Pergamon

Tetrahedron Letters 43 (2002) 2807–2810

TETRAHEDRON LETTERS

Synthesis of fluorous azodicarboxylates: towards cleaner Mitsunobu reactions

Adrian P. Dobbs* and Caroline McGregor-Johnson

School of Chemistry, University of Exeter, Stocker Road, Exeter EX4 4QD, UK

Received 31 January 2002; accepted 18 February 2002

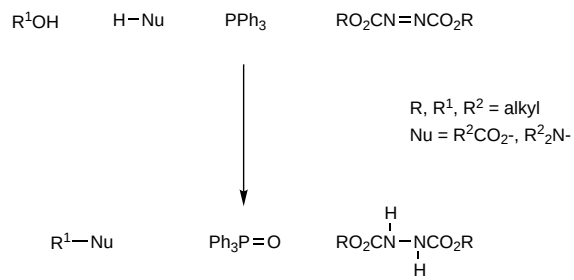
Abstract—The synthesis of a fluorous analogue of diethyl azodicarboxylate (DEAD) is described and preliminary results for its use in the Mitsunobu reaction given. Use of fluorous extraction methods have shown that chromatography is not necessary for reaction purification.

Perfluorocarbon liquids are poor solvents for organic compounds and also have limited, but thermally controlled miscibility with organic solvents. Horváth used these properties to introduce the concept of the fluorous biphasic system in 1994[1] and Curran[2] further elaborated this in his concept of an 'ideal purification.' The concept is a simple one: the product(s) of a particular reaction are separated into a different phase from the starting reagents and reaction byproducts. To date, fluorous biphasic chemistry has found particular application in the field of catalysis, but is rapidly becoming more important in organic synthesis, since it permits easy purification or removal of fluorous compounds from organic ones by simple liquid–liquid extraction. Fluorous reagents for synthesis are rapidly emerging as clean alternatives to conventional reagents and recent examples have included fluorous-tin hydrides,[3–5] fluorous-allyltin reagents,[6] fluorous-organoselenium reagents,[7,8] fluorous-phosphines[9–11] and fluorous-protecting groups.[12–17]

The condensation reaction of an alcohol using the redox couple of a trialkyl or triaryl phosphine and a dialkyl azodicarboxylate is known as the Mitsunobu reaction, based on work performed in the 1960's. The reaction has been extensively reviewed[18,19] and may be summarised as in Scheme 1.

An alcohol (R^1OH) and an acidic component (H-Nu) are condensed to form the product (R^1-Nu), while triphenylphosphine is oxidised to triphenylphosphine oxide and the dialkyl azodicarboxylate is reduced to the hydrazine. Diethyl azodicarboxylate (DEAD) is the usual carboxylate of choice, along with triphenylphosphine, although other combinations are known.[18,19] One of the major uses of the Mitsunobu reaction is with optically active substrates, it proceeds with complete inversion of configuration.[18,19]

With the development of new technologies for cleaner synthesis, the Mitsunobu reaction has been the focus of considerable attention. Triphenylphosphine oxide is known to be problematic to remove from reactions and variations have been developed in an attempt to overcome this e.g. solid-supported triphenylphosphine and fluorous-triphenylphosphines.[9,10] Both reagents have greatly simplified the ease of purification of many reactions involving triarylphosphines.[11,20] While the problem of the triphenylphosphine has been largely overcome, it is often the removal of the hydrazine by-product that has been more problematic. This has received much less attention,[21] although a solid-supported version of DEAD has been reported.[22] Therefore, we believed this reaction, and in particular the DEAD reagent, to be ripe for study using fluorous technologies. Concurrent with this study, the group of



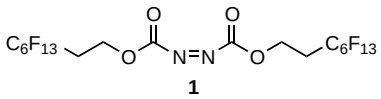
Scheme 1. The Mitsunobu reaction.

* Corresponding author. Tel.: +44 1392 263410; fax: +44 1392 263434; e-mail: a.dobbs@exeter.ac.uk

0040-4039/02/$ - see front matter
PII: S0040-4039(02)00322-2

Curran in Pittsburgh have also been developing a fluorous-based version of the Mitsunobu reaction, based on a solid–liquid fluorous separation approach.[23] Pleasingly, their results concur with those described here and will be reported shortly. Herein we describe the synthesis of a fluorous-DEAD reagent and preliminary results for its use in the Mitsunobu reaction.

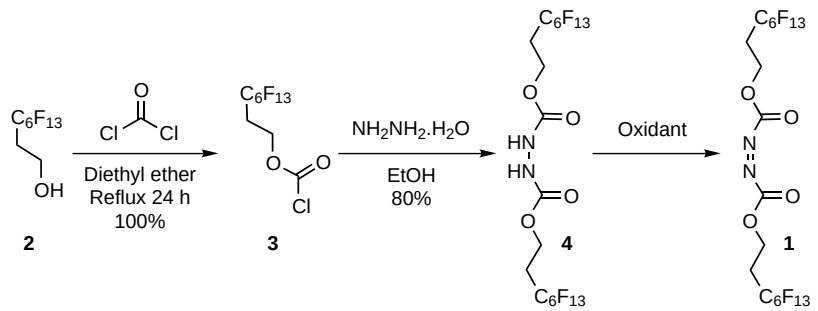
In designing a fluorous-DEAD reagent, we were conscious of the need for ca. 60% fluorine content to ensure selective solubility of the compound in fluorous solvents,[24] while also requiring a spacer group to protect the azocarboxylate function from the electron withdrawing effects of the fluorine atoms.[24] Thus, **1** appeared to be a suitable target, with 60.9% fluorine content and also an ethylene spacer group.



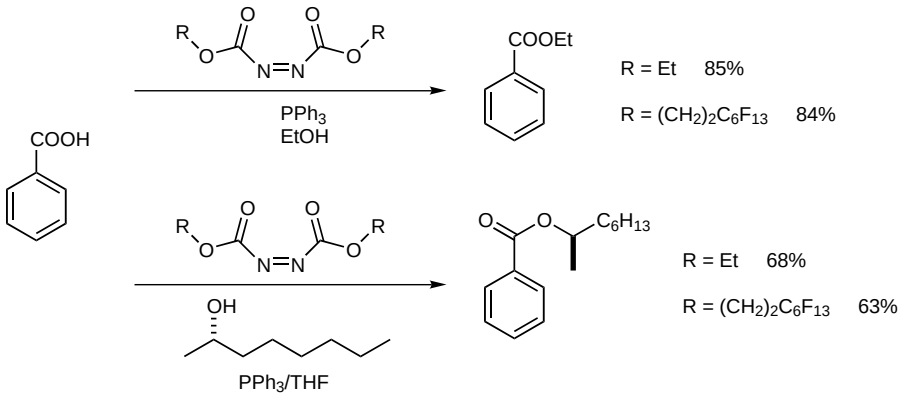
1

The synthesis of the fluorous-DEAD reagent was relatively easy, employing literature methods (Scheme 2). Commercially available 1,1,2,2*H*-tridecafluoro-1-octanol **2** was chosen as a suitable starting material, since it possessed a suitable fluorous pony-tail, and also an ethylene 'spacer' unit, to shield the hydrazine from the fluorous pony-tail. Reaction of this with phosgene[25] (commercial solution in toluene) gave, after 24 h reflux, the fluorous chloroformate **3**, in quantitative yields. Although isolated and purified by column chromatography, this compound could be used without further purification in the subsequent reaction with hydrazine hydrate in ethanol, employing the conditions of Rabjohn.[26] The fluorous hydrazine **4** was obtained as a white solid that could be recrystallised from methanol (80%).[27] The crucial step was the oxidation of the fluorous diethylcarboxyhydrazine. Several oxidants were attempted: manganese dioxide (0%), lead tetraacetate[28] (29%) and finally, the reagent of choice, *N*-bromosuccinimide[29–31] in pyridine (79%). The fluorous-DEAD reagent **1** was obtained as a pale cream/yellow solid, after recrystallisation from ethanol and in 63% overall yield.[27]

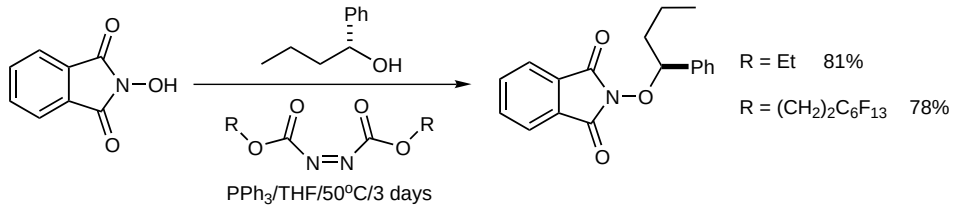
The fluorous-DEAD has been utilised in three test reactions, which are typical examples of Mitsunobu reactions. First was a simple esterification reaction, to form ethyl benzoate from benzoic acid and ethanol (Scheme 3). The reaction was performed twice, using both DEAD and fluorous-DEAD. Identical reaction conditions were employed in each case (using ethanol both as reagent and solvent at room temperature for 12 h) and comparable yields obtained (85% (DEAD) and 84% (fluorous-DEAD)). Column chromatography was required to purify the traditional reaction. However, for the fluorous reaction, the excess ethanol was removed under reduced pressure and the residue partitioned between dichloromethane and the fluorous solvent FC-72 (perfluorohexane). Separation of the two phases showed complete removal of the fluorous-hydrazine by-product from the reaction mixture, thus leaving only triphenylphosphine oxide to be separated from the desired product. Repeating this reaction using *S*-(+)-2-



Scheme 2. Synthesis of fluorous-DEAD.



Scheme 3. Fluorous-DEAD in esterification reactions.



Scheme 4. Fluorous-DEAD in phthalimide coupling reactions.

octanol gave the corresponding *R*-(−) octyl benzoate in equally good yield (68% (DEAD) and 63% (fluorous-DEAD)) and with the expected inversion of configuration, a typical characteristic of the Mitsunobu reaction. We are currently calculating the partition coefficients of fluorous-DEAD for a range of fluorous and organic solvents, and these will be reported shortly.

Finally, to demonstrate that the fluorous-DEAD reagent was not limited just to esterification reactions, a phthalimide coupling reaction was performed, using *N*-hydroxyphthalimide and *R*-(+)-1-phenylbutanol (Scheme 4). The traditional reagents gave *S*-(−)-*N*-(1-phenylbutoxy)phthalimide (i.e. complete inversion of configuration) in 81% after three days and column chromatography.[32] Repeating the reaction using fluorous-DEAD again required long reaction time and gave the desired product in almost identical yield and with complete inversion of configuration.

In conclusion, a high yielding synthesis of a fluorous analogue of diethyl azodicarboxylate has been developed and the reagent utilised in a range of Mitsunobu reactions. Separation of the fluorous by-products is easily achieved by fluorous liquid extraction, using a perfluorosolvent. Thus, this procedure offers an easy method for the purification of the hydrazine by-product from Mitsunobu reactions. Further, this method offers a complementary fluorous-separation technique to the fluorous solid–liquid separation method of Curran.[23] We are currently investigating the use of this reagent in conjunction with alternatives to triphenylphosphine e.g. fluorous-phosphines and solid-supported phosphines, in order to remove completely the need for any form of chromatography and to further the 'greening' of the Mitsunobu reaction. These results will be reported in due course.

Acknowledgements

We are grateful to the University of Exeter for funding (C.M.-J.).

References

1. Horváth, I. T.; Rábai, J. *Science* **1994**, *266*, 72–75.
2. Curran, D. P. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 1174–1196.
3. Curran, D. P.; Hadida, S. *J. Am. Chem. Soc.* **1996**, *118*, 2531–2532.
4. Horner, J. H.; Martinez, F. N.; Newcombe, M.; Hadida, S.; Curran, D. P. *Tetrahedron Lett.* **1997**, *38*, 2783–2786.
5. Curran, D. P.; Hadida, S.; Kim, S.-Y.; Luo, Z. *J. Am. Chem. Soc.* **1999**, *121*, 6607–6615.
6. Ryu, I.; Curran, D. P. *Tetrahedron Lett.* **1999**, *40*, 2367–2370.
7. Crich, D.; Hao, X.; Lucas, M. *Tetrahedron* **1999**, *55*, 14261–14268.
8. Crich, D.; Hao, X.; Lucas, M. A. *Org. Lett.* **1999**, *1*, 269–271.
9. Bhattacharyya, P.; Gudmunsen, D.; Hope, E. G.; Kemmitt, R. D. W.; Paige, D. R.; Stuart, A. M. *J. Chem. Soc., Perkin Trans. 1* **1997**, 3609–3612.
10. Chen, W.; Xiao, J. *Tetrahedron Lett.* **2000**, *41*, 3697–3700.
11. Galante, A.; Lhoste, P.; Sinou, D. *Tetrahedron Lett.* **2001**, *42*, 5424–5427.
12. Curran, D. P.; Ferritto, R.; Hua, Y. *Tetrahedron Lett.* **1998**, *39*, 4937–4940.
13. Wipf, P.; Reeves, J. T. *Tetrahedron Lett.* **1999**, *40*, 4649–4652.
14. Wipf, P.; Reeves, J. T. *Tetrahedron Lett.* **1999**, *40*, 5139–5142.
15. Röver, S.; Wipf, P. *Tetrahedron Lett.* **1999**, *40*, 5667–5670.
16. Pardo, J.; Cobas, A.; Guitián, E.; Castedo, L. *Org. Lett.* **2001**, *3*, 3711–3714.
17. Luo, Z.; Williams, J.; Williams, R. W.; Read, R. W.; Curran, D. P. *J. Org. Chem.* **2001**, *66*, 4261–4266.
18. Mitsunobu, O. *Synthesis* **1981**, 1–28.
19. Hughes, D. L. *Organic Reactions*; Paquette, L. A., Ed.; John Wiley & Sons; Vol. 42, pp. 335–645.
20. Pollastri, M. P.; Sagal, J. F.; Chang, G. *Tetrahedron Lett.* **2001**, *42*, 2459–2460.
21. Pelletier, J. C.; Kincaid, S. *Tetrahedron Lett.* **2000**, *41*, 797–800.
22. Tunoori, A. K.; Dutta, D.; Georg, G. I. *Tetrahedron Lett.* **1998**, *39*, 8751–8754.
23. Personal communication from Professor Dennis Curran; Dandapani, S.; Curran, D. P. *Tetrahedron*, in press.
24. Barthel-Rosa, L. P.; Gladysz, J. A. *Coord. Chem. Rev.* **1999**, *190–192*, 587–605.
25. Forbes, J. E.; Saicic, R. N.; Zard, S. Z. *Tetrahedron* **1999**, *55*, 3791–3802.
26. Rabjohn, N. *Org. Synth. Collect. Vol. III*, 375–377.
27. All compounds gave satisfactory analytical data. Both the fluorous hydrazine (**4**) and fluorous-DEAD (**1**) reagents are now commercially available from Fluorous Technologies Inc. (www.fluorous.com).

28. Rutjes, F. P. J. T.; Paz, M. M.; Hiemstra, H.; Speckamp, W. N. *Tetrahedron Lett*. **1991**, *32*, 6629–6632.
29. Carpino, L. A.; Crowley, P. J. *Org. Synth. Collect*. **1973**, *5*, 160–162.
30. Yamamoto, Y.; Yumoto, M.; Yamada, J.-I. *Tetrahedron Lett*. **1991**, *32*, 3079–3082.
31. Brimble, M. A.; Lee, C. K. Y. *Tetrahedron: Asymmetry* **1998**, *9*, 873–884.
32. The authors wish to thank Professor Chris Moody (University of Exeter) for providing experimental information and data for this reaction.