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Purification of Fluorous Mitsunobu Reactions by Liquid-Liquid Extraction

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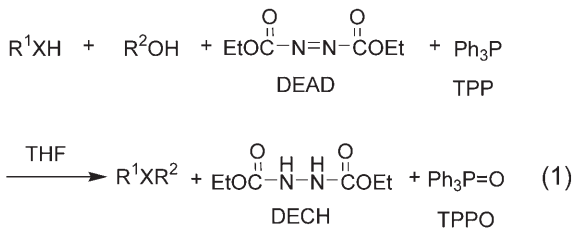
Abstract: Solvent tuning and partition coefficient measurements have identified suitable reagent and solvent combinations for the purification of fluorous Mitsunobu reaction products. The crude reaction mixtures are partitioned between 2/1 HFE-7100/FC-72 and DMF/10% water to provide reagent (fluorous) and product (organic) fractions.

Keywords: diazodicarboxylates; fluorous; liquid-liquid extraction; Mitsunobu reaction

Introduction

The Mitsunobu reaction [Eq. (1)] is a workhorse transformation in small-scale discovery chemistry because of its reliability and scope.[1] Many primary and some secondary alcohols can be displaced in a single-step reaction to provide an assortment of new functionalities including esters, amides and related groups, aryl ethers, thioethers, and many more. The power and popularity of the Mitsunobu reaction span the small-scale synthesis enterprise from traditional synthesis of single compounds through diversity oriented synthesis to large combinatorial library synthesis.



unreacted diethylazodicarboxylate (DEAD) triphenylphosphine (TPP) and spent diethyl carboxyhydrazide (DECH) and triphenylphosphine oxide (TPPO) are difficult to remove from reaction products

To accomplish its dehydration, the Mitsunobu reaction consumes stoichiometric quantities of a diazodicarboxlate (or related reagent) and a phosphine to generate reduced hydrazide and oxidized phosphine oxide by-products. The removal of these by-products (and unreacted starting reagents) was originally accomplished by chromatography, but more recently a diverse collection of modified reagents has been introduced to facilitate the needed separation. Indeed, the Mitsunobu reaction has become somewhat of a proving ground for the introduction and trial of new separation methods and reagents.[2]

Despite the large amount of work devoted towards separation-friendly Mitsunobu reactions,[2] we are not aware of any procedure in which the reagents and reagent by-products of a Mitsunobu reaction can be directly removed by a liquid-liquid extraction. To date, procedures that rely on liquid-liquid extraction are indirect in that they require a separate reaction after the Mitsunobu reaction to convert the reagents into extractable form.[2,3] Conducting the second reaction requires additional effort and imposes its own set of constraints on the kinds of Mitsunobu products that can be formed.

We report herein that, by selection of appropriate fluorous reagents and extraction solvents, crude products from a fluorous Mitsunobu reaction[4] can be separated from reagents and reagent-derived by-products by direct liquid-liquid extraction. The new procedure complements an existing procedure for the Mitsunobu reaction that uses fluorous diazodicarboxlate $C_6F_{13}(CH_2)_3OCON{=}NCO_2(CH_2)_3C_6F_{13}$ (**1**) and phosphine $(C_6H_5)_2P(C_6H_4\text{-}p\text{-}CH_2CH_2C_8F_{17})$ reagents and separates reagents and derived products from target products by fluorous solid phase extraction.[5–7]

Results and Discussion

To identify reagent and solvent combinations that pair well for liquid-liquid extractions, we started by measuring partition coefficients of a series of fluorous compounds (Figure 1) including fluorous diazodicarboxylate **1** and reduced hydrazide **2**, phosphines **3a** (with 26 fluorines) and **3b** (with 34 fluorines), and the phosphine oxide **4a**, corresponding to **3a**. We also added the representative Mitsunobu product **5** as an organic control. A standard procedure[8] was used to measure the partition coefficients, K_P, and the results of these experiments are summarized in Table 1.

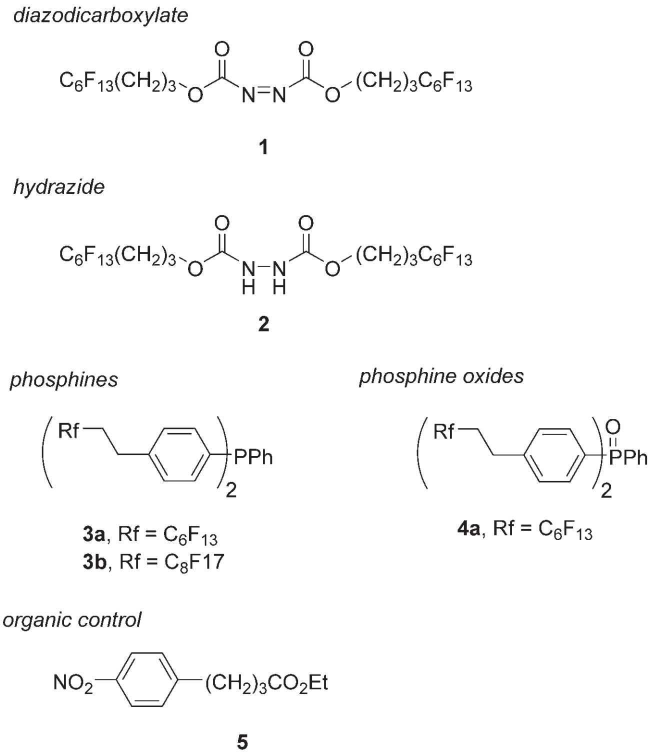


Figure 1. Structures of Mitsunobu reagents and control for partitioning studies.

Preliminary partitioning experiments of the fluorous reagents between FC-72 (perfluorohexanes)[9] and DMF/10 % water were satisfactory for four of the five reaction components, but a significant amount (14 %) of the polar phosphine oxide **4a** partitioned into the DMF/water phase (Table 1, first column).

To optimize the partition coefficients, we conducted solvent tuning experiments like those recently reported by Yu and co-workers.[10] FC-72 was replaced by HFE-7100 (perfluorobutyl methyl ether) and the compounds were partitioned between this solvent and polar solvents (MeOH, CH_3CN, DMF) with increasing amounts (5–20 %) of water. The results are summarized in Table 1 as the percentage of the solute present in the fluorous solvent. In these experiments, the fluorous hydrazide by-product always shows a considerably higher partition coefficient than its azodicarboxylate precursor while the phosphine precursor shows a higher partition coefficient than its phosphine oxide by-product. Thus, if the phosphine oxide and azodicarboxylate have suitably high partition coefficients, an extraction procedure should work to remove all unreacted and spent reagents.

These experiments identified DMF/H_2O as a promising countersolvent to HFE-7100 since all of the fluorous compounds showed high partition coefficients that increased as expected with increasing water content. Especially attractive were the high partition coefficients exhibited by the lighter phosphine oxide **4b** in HFE-7100/DMF-H_2O; about 99 % of the phosphine oxide partitioned into the HFE-7100 phase. However, back extraction of the control organic compound **5** was too high (11–26 %) in this solvent combination.

To further fine tune the fluorous solvent, we used a blend of 2/1 HFE-7100/FC-72 against CH_3CN/10 % water and DMF/10 % water, and the results of these partitioning experiments are also shown in Table 1 at the far right. The results with the fluorous solvent blend and DMF/water were especially favorable, with

Table 1. Partitioning of reagents **1–4** and control **5** expressed as percentage in the fluorous phase.

Comp.	FC72/ DMF	HFE-7100/MeOH			HFE-7100/CH_3CN			HFE-7100/DMF			HFE-7100/FC72	
											CH_3CN	DMF
	10 % H_2O	5 % H_2O	10 % H_2O	20 % H_2O	5 % H_2O	10 % H_2O	20 % H_2O	5 % H_2O	10 % H_2O	20 % H_2O	10 % H_2O	10 % H_2O
1	98.2	-	67.6	-	-	77.0	-	-	100[a]		100[a]	100[a]
2	97.0	65.2	94.8	100[a]	84.8	90.6	99.7	99.7	99.9	100[a]	99.9	100[a]
3a	98.8	-	100	-	-	-	-	-	98.8	-	99.4	100[a]
3b	-	93.4	100[a]	100[a]	98.6	100[a]	100[a]	98.6	100[a]	100[a]	-	-
4a	86.0	-	-	-	-	-	-	98.9	99.4	-	64.4	99.5
5	0[b]	21.9	23.6	42.5	21.2	21.9	38.0	11.5	13.4	23.6	2.0	2.9

[a] < 0.1 % of this compound was detected in the non-fluorous phase.
[b] < 0.1 % of this compound was detected in the fluorous phase.

all the fluorous compounds partitioning > 99 % into the fluorous phase and a relatively low level of back extraction of the organic control (2.9 %). Accordingly, these conditions were selected for the subsequent preparative experiments.

The results of the preparative Mitsunobu reactions with separation by liquid-liquid extraction are summarized in Figure 2. In a typical reaction, a solution of fluorous azodicarboxylate **1** (1.5 equivs.) in dry THF was added to a solution of 4-(4-nitrophenyl)butanoic acid (1.5 equivs.), fluorous phosphine **3a** (1.5 equivs.) and ethanol (1 equiv.) in THF. After 24 h, the THF was evaporated and the residue was partitioned between 2/1 HFE-7100/FC-72 and DMF/10 % water. The layers were separated and the DMF/water layer was washed twice more with HFE-7100/FC-72, then worked up as usual (see below) to provide product **5** in 82 % yield and 93 % GC purity.

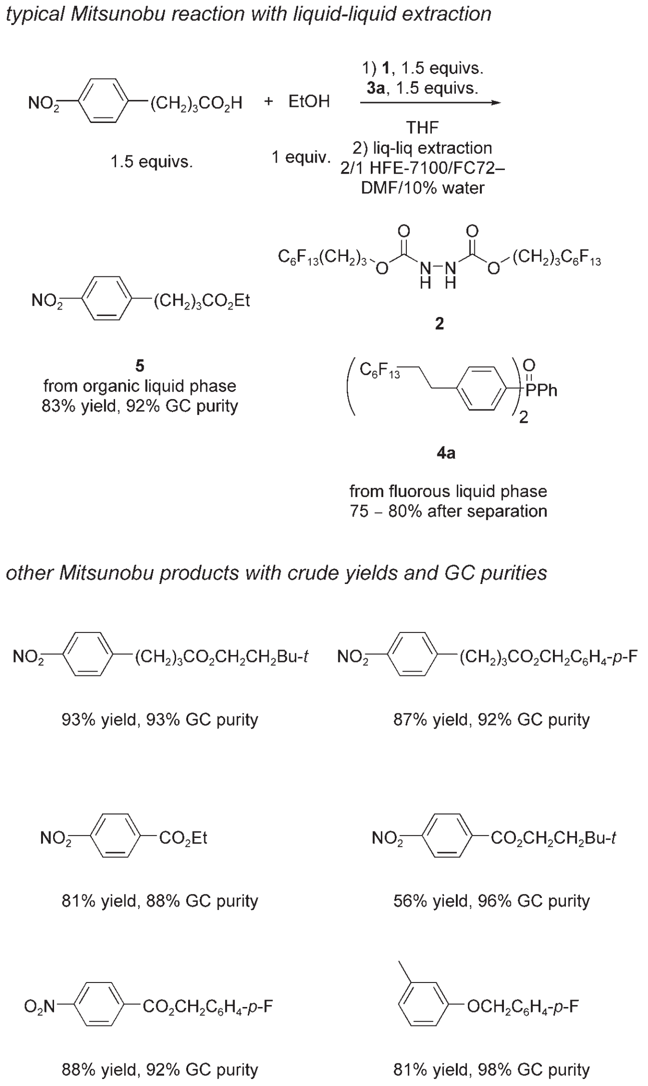


Figure 2.

Likewise, six other Mitsunobu reactions were conducted, and the yields of crude products (56–94 %) and purities as assessed by GC (88–98 %) and NMR spectroscopy were generally quite good. Copies of these GC chromatograms and NMR spectra are enclosed in the Supporting Information. In general, the ^{1}H NMR spectra look quite clean, while the GC chromatograms revealed small fluorous and unknown impurities typically at the level of < 2 % each.

The purities of the three products containing fluorine were also assessed by ^{19}F NMR spectroscopy by using the single fluorine in the product as an integration standard. Since all the fluorous reagents and reagent-derived by-products have identical ^{19}F NMR spectra, this analysis provides a total of all the fluorous impurities, which was 1.5–2 % for each sample. This is somewhat higher than expected from the partition coefficient experiments, but is still acceptable for most applications.

If desired, the fluorous products can be recovered as a mixture by evaporation of the fluorous layers. Subsequently, the hydrazide **2** and the phosphine oxide **4a** can readily be separated by flash chromatography, and each can typically be recovered in about 75–80 % for recycle by conversion back to the starting reagents.

Conclusions

Solvent tuning experiments have identified a pair of fluorous reagents and an extraction protocol that should be generally useful for conducting fluorous Mitsunobu reactions with separation of the target products from the excess reagents and reagent-derived by-products by simple liquid-liquid extraction. All the solvents and reagents are commercially available,[11] and this procedure nicely complements the existing fluorous Mitsunobu procedure with separation based on solid phase extraction.[6] One or the other of these procedures will be attractive in a diverse range of small scale Mitsunobu reactions.

Experimental Section

Representative Experimental Procedure

A solution of ^{F}DEAD **1** (132 mg, 0.16 mmol) in anhydrous THF (1 mL) was slowly added to a solution of 4-(4-nitrophenyl)butanoic acid (33 mg, 0.16 mmol), ethyl alcohol (6 μL, 0.11 mmol) and ^{F}TPP **3a** (150 mg, 0.16 mmol) in THF (1 mL) at room temperature. After 24 h, the reaction mixture was concentrated and solvent was completely removed under vacuum. The reaction mixture was then completely dissolved in dry DMF (9 mL) and transferred into a separatory funnel. Water (1 mL) was then added. This organic layer was then washed thrice with a 2:1 mixture of HFE-7100 and FC-72 (7 mL). The organic layer was then diluted with water (20 mL) and the product was extracted into ether (3×10 mL). The combined organic layer was then washed with saturated sodium bicarbonate solution (2×10 mL) and with brine (2×10 mL). The solvent was evaporated under vacuum to give the product (20.3 mg) as yellow oil.

Supporting Information

Contains copies of ^{1}H and ^{19}F NMR spectra and GC chromatograms for all the crude products in Figure 2.

Acknowledgements

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References

[1] a) J. W. Corbett, *Org. Prep. Proced. Int.* **1998**, *30*, 489; b) C. Simon, S. Hosztafi, S. Makleit, *J. Heterocycl. Chem.* **1997**, *34*, 349–365; c) M. Makosza, K. Wojciechowski, *Liebigs Ann. Chem.* **1997**, 1805–1816; d) D. L. Hughes, *Org. Prep. Proced. Int.* **1996**, *28*, 127–164; e) D. L. Hughes, *Org. React. (N. Y.)* **1992**, *42*, 335–656; f) O. Mitsunobu, in: *Comprehensive Organic Synthesis*, (Eds.: B. M. Trost, I. Fleming), Pergamon Press, Oxford, **1991**, Vol. 6, p 1.

[2] a) R. Dembinski, *Eur. J. Org. Chem.* **2004**, 2763–2772; b) S. Dandapani, D. P. Curran, *Chem. Eur. J.* **2004**, *10*, 3130–3138.

[3] G. W. Starkey, J. J. Parlow, D. L. Flynn, *Bioorg. Med. Chem. Lett.* **1998**, *8*, 2385–2390.

[4] a) R. Dembinski, in: *Handbook of Fluorous Chemistry*, (Eds.: J. A. Gladysz, D. P. Curran, I. T. Horvath), Wiley-VCH, Weinheim, **2004**, p 190–202; b) N. M. Paul, C. J. Gabriel, J. R. Parquette, *Chemtracts* **2002**, *15*, 617–622.

[5] Introduction of fluorous Mitsunobu reagents: a) A. P. Dobbs, C. McGregor-Johnson, *Tetrahedron Lett.* **2002**, *43*, 2807–2810; b) S. Dandapani, D. P. Curran, *Tetrahedron* **2002**, *58*, 3855–3864; fluorous nucleophiles: c) M. W. Markowicz, R. Dembinski, *Org. Lett.* **2002**, *4*, 3785–3787; fluorous alcohols: d) J. Rabai, D. Szabo, E. K. Borbas, I. Kovesi, I. Kovesdi, A. Csampai, A. Gomory, V. E. Pashinnik, Y. G. Shermolovich, *J. Fluorine Chem.* **2002**, *114*, 199–207; e) A.-M. Balint, A. Bodor, A. Gomory, K. Vekey, D. Szabo, J. Rabai, *J. Fluorine Chem.* **2005**, *126*, 1524–1530.

[6] Dobbs and McGregor-Johnson (ref.[5a]) have reported that the hydrazide derived from $C_6F_{13}(CH_2)_3OCON{=}NCO_2(CH_2)_3C_6F_{13}$ can be removed by partitioning between FC-72 and CH_2Cl_2. Partition coefficients for this diazodicarboxylate and the derived hydrazide are in the *M. Sc. Thesis* of C. McGregor-Johnson, University of Exeter, **2003**. We kindly thank A. Dobbs for providing this information.

[7] Currently preferred reagents and procedure for Mitsunobu reaction with fluorous spe separation: S. Dandapani, D. P. Curran, *J. Org. Chem.* **2004**, *69*, 8751–8757.

[8] Each reagent was partitioned between the two solvents with vigorous stirring for 15 min, then small amounts of each layer were injected into GC in triplicate. The partition coefficients were derived from the ratios of the absolute area counts of each layer.

[9] Reviews of fluorous solvents: a) J. A. Gladysz, C. Emnet, in: *Handbook of Fluorous Chemistry*, (Eds.: J. A.Gladysz, D. P. Curran, I. T. Horvath), Wiley-VCH, Weinheim, **2004**, p 11–23; b) I. Ryu, H. Matsubara, C. Emnet, J. A. Gladysz, S. Takeuchi, Y. Nakamura, D. P. Curran, in: *Green Reaction Media in Organic Synthesis* (Ed.: K. Mikami), Blackwell, Oxford, **2005**, p 59–124.

[10] M. S. Yu, D. P. Curran, T. Nagashima, *Org. Lett.* **2005**, *7*, 3677–3680.

[11] HFE-7100 and FC-72 are available from 3M and other sources. The reagents are sold by Fluorous Technologies, Inc., Aldrich, Fluka, and Waco (in Japan). DPC owns an equity interest in Fluorous Technologies.