Pergamon

Tetrahedron Letters 39 (1998) 7787–7790

TETRAHEDRON LETTERS

DPPE: A Convenient Replacement for Triphenylphosphine in the Staudinger and Mitsunobu Reactions

Ian A. O'Neil[1]*, Stephen Thompson[1], Clare L. Murray[1] and S. Barret Kalindjian[2]

[1] Department of Chemistry, University of Liverpool, Crown St, Liverpool L69 7ZD, UK.

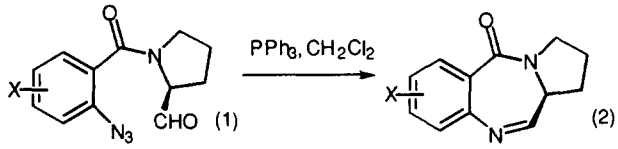
[2] James Black Foundation, 68, Half Moon Lane, Dulwich, London SE24 9JE, UK.

Received 3 July 1998; accepted 11 August 1998

Abstract: DPPE has been shown to replace triphenylphosphine in the Staudinger and Mitsunobu reactions. The resulting bis(phosphine oxide) by-product is readily removed allowing for rapid and simple purification of the reaction mixture.

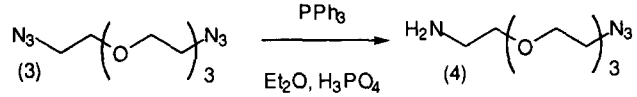
We and others have recently disclosed an expedient and high yielding approach to the synthesis of pyrrolo-[1,4]-benzodiazepines (PBDs)[1], a family of antitumor antibiotics that exhibit sequence specific binding to the minor groove of DNA[2]. The key step is a Staudinger/intramolecular aza-Wittig reaction on azido aldehyde (1), giving the desired PBD (2). The reaction is clean and high yielding, the only by-product being triphenylphosphine oxide.

Scheme 1.



We have however experienced difficulty in separating the triphenylphosphine oxide from the PBD product on column chromatography, the materials often coeluting. This has been attributed to the strong hydrogen bond forming ability of triphenylphosphine oxide[3] and also hydrophobic effects[4]. Others have noted the tendency of triphenylphosphine oxide to co-elute with reaction products[5], and to overcome this problem, the use of several modified phosphines has been reported; notably phosphines bearing a basic group allowing acid extraction of the phosphine oxide by-product[6]. Schwabacher *et al*[7] have recently experienced this problem in the reduction of diazide (3) to the amino azide (4) (Scheme 2). In this case they maintained the organic layer in contact with aqueous phosphoric acid which extracted the monoamine as soon as it was formed. The triphenylphosphine oxide remained in the organic layer.

Scheme 2



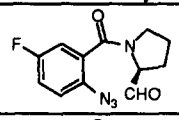
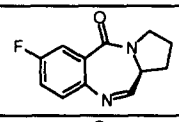
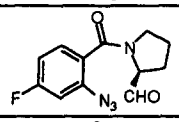
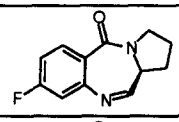
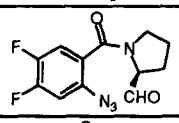
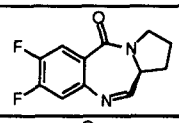
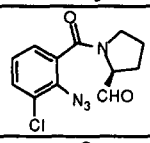
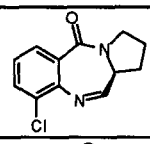
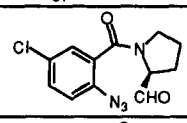
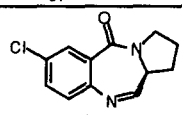
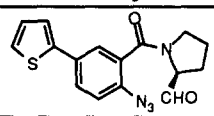
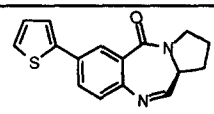
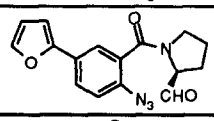
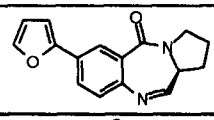
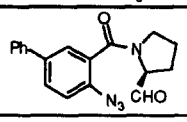
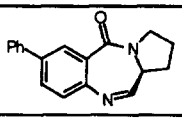
Given the sensitivity of PBDs to acid this strategy was inapplicable in our case. The use of polymer bound triphenylphosphine[8] was also examined and although successful this reagent is expensive and accordingly its use on a large scale prohibitive.

0040-4039/98/$ - see front matter
PII: S0040-4039(98)01702-X

In order to facilitate the purification of these compounds we have examined the use of 1,2-bis(diphenylphosphino)ethane (DPPE) as a replacement for triphenylphosphine in the key Staudinger/aza-Wittig cyclisation. In particular, we anticipated that use of half an equivalent of DPPE should give rise to a bis(phosphine oxide) by-product if both phosphines participate in the cyclisation. Being considerably more polar than triphenylphosphine oxide this by-product should be easily removed. It was gratifying to find that the reaction proceeded according to our plans. Thus reaction of the azido aldehyde precursor with 0.55 eq of DPPE in CH_2Cl_2 at room temperature gave the desired PBD in good to excellent yields[9]. The bis(phosphine oxide) by-product was removed by filtration and the crude product purified by flash chromatography. We have used this methodology on a range of azido aldehyde precursors, notably compounds which bear a C-substituent on the aromatic A ring. This family of PBDs has not been reported previously. The results of the Staudinger/aza-Wittig cyclisation using DPPE on these substrates are given in Table 1.

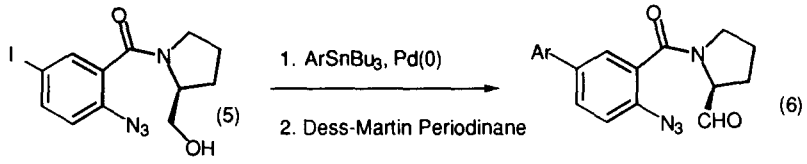
Table 1. DPPE mediated cyclisation of azido aldehydes:

* % yield refers to pure isolated material

Entry	Azido aldehyde	PBD	% Yield*
1			77
2			71
3			88
4			59
5			53
6			45
7			56
8			60

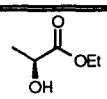
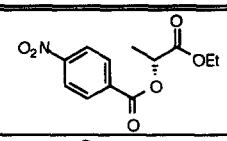
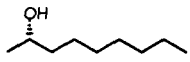
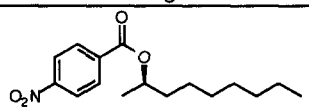
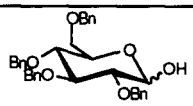
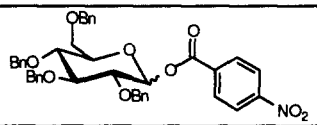
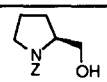
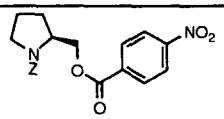
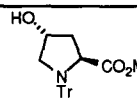
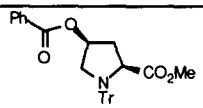
The precursor azido aldehydes were prepared by the route shown in scheme 3. Full details of this work will be reported shortly[10].

Scheme 3



Given the success of DPPE in these reactions, we have also investigated its efficacy in the Mitsunobu reaction[11], a procedure which finds widespread synthetic use. Again it was found that DPPE could be used in place of triphenylphosphine, allowing for simple purification of the reaction mixture. In several cases use of 1 equivalent of DPPE was necessary to ensure the reaction went to completion. Examples are given in table 2.

Table 2. DPPE mediated Mitsunobu reactions.

Entry	Substrate	Conditions	Product	% Yield*
1		DPPE (0.6eq), DEAD (1.2eq), 4-$NO_2C_6H_4CO_2H$ (1.2eq), $PhCH_3$		67
2		DPPE (1eq), DEAD (1.4eq), 4-$NO_2C_6H_4CO_2H$ (1.4eq), thf		98
3		DPPE (0.75eq), DIAD (1.5eq), 4-$NO_2C_6H_4CO_2H$ (1.3eq), thf		57
4		DPPE (0.6eq), DEAD (1.2eq), 4-$NO_2C_6H_4CO_2H$ (1.2eq), $PhCH_3$		59
5		DPPE (1eq) $PhCO_2H$ (2eq), $PhCH_3$ DEAD (2eq)		86

* % yield refers to pure isolated material

In summary, we have shown that DPPE is a convenient replacement for triphenylphosphine in both the Staudinger and Mitsunobu reactions. The ease of separation of the reaction products from the phosphine oxide by-product and the neutral reaction conditions, makes this the method of choice for these reactions.

Acknowledgements: This work was supported by EPSRC CASE awards to ST and CLM.

References:

1. I. A. O'Neil, C. L. Murray, R. C. Hunter, S. B. Kalindjian and T. C. Jenkins, *Synlett* **1997**, 75.
   I. A. O'Neil, C. L. Murray, A. J. Potter and S. B. Kalindjian, *Tetrahedron Lett.* **1997**, *38*, 3609.
   P. Molina, D. Diaz and A. Tarraga, *Tetrahedron* **1995**, *51*, 5617.
   S. Eguchi, K. Yamashita, Y. Matsushita and A. Kakehi, *J. Org. Chem.* **1995**, *60*, 4006.
2. D. E. Thurston and D. S. Bose, *Chem. Rev.* **1994**, *94*, 433.
3. M. C. Etter and P. W Baures, *J. Am. Chem. Soc.* **1988**, *110*, 639.
4. R. Castro, K. R. Nixon, J. D. Evansneck and A. E. Kaifer, *J. Org. Chem.* **1996**, *61*, 7298.
5. I. D. Jenkins, in "Encyclopedia of Organic Reagents" **1995**, *8*, 5380, Ed. L. A. Paquette, Wiley.
6. D. Camp and I. D. Jenkins, *Aust. J. Chem.* **1988**, *41*, 1835.
   M. Von Itzstein and M. Mocerino, *Synth. Commun.* **1990**, *20*, 2049.
   M. Von Itzstein and M. Mocerino, *Carbohydr. Res.* **1990**, *208*, 287.
7. A. W. Schwabacher, J. W. Lane, M. W. Schiesher, K. M. Leigh and C. W. Johnson, *J. Org. Chem.* **1998**, *63*, 1727.
8. R. A. Amos, R. W. Emblidge and N. Havens, *J. Org. Chem.* **1983**, *48*, 3598.
9. Preparation of (11a*S*)-7-fluoro-1,2,3,11a-tetrahydro-5*H*-pyrrolo(2,1-c)[1,4]benzodiazepine-5-one:
   To a stirred solution of the azido aldehyde (0.082g, 0.31mmol) in dry CH_2Cl_2 (5 ml) was added DPPE (0.068g, 0.17mmol). The reaction was stirred at room temperature for 30 minutes and then filtered. The solution was concentrated *in vacuo*, and the crude residue was purified by flash chromatography on silica gel, eluting with EtOAc, to give the product, (0.053g, 77%) as a pale yellow oil, $[\alpha]_D$ = 57.14 (c = 1.05, MeOH); υ_{max} (CH_2Cl_2)/cm^{-1} 1685 and 1633; δ_H (200MHz, $CDCl_3$) 2.07 (2H, m, H-2), 2.35 (2H, m, H-1), 3.56 (1H, m, H-11a), 3.85 (2H, m, H-3), 7.23 (2H, m, aromatic), 7.71 (1H, d, J = 2.9, aromatic) and 7.75 (1H, d, J = 4.3, H-11); δ_C (50MHz, $CDCl_3$), 165.52, 162.98, 129.5, 127.29, 120.93, 118.9, 116.25, 53.49, 46.76, 29.64 and 24.06; m/z (EI) 218 (M^+, 75%), 217 (M^+ -H, 33), 190 (M^+ -H_2CN), found M^+, 218.08556. $C_{12}H_{11}FN_2O$ requires M^+, 218.08554.
10. I. A. O'Neil, C. L. Murray, S. Thompson and S. B. Kalindjian, manuscript in preparation.
11. O. Mitsunobu, in "Comprehensive Organic Synthesis" **1991**, *6*, 65., Ed. B. M. Trost and I. Fleming, Pergamon Press.