	+36.0°	+33.1°

+ C = 1 in MeOH ‡ C = 1 in 6N HCl

Dpp derivative of tryptamine it was found that monomethylation gave (4), m.p. 88-90° as a result of faster reaction at the indolic N-H. Dimethylation afforded (5), m.p. 106-8° which may be cleaved to give the corresponding dimethyltryptamine (picrate, m.p. 172-6°). The methylated compounds (2) exhibit the expected $^{31}P-^{1}H$ coupling in the NMR signal of the N-Me group (J, 11 Hz).



(4)



(5)

N_{α}-monomethylamino acids occur in nature as constituents of peptide and depsipeptide antibiotics, however suitably crystalline derivatives incorporating acid-labile protecting groups are not readily available. N_{α}-methylamino acids can be prepared from N-tosylamino acids[10] (with subsequent difficulty in removal of the N-tosyl group) and N-benzylamino acids.[11] The most important derivatives in current use are (6) which have been studied thoroughly by Benoiton[12] who found that they can be prepared from Z-amino acids using NaH/MeI in THF without appreciable esterification. This is important since saponification of methyl esters of (6) is thought to lead to partially racemised products.

$PhCH_2O.CO.NMe.CHR.COOH$ (6) $Ph_2PO.NH.CHR.COOH$ (7) $Ph_2PO.NMe.CHR.COOH$ (8)

It was thus decided to extend the synthetic utility of phosphinamide alkylation to the synthesis of Dpp-derivatives of N_{α}-methylamino acids (8) from the corresponding Dpp-amino acids (7) reported previously.[1] Using the conditions recommended by Benoiton[12,13] (8 eq. MeI, 3 eq. NaH in THF) it has been possible to prepare the derivatives (8) shown in Table 2, except for methionine where 1 eq. MeI was used to prevent S-methylation. Tryptophan was found to methylate faster at the indolic N-H in agreement with the tryptamine case discussed earlier. All of the derivatives (8) (Table 2) are highly crystalline and exhibit better crystallisation properties than the corresponding Z-series (6). Treatment of the Dpp-N-methylamino acids with 6N HCl afforded Ph_2POOH which was filtered to give solutions of the corresponding N-methylamino acids having optical rotations in close agreement with literature values (Table 2). An investigation of the stereochemical integrity and synthetic utility of these acid labile derivatives of N-methylamino acids is being undertaken.

Acknowledgements

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References

1. G.W. Kenner, G.A. Moore and R. Ramage, Tetrahedron Lett., 1976, in press.

2. T. Koizumi and P. Haake, J.Amer.Chem.Soc., 95, 8073 (1973); D.A. Tyssee, L.P. Bauscher, and P. Haake, J.Amer.Chem.Soc., 95, 8066 (1973).

3. G. Tomashewski and G. Kühn, J.prakt.Chem., 38, 222 (1968); M.J.P. Harger, J.C.S. Chem. Comm., 520 (1976).

4. J.B. Hendrickson and R. Bergeron, Tetrahedron Lett., 345 (1970).

5. J.B. Hendrickson and R. Bergeron, Tetrahedron Lett., 3839 (1973).

6. V. Gutmann, G. Mörtl and K. Utvary, Monatschefte für Chemie, 93, 1114 (1962).

7. V. Gutmann, G. Mörtl and K. Utvary, Monatschefte für Chemie, 94, 898 (1963).

8. Ph_2POCl is readily prepared by oxidation of commercially available Ph_2PCl (Fluka) according to the method cited in reference 2.

9. All new compounds have satisfactory analytical data.

10. E. Fischer and W. Lipschitz, Berichte, 48, 360 (1915).

11. P. Quitt, J. Hellerbach and K. Vogler, Helv.Chim.Acta, 46, 327 (1963).

12. J.R. Coggins and N.L. Benoiton, Can.J.Chem., 49, 1968 (1971); J.R. McDermott and N.L. Benoiton, Can.J.Chem., 51, 1915 (1973); J.R. McDermott and N.L. Benoiton, Can.J.Chem., 51, 2555 (1973).

13. B.A. Stroochnoff and N.L. Benoiton, Tetrahedron Lett., 21 (1973).