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Chromatography-free product separation in the Mitsunobu reaction

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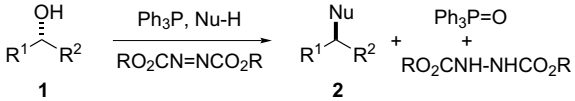
Abstract—Mitsunobu products can be isolated pure without column chromatography by first washing a solution of the crude reaction mixture in dichloromethane with 15% aqueous hydrogen peroxide followed by aqueous sodium sulfite. A final filtration through silica gel secures the pure Mitsunobu product.

Despite enhanced levels of sophistication, chromatography is increasingly a technique to be avoided if possible, especially in these more environmentally conscious times. Additionally, of course, it is often a tedious and time-consuming procedure. This is most certainly true of its use in the Mitsunobu reaction (Scheme 1),[1] to such an extent that a recent microreview[2] has highlighted chromatography-free procedures for this ubiquitous and exceptionally useful reaction. The level of complexity of some of these procedures attests both to the importance of the Mitsunobu reaction and to the tedium of most current separation procedures. Examples include the use of functionalised phosphines having pyridyl, crown ether or fluorocarbon residues decorating one of the aryl rings. Alternative azodicarboxylates also feature the use of perfluorocarbon esterifying groups, along with a number of otherwise highly modified derivatives. Some of these are converted into relatively polar by-products, which can assist with the final product separation.

Alternatively, the principle of 'impurity annihilation' using an azodicarboxylate having a norbornenyl residue



Scheme 1.

and post-reaction conversion into insoluble material by ring-opening metathetic polymerisation provides a solution which is useful in combinatorial chemistry at least.[3] However, the elaborate nature of many of these reagents, coupled with their lack of commercial availability, probably precludes their use in 'everyday' synthesis. Fundamentally a dehydration process,[4] the Mitsunobu reaction is of central importance for ester formation and as a means of introducing nitrogen into a molecule. Usually proceeding with perfect S_N2 inversion at a secondary alcohol site (**1**, Scheme 1), the reaction can also be applied with great effect to various ring closures. It has certainly been the saviour of many a synthetic scheme which has produced the incorrect stereochemistry at a secondary stereogenic centre. The problem of product isolation is generated by the typical reagent combination of a tertiary phosphine, typically triphenylphosphine, an azodicarboxylate, usually the diethyl or diisopropyl ester (DEAD or DIAD, respectively), together with the reacting nucleophile. The latter is often a carboxylic acid, hydrazoic acid or an amine derivative. Unfortunately, it is often only after relatively Herculian column chromatography that the desired product **2** can be cleanly separated from the phosphine oxide and hydrazine by-products and the (often slight) excess of starting reagents which are necessary to obtain high yields (Scheme 1). Further irritation is commonly encountered by the presence of this slight excess of the less polar phosphine, which is often of similar polarity to the product **2**.

When we recently required a series of unsaturated, and ultimately chiral, non-racemic, *O*-alkyl hydroxylamine

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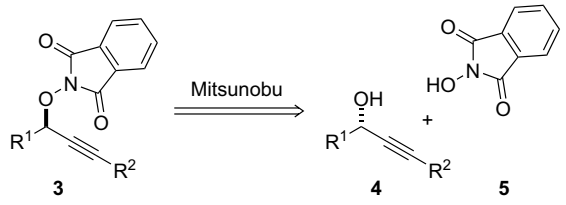
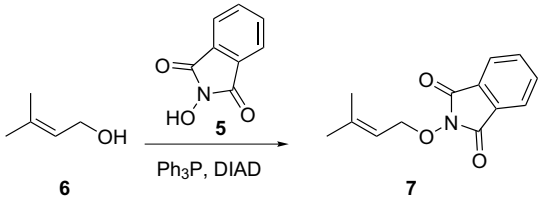


Scheme 2.



Scheme 3.

derivatives **3**, a Mitsunobu reaction between (homochiral) secondary propargylic alcohols **4** and *N*-hydroxyphthalimide **5** seemed the most viable option (Scheme 2). Although initial efforts delivered poor yields, an optimisation study revealed tetrahydrofuran to be a solvent of choice and an optimum order of addition of triphenylphosphine, DIAD, the alcohol **4** and, finally, the hydroxy-phthalimide **5**. Despite routinely isolating the desired products **3** in yields in excess of 85%, there remained the requirement for very careful column chromatography, made even more tedious by the need to produce a diverse series of such hydroxylamines, in order to properly test some novel chemistry.

Even though our optimised recipe required only marginal reagent excesses (1.01–1.2 equiv) and, crucially tetrahydrofuran rather than the commonly used ethyl acetate as solvent, in order to secure complete conversion of the precursor propargylic alcohols **4** into the phthalimides **3**, contamination of the latter by small quantities of triphenylphosphine was not uncommon, despite due care being taken during the chromatographic separation. This provoked the thought that perhaps complete removal of this contaminant could be facilitated by prior oxidation to the much more polar phosphine oxide. Clearly, if such a tactic was to be viable, the oxidising reagent would have to be readily available, cheap and, especially, easily destroyed afterwards, as it would inevitably be present in some excess, because of the uncertainty of precisely how much phosphine is needed to be oxidised. We further speculated that such an oxidant might interact with the by-product hydrazine dicarboxylate and also any excess azodicarboxylate. If these reactions were all to lead to more polar products, such transformations could facilitate the final chromatographic separation.

In view of its ability to rapidly oxidise phosphines without the need for a catalyst, we first examined the use of hydrogen peroxide. We were delighted to observe that a simple wash, using hydrogen peroxide, of a dichloromethane solution of a crude Mitsunobu reaction product left only the desired product as a significantly mobile spot on TLC analysis in dichloromethane. This suggested the possibility that a simple filtration through silica gel could suffice to remove all the by-products. After some experimentation, we developed the following simple and chromatography-free procedure for product isolation. A subsequent wash with aqueous sodium sulfite was included to ensure complete removal of any excess peroxide. These trials also revealed that 15 wt % aqueous hydrogen peroxide was quite strong enough to drive the desired oxidations to completion. A typical procedure is as follows for the reaction shown in Scheme 3.

N-(3-Methylbut-2-en-1-yloxy)phthalimide **7**: To a stirred solution of triphenylphosphine (10.96 g, 41.785 mmol) in dry tetrahydrofuran (300 ml), maintained at 0 °C under an atmosphere of dry nitrogen, was added DIAD (6.92 ml, 35.17 mmol) dropwise. The resulting solution was stirred at the same temperature for 15 min whereupon it had become creamy white in colour. 3-Methylbut-2-en-1-ol **6** (3.00 g, 34.82 mmol) was next added dropwise and stirring continued for 20 mins prior to the addition of *N*-hydroxyphthalimide **5** (5.76 g, 35.17 mmol) in one portion. The resulting mixture was stirred for 16 h without further cooling and then the bulk of the solvent was evaporated to leave a thick, orange oil, which was dissolved in a minimum of dichloromethane. This was applied to a pad of silica gel (11 cm diameter, 7 cm deep) packed using dichloromethane. The pad was washed through with 750 ml of dichloromethane which was then evaporated to approximately 300 ml. This solution was washed sequentially with 15% aqueous hydrogen peroxide (300 ml), saturated aqueous sodium sulfite (300 ml) and water (300 ml). This final water wash was back-extracted with dichloromethane (200 ml) and the combined dichloromethane solutions dried over dried magnesium sulfate for 5 min. The resulting mixture was filtered through a second pad of silica gel (11 cm diameter, 5 cm deep), which was finally washed with dichloromethane (300 ml). Evaporation gave pure *phthalimide* **7** as a colourless powdery solid (7.735 g, 96%), mp 94–95 °C, [Found: C, 67.38; H, 5.60; N, 6.01%. $C_{13}H_{13}NO_3$ requires C, 67.52; H, 5.67; N, 6.06%], δ_H ($CDCl_3$, 400 MHz) 1.74 (3H, s, Me), 1.77 (3H, s, Me), 4.73 (2H, d, *J* 7.7 Hz, 1-CH_2), 5.54 (1H, br t, *J* ca. 7.7 Hz, 2-H), 7.75 (2H, dd, *J* 5.5 and 3.1 Hz, 2 × ArH), 7.84 (2H, dd, *J* 5.5 and 3.1 Hz, 2 × ArH), δ_C ($CDCl_3$, 100 MHz) 18.1 (Me), 26.0 (Me), 74.1 (1-CH_2), 117.1 (2-CH), 123.5 (2 × ArCH), 128.9 (C), 134.4 (2 × ArCH), 143.7 (2 × C), 163.9 (2 × C=O), ν_{max}/cm^{-1} ($CHCl_3$) 1783, 1728, 1673, 1464, 1392, 1358, *m/z* (APCI) 232 (M^++H, 100%) [Found: M^++H, 232.0984. $C_{13}H_{14}NO_3$ requires M, 232.0973].

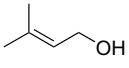
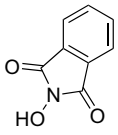
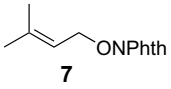
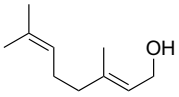
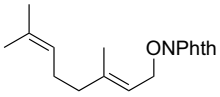
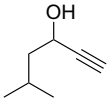
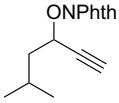
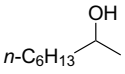
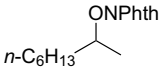
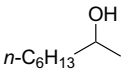
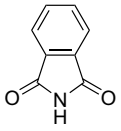
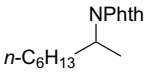
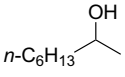
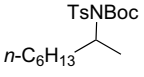
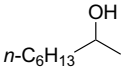
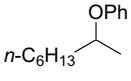
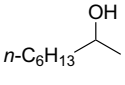
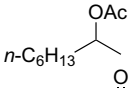
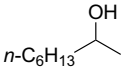
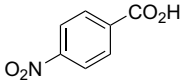
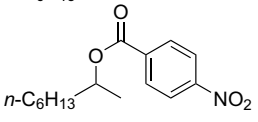
Occasionally, the initial solution from the first filtration was slightly contaminated with DIAD, but this was easily removed during the second filtration. We found that yields were reduced considerably if less dichloromethane was used, especially in the first passage through silica gel, hence occasional slight contamination by DIAD was unavoidable. During both filtrations through silica

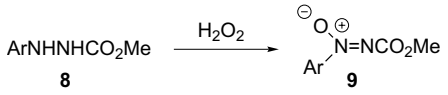
gel, much larger quantities of dichloromethane could be used, which indeed must be used with more polar products. However, this usually does not result in any further contamination, in the case of the first column, given that the highly coloured (orange) band remains on the column. It is also worth noting that larger scales can easily be accommodated, either by employing a larger amount of silica gel or, preferably, by repeating the first silica gel filtration prior to washing, that is, performing the first step of the above process twice. Using this modification, we were able to isolate over 20 g of the phthalimide **7** in a pure state in less than 30 min. Column chromatography on this scale would certainly have taken much longer!

We have successfully applied this work-up procedure to a range of exemplifying Mitsunobu reactions and the results from these are collected in Table 1. Some of the relatively lower yields probably represent the minimum obtainable, as these are unoptimised. *N*-Hydroxyphthalimide **5** worked well with both prenyl and geranyl allylic alcohols (entries 1 and 2) and also with both secondary alcohols tested (entries 3 and 4 [Ref. 3]). It should be noted that essentially correct microanalysis results for the products of entries 2 and 3 were obtained without recrystallisation, following the present work-up procedure. Phthalimide itself also worked well with 2-octanol (entry 5).[5] An alternative strategy for nitrogen introduction was also successful using the *N*-tosyl *t*-butylcarbamate reagent TsNHBoc introduced by Weinreb (entry 6).[6,7] By contrast, phenol delivered a poorer yield from 2-octanol (entry 7).[8] Optimisation of the reaction between 2-octanol and acetic acid revealed that, by using 2 equiv of the latter, an essentially quantitative yield of the expected acetate could be obtained (entry 8).[9] Finally, it has been established by the Ragnarsson group[10] that Mitsunobu nucleophiles should have pK_a values of less than 13.5, hence, the recommendation made by Martin and Dodge to employ 4-nitrobenzoic acid in Mitsunobu displacements.[11] Using the new work-up protocol, the latter with 2-octanol delivered an excellent yield of the desired product (entry 9).[12]

As for what is happening during the peroxide wash, there is no doubt from TLC evidence that any excess trivalent phosphine is being oxidised completely to the corresponding and much more polar oxide. The fate of the hydrazine dicarboxylate and any excess azodicarboxylate is less certain. Hydrazine itself is well known as a precursor to dimide [HN=NH][13] following treatment with various oxidants, hydrogen peroxide among

Table 1. Examples of chromatography-free Mitsunobu reactions

	Electrophile	Nucleophile	Product	Yield (%)
1		 **5**	 **7**	96
2		**5**		63
3		**5**		85
4		**5**		81
5				76
6		TsNHBoc		79
7		PhOH		56
8		AcOH (2 equiv)		99
9				84



Scheme 4.

them,[14] but in the presence of a copper(I) salt. Standard protocols for the oxidation of hydrazine dicarboxylates to azodicarboxylates are to use a bromonium ion source (Br_2, NBS) in the presence of pyridine,[15] or related methods using chlorine.[16] Alternatives include fuming nitric acid[17] and, more recently hypervalent iodonium reagents.[18] β-Hydroxy hydrazines have been oxidised using air and copper(II) acetate as catalyst and the resulting azo compounds further oxidised to a mono-*N*-oxide using *t*-butyl hydroperoxide in the presence of $VO(acac)_2$.[19] Although the reaction between azodicarboxylates and peroxides appears not to have been reported, hydrogen peroxide has been used to oxidise the *N*-aryl carbazates **8** to the *N*-oxides **9** in the presence of maleic anhydride (Scheme 4).[20] In our experiments, exposure of both diisopropyl azodicarboxylate and hydrazide to the oxidative work-up induced no change, according to ^1H NMR analysis. This is perhaps not surprising given the rather brief exposure to peroxide in the absence of a catalyst. Even so, it would seem advisable to take the appropriate precautions when handling the silica gel residues from this new work-up procedure, in view of the possible presence of some level of *N*-oxides.

In summary, this simple procedure should obviate the need for formal chromatography in Mitsunobu reactions in general. No doubt, it will not be suitable for every Mitsunobu reaction. For example, divalent sulfur atoms might be vulnerable to at least partial oxidation during the brief exposure to peroxide. However, the exposure time required is less than 2 min. When a sample of 1,3-dithiane was exposed to 15% hydrogen peroxide, in a close mimic of the work-up procedure, there was no oxidation at sulfur according to ^1H NMR analysis. Although we cannot be completely confident that this will always be the case, the signs are clearly good. Amines would normally be protected anyway, so should not undergo oxidation, as indicated by entries 1–6 in Table 1. The neutrality of the work-up also suggests that epoxidations of olefinic bonds conjugated to carbonyl groups, by a Michael addition mechanism, should not occur.

Hence, this procedure, while not completely free of the need for silica gel, should represent a very significant saving of time and effort.

Acknowledgements

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