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Efficient, mild, parallel and purification-free synthesis of aryl ethers via the Mitsunobu reaction

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Abstract

A wide range of commercial diazodicarboxylates and phosphines were screened in an attempt to find purification-free conditions for application in parallel synthesis. The combination of immobilized triphenylphosphine and TMAD proved to be suitable for the synthesis of aryl ethers via the Mitsunobu reaction. Nine ethers were synthesized in good yield and excellent purity, the purification being limited to a filtration step.

Keywords: Mitsunobu; Aryl ethers; Parallel synthesis; Purification-free; Polymer-supported; TMAD

The Mitsunobu reaction provides an efficient synthetic tool for the synthesis of aryl ethers.[1] The reaction has the advantage to take place under mild conditions, and is as such compatible with a large array of functional groups. However, the reagents used in this reaction are often hard to remove, and the parallel solution-phase approach to Mitsunobu reactions often remains tedious to carry out, although some newer methods have been reported.[2]

DEAD **1** and DIAD **2**, which are commonly used in Mitsunobu reactions, can usually be readily removed from the product mixture by flash chromatography but this aspect makes them unattractive for parallel synthesis. New coupling reagents have been reported such as ADDP[3] **3** and TMAD[4] **4** (Fig. 1), and other diazocarbonyl equivalents derived from morpholine and *N*-methylpiperazine,[1] but few are commercially available. Di-*tert*-butylazodicarboxylate **5** (DBAD) has also been used in order to avoid chromatographic separation.[5] After reaction, 4 M HCl in dioxane is added to the reaction mixture, which results in the decomposition of the azodicarboxylate products into volatile compounds and hydrazine. However, this technique is unsuitable for substrates sensitive to acidic conditions.

The predominant and persistent hurdle in the Mitsunobu reaction has been the tedious purification to remove after reaction the by-product triphenylphosphine oxide as well as excess triphenylphosphine **6**. Thus, many research

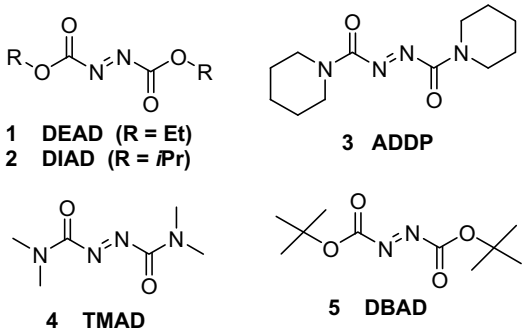

Fig. 1. Mitsunobu coupling reagents.

Abbreviations: ADDP, 1,1′-(azodicarbonyl) dipiperidine; *DAP-DP*, (*p*-dimethylaminophenyl)-diphenylphosphine; DBAD, di-*tert*-butyl azodicarboxylate; DEAD, diethylazodicarboxylate; DIAD, diisopropylazo-dicarboxylate; PS, polystyrene; TAP, tris(dimethylamino)-phosphine; TBS, *tert*-butyl-dimethyl-silyl; TMAD, *N,N,N′,N′*-tetramethyl-azodicarbonamide.

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groups have focused on developing modified phosphines to allow easy removal of the phosphines reagent from the completed reaction mixture, along with the corresponding phosphine oxide by-products (Fig. 2). DPPE **10** can replace advantageously triphenylphosphine in the Mitsunobu reaction,[6] as the enhanced polarity of its oxide by-product makes it insoluble in many organic solvents. Other phosphines include DAP-DP **8**,[7] Py-PPh_2 **9**,[5] and TAP.[8] Solid-supported triphenylphosphine **11** has become a standard procedure for Mitsunobu reactions.[9] In particular it has been used along with DBAD **5** for parallel synthesis of alkyl aryl ethers.[10] However as explained before, DBAD **5** is not suitable for all types of substrates.

As part of a chemical biology project, the synthesis of aryl ethers synthesized using various alkyl diols was targeted. As over 40 aryl ethers had to be synthesized, the interest of finding conditions for the Mitsunobu reaction that would be truly applicable for parallel synthesis and possibly automatized was obvious. In addition, the presence of a TBS group in some of the substrates required relatively mild reaction conditions, and reagents like DBAD **5** were not applicable due to the need of strong acidic conditions after reaction.

In order to evaluate several methods, the synthesis of aryl ether **13** was chosen as a representative reaction for the targeted library (Scheme 1). Therefore, classical conditions using solid-supported triphenylphosphine (purchased from Novabiochem) and DIAD **2** were first investigated (Table 1). Surprisingly, the immobilized phosphine performed very poorly. The experiment was repeated with a different batch of resin, but it still failed to give good results. Thus, the use of other immobilized triphenylphosphines from different suppliers was investigated (Table 1). Similar to the Novabiochem PS-PPh_3, Fluka's reagent performed poorly, while Polymer Lab's reagent performed extremely well, resulting in total conversion. However, LCMS analysis showed the presence of DIAD by-products in the mixture that were not detected by ELSD. The differences observed between immobilized-triphenylphosphines

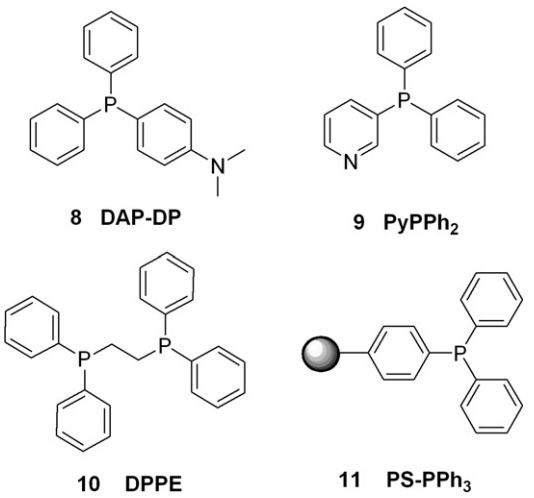


Fig. 2. Phosphines for the Mitsunobu reaction.

Table 1
Screening of immobilized triphenylphosphine using DIAD as coupling reagent for the synthesis of ether **13**

Entry	Phosphine	Purity[a]
1	PS-PPh_3 (Novabiochem)	11
2	PS-PPh_3 (Fluka)	06
3	PS-PPh_3 (Polymer Labs)	100[b]

[a] Determined by ELSD.
[b] DIAD by-products were not detected by ELSD but their presence was confirmed by MS.

purchased from different suppliers were striking. One reason could be the likely presence of oxide in the PS-PPh_3 from Fluka and Novabiochem. Indeed, Polymer lab's reagent is manufactured through copolymerization which minimizes the extent of immobilized phosphine oxide. Another explanation could be the loading of the resin, as Fluka's 3 mmol/g may result in high steric hindrance and thus poor accessibility to the reactive sites. Polymer Lab's 1.5 mmol/g in comparison may represent a good compromise. This explanation is, however, not consistent with Novabiochem's 1.3 mmol/g resin.

Due to the cost of PS-PPh_3, the possibility of using the so-called 'water-extractable' phosphines was investigated and replacement reagents for DIAD were screened for the synthesis of aryl ether **13**. The combinations of suitable and commercially available coupling reagents (DIAD **2**, TMAD **4**, and ADDP **3**) and phosphines (PPh_3 **6**, PBu_3 **7**, DAP-DP **8**, Py-PPh_2 **9**, DPPE **10**, and PS-PPh_3**11**) were investigated in parallel. The conditions were adapted from the reported synthesis of alkyl aryl ethers,[11] and in particular alkyl aryl ethers involving diols.[12] An excess of diol (1.5 equiv) to the phenol (1 equiv) was used in order to

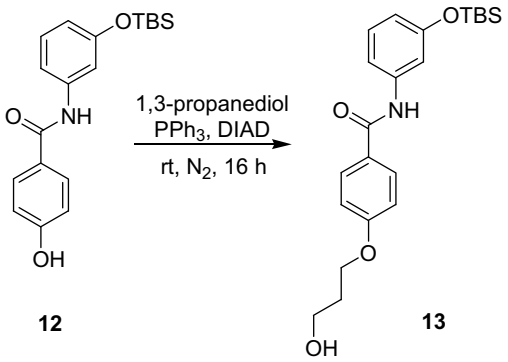
Table 2
Screening of phosphines and Mitsunobu coupling reagents for the synthesis of ether **13**

Entry	Coupling reagent	Phosphine	Purity[a]
1	DIAD	PPh_3	29
2		PBu_3	51
3		Py-PPh_2	40
4		DAP-DP	13
5		DPPE	15
6		PS-PPh_3	100[b]
7	TMAD	PPh_3	2
8		PBu_3	26
9		Py-PPh_2	1
10		DAP-DP	0
11		DPPE	5
12		**PS-PPh_3**	**100**
13	ADDP	PPh_3	51
14		PBu_3	36
15		Py-PPh_2	72
16		DAP-DP	21
17		DPPE	11
18		**PS-PPh_3**	**100**

Bold values indicate the best 2 results.
[a] Determined by ELSD.
[b] DIAD by-products were not detected by ELSD but their presence was confirmed by MS.

prevent a double Mitsunobu reaction, and the phosphine and the coupling reagent were used accordingly (1.5 equiv). A mixture of DCM and THF was used to allow swelling of the resin, and the coupling reagent was added portion-wise over 2 h. After reaction, the mixtures were filtered through SPE extractors containing a mixed bed of acidic/basic macroporous ion exchange resin, and were used as a mimetic of aqueous workup for parallel use. In the case of ADDP **3** and TMAD **4**, the hydrazine by-products formed during the reaction (insoluble in THF) were filtered off at the same time than the elution through SPE extractors. The filtrates were analyzed by LCMS and HPLC (ELSD) with attention focused on the presence of phosphine oxide or coupling reagent by-products (Table 2, Fig. 3).

Unfortunately, none of the 'water-extractable' phosphines proved to be removed efficiently from the reaction mixtures, contrasting with the supported triphenylphosphine which gave excellent results. It was noticeable that TMAD **4** and ADDP **3** did not leave any trace in the mixture in comparison to DIAD **2**. Thus, when the supported triphenylphosphine was used in combination with TMAD **4** or ADDP **3** (entries 12 and 18), no by-product from the reagents was present in the mixture at the end of the reaction. TMAD **4** appeared to be more reactive than ADDP **3** as the solution color rapidly changed from orange to colorless. These results highlighted the importance in the choice of the phosphine and only the immobilized triphenylphosphine proved to promote the Mitsunobu reaction with high purities. To the best of our knowledge this study



Scheme 1. synthesis of aryl ethers.

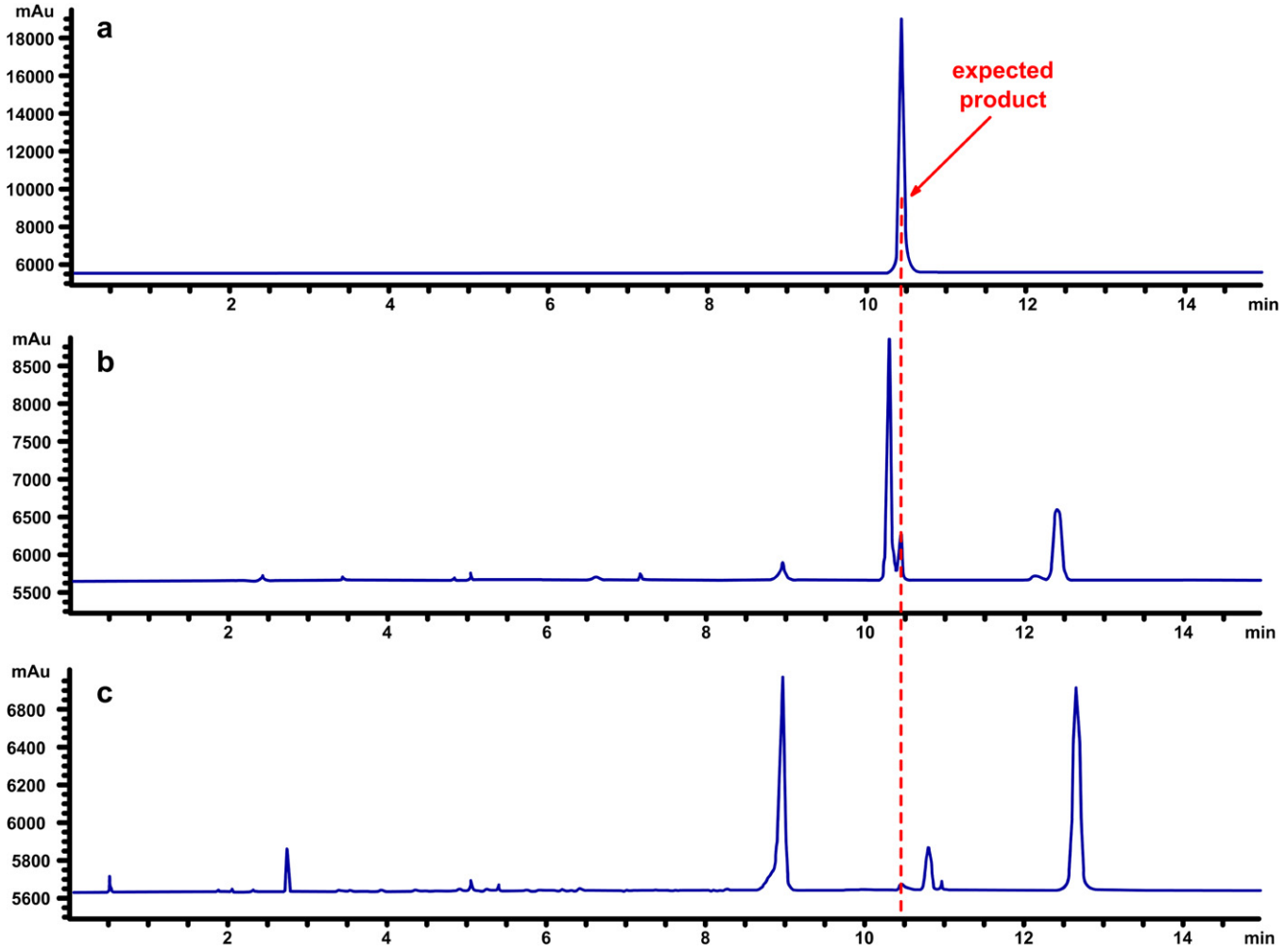


Fig. 3. Comparison of the product purity by HPLC (ELSD) with (a) PS-PPh_3/TMAD, (b) DAP-DP/ADDP, and (c) DIAD/PPh_3.

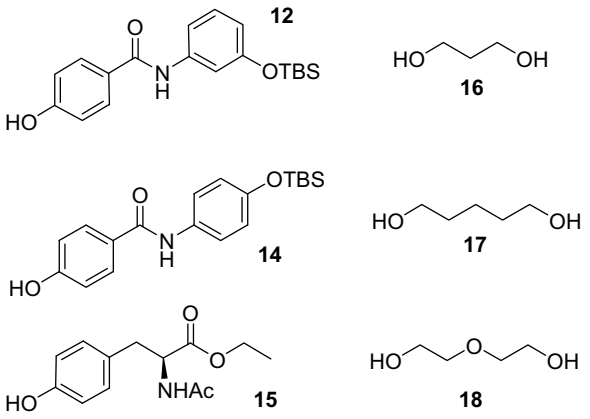


Fig. 4. Substrates for the validation library.

Table 3
Library of aryl ethers

Entry	Phenol	Diol	Yield	Purity[a]
1	**12**	**16**	97	99
2		**17**	88	96
3		**18**	94	100
4	**14**	**16**	77	100
5		**17**	77	100
6		**18**	95	98
7	**15**	**16**	69	100
8		**17**	82	96
9		**18**	43	96

[a] Determined by ELSD.

constitutes the first practical comparison of the newly developed Mitsunobu coupling reagents and phosphines.

In order to validate the conditions found, a small library of three phenols and three diols was synthesized (Fig. 4). The aryl ethers were synthesized in moderate to excellent yields and excellent purities (Table 3), thus validating the conditions developed. No purification was required: after reaction the resin was washed with DCM and MeOH, and the filtrates were combined and concentrated in vacuo. The residues were simply taken up in cold THF and filtered, resulting in the removal of the insoluble TMAD by-products.

In conclusion, the screening of the so-called water-extractable phosphines proved that these reagents cannot be entirely removed from the reaction simply by an acid/base workup. The origin of the immobilized phosphine also seems to be critical, as two out of three proved to give very poor results. Polymer-supported triphenylphosphine (Polymer Laboratories) in conjunction with TMAD is the reagent of choice to obtain aryl ethers in a purification-free manner, making high-throughput synthesis via the Mitsunobu reaction finally possible.[13]

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13. Typical procedure for the synthesis of aryl ethers: Polymer-supported triphenylphosphine (Polymer Laboratories, 1.50 mmol/g, 3 equiv) was swollen in THF/DCM (1:1, 1.5 mL/100 mg of resin). Under a nitrogen atmosphere, phenol (1 equiv) and diol (1.5 equiv) were added followed by the addition of TMAD (1.5 equiv, in solution in THF/DCM 1:1, 1 mL) over 2 h. The reaction mixture was shaken at room temperature for 16 h. The mixture was filtered, and the resin was washed with three cycles of DCM/MeOH. The filtrates were combined and concentrated in vacuo. The residue was suspended in cold THF and filtered, and concentration of the filtrate afforded the aryl ether without the need for further purification.