

Methylation of Polyols with Trimethylphosphate in the Presence of a Lewis or Brønsted Acid Catalyst

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The alkylation of alcohols and polyols has been investigated with alkylphosphates in the presence of a Lewis or Brønsted acid catalyst. The permethylation of polyols was developed under solvent-free conditions at 100 °C with either iron triflate or Aquivion PW98, affording the isolated products in yields between 52 and 95%. The methodology was also adjusted to carry out peralkylation with longer alkyl chains.

Interest in oxygenated bio-based molecules has increased with the research into alternatives to petroleum-based products.^[1,2] Even in light of research into new solvents,^[3] hydrotropes,^[4] surfactants,^[5] or additives for gasolines,^[6] the transformation of glycerol and other polyols remains in strong demand. Ether derivatives are generally preferred to esters because of their stability, notably in the presence of water. In addition, a recent study dealing with the toxicity of glycerol ethers has further increased interest in the selective synthesis of such compounds.^[7,8] Although the alkylation of glycerol has been studied under a wide range of reported conditions,^[6] the peralkylation of polyols has rarely been described and, in particular, their methylation remains problematic.

Methylation is usually performed under Williamson conditions,^[9] utilizing toxic reagents such as iodomethane or dimethylsulfate in nonprotic dipolar solvents.^[6] The use of less toxic reagents, such as dimethylcarbonate^[10] or dimethylsulfite,^[11] has also been explored. In these cases, the required temperatures can limit the application of the conditions to specific substrates. More precisely, at high temperatures (above 160 °C) the alkylation of glycerol is in competition with the formation of acrolein.^[12] An alternative was recently proposed as 1,2-dimethoxyethane was synthesized in a continuous flow reactor, with methanol and microporous zeolite as catalyst.^[13] Among the targeted compounds, 1,2,3-trimethoxypropane was prepared from glycerol with dimethylsulfate under solvent-free conditions. This development allowed the preparation of this product to evaluate its toxicity and its applicability as a solvent.^[14] The results of these studies prompted us to look for an alternative pathway for the methylation of alcohols and polyols.

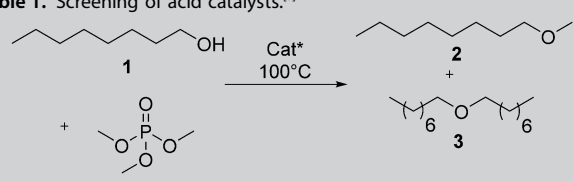
Among possible methylating agents, trimethylphosphate (TMP) has mainly been reported as an alkylating agent for amines,^[15] whereas its use with alcohols is unusual. Methylation and alkylation (using trialkylphosphate) of phenolic alcohols were realized by using a Lewis acid or a base, respectively.^[16–18] To our knowledge, only two reports have described the methylation of aliphatic alcohols with trimethylphosphate. In 1944, Toy described the methylation of alcohols in moderate yield by heating both reagents at reflux.^[19] Unfortunately, as mentioned by the author, this procedure is not compatible with alcohols with a boiling point lower than 160 °C. Later, similar conditions were developed by Van Dyke Tiers, with polyphosphoric acid as catalyst at a temperature of almost 180 °C.^[20] In this study, the author noted that a distillation of the crude at atmospheric pressure can be dangerous and an explosion can occur. In addition, experiments on rats have demonstrated the low toxicity of trimethylphosphate.^[21] Herein we propose a simple procedure to carry out the methylation of alcohols and polyols at 100 °C in the presence of a Lewis acid or a Brønsted acid catalyst.^[22]

To determine the best conditions, octanol was retained as the starting material. In agreement with previous reports, of trimethylphosphate exhibited a lack of reactivity was also noticed without catalyst at temperatures lower than 160 °C. To increase the reactivity of the phosphate, the influence of different catalysts on the formation of methyl octyl ether was evaluated. We first explored the influence of the addition of a Brønsted acid to the reaction mixture. At 100 °C in the presence of sulfuric acid (20 mol%), the octanol was almost quantitatively converted (94%) and methyl octyl ether was obtained in 70% yield (Table 1, entry 1). The other product was identified as dioctyl ether (24%). The use of a stronger acid—triflic acid (20 mol%)—was also evaluated. In this case, the conversion was lower but the selectivity towards the methylated product was higher (Table 1, entry 2). Next, a range of Lewis acids (all triflate) were also tested under similar conditions. For all triflates tested, good conversions were obtained but the best results were observed with bismuth and iron triflates (Table 1, entries 4, 7, and 8).

With lanthum, cerium, and yttrium triflates, the conversions of octanol were lower (Table 1, entries 3, 5, 6), and the only tested sulfate (FeSO₄) gave a very low conversion (Table 1, entry 9). Reactions were performed in a pressure tube and overpressure was never detected, indicating no formation of volatile compounds such as dimethyl ether. To select the best Lewis acid catalyst, bismuth and iron triflates were tested in parallel with loadings of 2 mol%. The best result was obtained

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Table 1. Screening of acid catalysts.^[a]



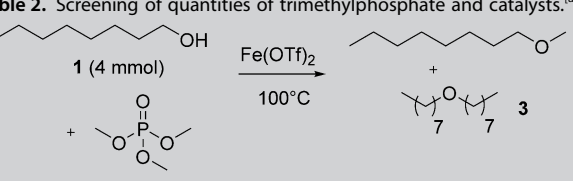
Entry	Catalyst	Conv. ^[b] [%]	2 [%]	3 [%]
1	H ₂ SO ₄ (20 mol %)	94	70	24
2	CF ₃ SO ₃ H (20 mol %)	65	65	0
3	La(OTf) ₃ (25 mol %)	78	72	6
4	Fe(OTf) ₂ (20 mol %)	100	85	10
5	Ce(OTf) ₃ (20 wt %)	68	67	1
6	Y(OTf) ₃ (10 mol %)	90	89	1
7	Bi(OTf) ₃ (10 mol %)	97	91	6
8	Fe(OTf) ₃ (20 mol %)	95	93	2
9	FeSO ₄ · 7H ₂ O (20 mol %)	7	5	2

[a] Reactions were performed in a pressure tube at 100 °C for 20 h from 4 mmol of octanol and 4 mmol of trimethylphosphate. [b] Conversions were determined as described in the Supporting Information.

with iron, as the desired product was obtained in 78% yield, as compared to 73% with the bismuth catalyst. Amongst the triflate salts, the cheapest was Fe(OTf)₂. As a consequence, it was retained for the rest of this study.

As iron triflate allows the formation of the desired product with good conversion, the influence of the catalyst loading on the conversion and the selectivity was studied (Table 2). In addition, the effects of modifying the trimethylphosphate/alcohol ratio were investigated. From a stoichiometric point of view, trimethylphosphate should provide three methyl groups. Unfortunately, to reach a good conversion of the alcohol, a 1:1 octanol:trimethylphosphate molar ratio is required (Table 2, entries 1–3). In all cases, traces of dioctyl ether were detected. The best results were achieved with an excess of trimethylphosphate (Table 2, entries 4 and 5). In these cases, the transformation of octanol was almost complete in 3 h. An increase in the

Table 2. Screening of quantities of trimethylphosphate and catalysts.^[a]



Entry	TMP	Fe(OTf) ₂	Conv. ^[b] [%]	2 [%]	3 ^[b] [%]
1	2 mmol	4 mol %	40	39	2
2	3 mmol	4 mol %	70	68	2
3	4 mmol	4 mol %	93	92	1
4	5 mmol	4 mol %	93	92.5	0.5
5	6 mmol	4 mol %	97	96.5	0.5
6	4 mmol	6 mol %	93	92	1
7	4 mmol	10 mol %	94	92	2
8	4 mmol	2 mol %	79	78.5	0.5

[a] Reactions were performed in a pressure tube at 100 °C for 20 h. [b] Conversions were determined as described in the Supporting Information.

quantity of the catalyst did not give better results (Table 2, entries 6 and 7), whereas a decrease in catalyst loading to 2 mol% led to a lower conversion with similar selectivity toward methyl octyl ether (Table 2, entry 8). From these results, we define the best conditions to pursue the study as follows: to methylate 1 mol of hydroxy group, 1.5 mol of trimethylphosphate per mol of alcohol was added with 4 mol% of Fe(OTf)₂. The reaction mixture was heated at 100 °C for 4 h to effect complete conversion of the octanol.

To evaluate the scope of the optimized conditions, different alcohols and polyols were engaged in the reaction. For this part of the study, the reaction was stopped after complete conversion, which was determined by GC considering the disappearance of the starting material. The separation of the desired product was adapted depending on the quantity of the starting material used and the difference in boiling points between the product and trimethylphosphate. The methylation of 2-octanol was carried out under the same conditions to give compound 4 and the result was similar to that with 1-octanol (Table 3, entry 2). The dimethylation of diols was performed on 1,2-octanediol. With a 1:1 molar ratio of diol to trimethylphosphate, a mixture of monomethylated products was detected. As a consequence, the quantity of trimethylphosphate was increased, and a 1:3 diol/trimethylphosphate molar ratio enabled the formation of dimethylated product 5 in 47% yield after isolation by distillation (Table 3, entry 3). Polyols were also subjected to the reaction. From glycerol, 1,2,3-trimethoxypropane (6) was isolated by distillation in good yield (67%; Table 3, entry 4). The permethylation of diglycerol was also accomplished and the product isolated in similar yield (compound 7; Table 3, entry 5).

A lower yield was isolated from erythritol (*meso*), which was attributed to the difficulty of separation from the phosphate. Compound 8 was difficult to separate from trimethylphosphate by distillation and could not be extracted by using nonpolar solvent. Finally separation by flash column chromatography was problematic due to a *R_f* close to the phosphate one. The synthesis of the tetramethylpentaerythritol (9) was very efficient as 95% of the product was obtained after extraction with pentane from the crude (Table 3, entry 7). The possible access to dimethylisorbide (10), a bio-sourced solvent, was also controlled. The desired product was isolated in 54% yield (Table 3, entry 8) but a higher yield was obtained from isomannide (75%). This difference can be explained by the possible extraction of dimethylisomannide with nonpolar solvent, which is not the case for dimethylisorbide. Moreover, dimethylisorbide was obtained in moderate yield and the same difficulties in purifications were encountered as for compound 8. Tartaric derivatives were also methylated. Dimethyl tartrate was first used and the dimethyl derivative 11 was isolated in good yield after 48 h. The reaction also occurred with tartaric acid and, in this case, the quantity of phosphate was increased to provide the same product 11 after 72 h.

These conditions also allowed esterification. From monopentyl dimethyl tartrate, the reaction was heated at 150 °C, leading to the formation of compound 12 after 48 h. This could be attributed to steric hindrance limiting the access to the alcoholic

Table 3. Scope of the reaction. ^[a]			
	$R-OH$ Alcohol		$R-O-CH_3$ Product
Entry	Alcohols	Products	Yield ^[b] [%]
1			78
2			77
3			93
4			67
5			66
6 ^[b]			52
7 ^[c]			95
8			54 (75)
9			80
10			67
11			73
12			62
13 ^[d]			55

[a] Unless otherwise stated, reactions were performed in a pressure tube at 100 °C for 15 h from 4 mmol of alcohols with a 1.5 ratio to the number of hydroxy groups to alkylate with 4 mol% of iron triflate. [b] Isolated products; value in parentheses is the isolated yield from isomannide. [c] The reaction was stopped after 20 h and 8 mol of phosphate per mol of tetraol were used. [d] The reaction was stopped after 27 h and 6 mol of phosphate per mol of catechol were used.

hydroxy groups to methylate. The ethylhexylglycerol monoether was also methylated and isolated in moderate yield by column chromatography (**13**). Finally, we evaluated the methylation of phenol under the developed conditions, which was previously reported to have been carried out with a base.^[17] From catechol, the rate of reaction was very slow; after 40 h only 55% yield of guaiacol (**14**) was detected alongside 25% of the monomethylated product. One limitation of this reaction concerns the methylation of carbohydrates. In this case,

dehydration, phosphorylation, and/or polymerization are in competition with the methylation.

The alkylation of alcohols with other alkylphosphates was then considered (Table 4). Under similar conditions at 100 °C during 20 h in the presence of $Fe(OTf)_2$, 1-ethoxyoctane (**16**), 1-isopropoxyoctane (**17**), and 1-butoxyoctane (**18**) were prepared from 1-octanol. The measured conversions of the octanol into the desired ethers were, respectively 70, 72, and 90%. Peralkylation was carried out on glycerol and dimethyltartrate with tributylphosphate. The peralkylation of glycerol (**20**; Table 4, entry 5) was efficient, but a lower yield was obtained from dimethyltartrate (**19**; Table 4, entry 4).

Table 4. Alkylation of alcohol using trialkylphosphate. ^[a]			
Entry	Alcohols	Phosphate	Product/GC ratio
1			 16: 70 (63%)
2	octanol		 17: 72 (73%)
3			 18: 90 (90%)
4	dimethyl tartrate		 19: 51 (30%) ^[b]
5	glycerol		 20: 84 (76%) ^[c]

[a] Unless otherwise stated, reactions were performed in a pressure tube at 100 °C for 15 h from 4 mmol of alcohols with a 1.5 ratio per hydroxyl to alkylate with 4 mol% of iron triflate or with 5 wt% of Aquivion. [b] Values in parentheses refer to yields of isolated product. [c] The reaction was stopped after 72 h.

One limitation of this method concerns the nonrecyclability of the iron triflate catalyst. Thus, we evaluated the efficiency of acid resin catalysts for the methylation of octanol under the previous developed conditions (Table 5). With Amberlyst resins, the ratio was the same whatever the nature of the Amberlyst, but was lower than that with $Fe(OTf)_2$ (Table 5, entries 1–3). The conversion of octanol did not exceed 67% and the selectivity to **3** was between 5 to 11%. Perfluorinated acid resin such as Nafion gave similar conversion (68%), but 100% selectivity was obtained for product **2** (Table 5, entry 4). Aquivion PW98 gave almost complete conversion (97%) and a GC ratio of 95% in methyl octyl ether (Table 5, entry 5).

Aquivion is a perfluorinated resin acid produced at industrial scale by Solvay. Recently, this resin was efficiently used as a recyclable catalyst, for example in glycosylation^[23] or hydrolysis

Table 5. Screening of acid catalysts.^[a]

Entry	Catalyst	Conv. ^[b] [%]	2 ^[b] [%]	3 ^[b] [%]
0	Fe(OTf) ₂ (4 mol %)	93	92	1
1	Amberlyst 15 (100 wt %)	62	57	5
2	Amberlyst 35 (100 wt %)	67	56	11
3	Amberlyst 36 (100 wt %)	61	56	5
4	Nafion (20 wt %)	68	68	0
5	Aquivion (20 wt %)	95.5	95	0.5

[a] Reactions were performed in a pressure tube at 100 °C for 20 h from 4 mmol of octanol and 4 mmol of trimethylphosphate. [b] GC ratio.

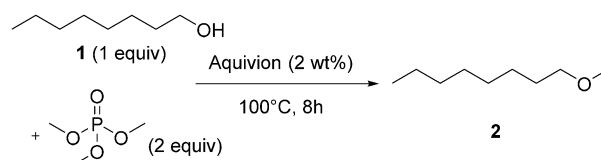
of triglycerides.^[24] The recyclability of the resin acid catalyst was evaluated over five cycles (Table 6). After each reaction, Aquivion was separated from the crude mixture, washed with methanol, and dried. Over five cycles, similar conversions (94–99%) and selectivities (ca. 97%) towards methyl octyl ether were obtained. In this study, 20 wt% of Aquivion was used, which equates to 2.6 mol% of SO₃H acid groups. By reducing the quantity of Aquivion to 2 wt% (0.26 mol% of SO₃H groups), 81% conversion was attained with 100% selectivity towards the desired product **2**, after 8 h (Scheme 1). The efficiency of the resin catalyst was also tested with other polyols, glycerol and dimethyl tartrate, to give 1,2,3-trimethoxypropane (**6**) and tetramethyltartrate (**11**) with similar yields to the previous conditions (67 and 52%, respectively).

To optimize the recyclability of the catalyst, the reaction is performed without extra solvent, but the excess should be recycled after distillation. The reaction was performed on a larger scale (10 g of octanol) to test whether the excess trimethylphosphate could be recovered by distillation under

Table 6. Recycling of the catalyst.^[a]

Entry	Recycling	Conv [%]	2 ^[b] [%]	3 ^[b] [%]
1	0	97	95	2
2	1	95	93	2
3	2	94	92	2
4	3	99	97	2
5	4	99	98	1
6	5	99	97	2

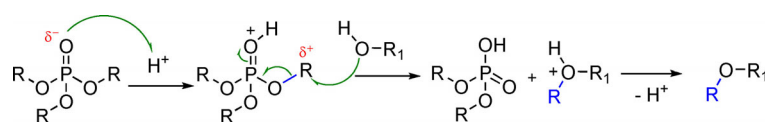
[a] Reactions were performed in a pressure tube at 100 °C for 15 h from 20 mmol of octanol and 30 mmol of trimethylphosphate. Aquivion was dried under vacuum after each use. [b] GC ratio.



Scheme 1. Methylation of octanol by using 2 wt% of Aquivion.

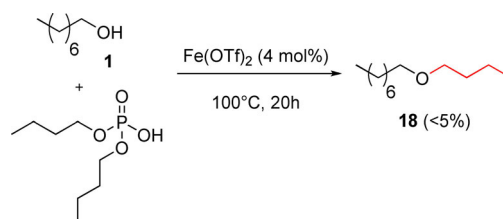
vacuum. After the reaction, 1-methoxyoctane (**2**) was distilled (40–45 °C, 5 mbar), followed by trimethylphosphate (60–65 °C, 5 mbar). The distilled mass of methylating agent was 10.5 g, indicating that 98% of the excess was recovered.

To understand the need for 1 equivalent of alkylphosphate, the crude material obtained after the reaction was analyzed, indicating formation of the corresponding dialkylphosphate (Scheme 2).



Scheme 2. Mechanism of the formation of dialkylphosphate.

To evaluate the reactivity of the dialkylphosphate, an additional reaction was performed with 1-octanol in the presence of iron triflate with dibutylphosphate (Scheme 3).



Scheme 3. Butylation of octanol by using dibutylphosphate.

After 15 h at 100 °C, the alkylated product was detected at a yield lower than 5%. The low reactivity of the dialkylphosphate explains the need for a stoichiometric amount of trialkylphosphate. The formation of trialkylphosphate from dialkylphosphate is reported in the literature with trimethyl formate or trimethylorthoacetate.^[25,26]

Classically, methylation is carried out in basic media in the presence of an electrophile, such as dimethyl sulfate, which generates a stoichiometric quantity of salt. In this study, a new, safer process was developed for the methylation of alcohols and polyols by using trimethylphosphate in the presence of a Lewis or a Brønsted catalyst. A Lewis catalyst such as iron(II) trifluoromethanesulfonate was used to methylate aliphatic alcohols, diols, and polyols in good yields. This level efficiency compares well to other low-toxicity methylating agents, such as dimethylcarbonate or dimethylsulfite, which are not able to

effect methylation of polyols. Methylation and esterification were carried out during the reaction with tartaric acid. Excess trimethylphosphate was recovered by distillation under vacuum. A resin catalyst, Aquivion, could also be used and the same good yields were obtained. This resin was recycled five times without loss of yield. Etherifications with longer alkyl chains, such as ethyl, isopropyl, and butyl, were also carried out efficiently by using the corresponding trialkylphosphates. This methodology constitutes an alternative to other alkylation methods.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: alkylation · Brønsted acids · methylation · polyols · phosphates

- [1] S. W. Snyder, J. H. Clark, *Commercializing Biobased Products: Opportunities, Challenges, Benefits, and Risks*, Royal Society of Chemistry, 2015.
[2] http://ec.europa.eu/growth/sectors/biotechnology/bio-based-products_fr.

- [3] M. Sutter, W. Dayoub, E. Métay, Y. Raoul, M. Lemaire, *ChemCatChem* 2013, 5, 2893–2904.
[4] R. Lebeuf, E. Illous, C. Dussenne, V. Molinier, E. Da Silva, M. Lemaire, J.-M. Aubry, *ACS Sustainable Chem. Eng.* 2016, 4, 4815–4823.
[5] V. Molinier, J.-M. Aubry, *Carbohydr. Chem.* 2014, 40, 51–72.
[6] M. Sutter, E. Da Silva, N. Duguet, Y. Raoul, E. Métay, M. Lemaire, *Chem. Rev.* 2015, 115, 8609–8651.
[7] J. I. García, E. Pires, L. Aldea, L. Lomba, E. Perales, B. Giner, *Green Chem.* 2015, 17, 4326–4333.
[8] E. Perales, J. I. García, E. Pires, L. Aldea, L. Lomba, B. Giner, *Chemosphere* 2017, 183, 277–285.
[9] A. Williamson, *Q. J. Chem. Soc. London* 1852, 4, 229–239.
[10] P. Tundo, S. Memoli, D. Herault, K. Hill, *Green Chem.* 2004, 6, 609–612.
[11] R. Mouselmani, E. Da Silva, M. Lemaire, *Tetrahedron* 2015, 71, 8905–8910.
[12] D. Sun, Y. Yamada, S. Sato, *Green Chem.* 2017, 19, 3186–3213.
[13] W. Yu, F. Lu, Q. Huang, R. Lu, S. Chena, J. Xu, *Green Chem.* 2017, 19, 3327–3333; and references therein.
[14] M. Sutter, L. Pehlivan, R. Lafon, W. Dayoub, Y. Raoul, E. Métay, M. Lemaire, *Green Chem.* 2013, 15, 3020–3026.
[15] F. W. Jones, G. O. Osborne, G. J. Sutherland, R. D. Topsom, J. Vaughan, *Chem. Commun.* 1966, 18–19.
[16] M. R. Saidi, F. Rajabi, *Phos. Sulf. Silicon* 2003, 178, 2343–2348.
[17] C. R. Noller, G. R. Dutton, *J. Am. Chem. Soc.* 1933, 55, 424–425.
[18] N. B. Randall, W. Shelton, US 4453017, 1984.
[19] A. D. F. Toy, *J. Am. Chem. Soc.* 1944, 66, 499.
[20] G. Van Dyke Tiers, *Acta Chem. Scand.* 1998, 52, 1223–1233.
[21] US Department of Health, *Bioassay of Trimethylphosphate for Possible Carcinogenicity*, National Institutes of Health, 1978.
[22] M. C. Duclos, E. Métay, M. Lemaire, Patent n° 16-53067, 2016.
[23] A. Karam, K. De Oliveira Vigier, S. Marinkovic, B. Estrine, C. Oldani, F. Jérôme, *ChemSusChem* 2017, 10, 3604–3610.
[24] H. Shi, Z. Fan, B. Hong, M. Pera-Titus, *ChemSusChem* 2017, 10, 3363–3367.
[25] M. H. Gelb, J. P. Svaren, R. H. Abeles, *Biochemistry* 1985, 24, 1813–1817.
[26] T. Yoshino, S. Imori, H. Togo, *Tetrahedron* 2006, 62, 1309–1317.

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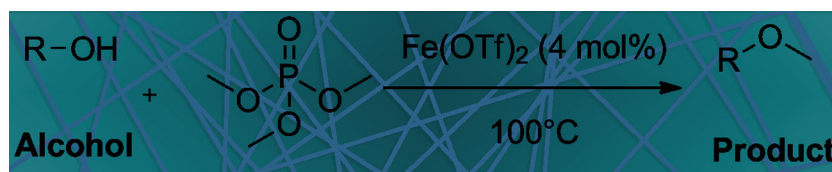
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COMMUNICATIONS

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Methylation of Polyols with Trimethylphosphate in the Presence of a Lewis or Brønsted Acid Catalyst



A new polyol methylation process has been developed by using trimethylphosphate and a Lewis or Brønsted acid catalyst, such as iron triflate or Aquivion, respectively. The unreacted trimethyl-

phosphate and the Aquivion resin can be recycled without loss of yield and activity. This methodology can be extended to the ethylation, isopropylation, or butylation of polyols in good yields.