Nucleophile-mediated oxa-Michael addition reactions of divinyl sulfone – a thiol-free option for step-growth polymerisations†

Simone Strasser and Christian Slugovc*

Triphenylphosphine and 4-dimethylaminopyridine promote the oxa-Michael addition reaction of alcohols and divinyl sulfone. Under solvent-free conditions, the reaction is particularly fast and allows for the preparation of polymers.

The Michael addition between thiols and electron-poor olefins such as (meth)acrylates, maleimides, unsaturated ketones, or vinyl sulfones is categorized as a click reaction and finds wide application in polymer and materials chemistry in both versions, the base-catalysed and the nucleophile-mediated pathways. Of particular interest is the nucleophile-mediated thiol-Michael addition which proceeds via a pathway different from base-catalysed reactions: the nucleophile adds to an electron-deficient vinyl group, generating a strongly basic carbon-centred anion deprotonating the thiol, which then initiates the thiol-Michael addition catalytic cycle. In this context, we became interested whether it is feasible to use less acidic and less nucleophilic alcohols instead of thiols. The substitution of thiols with alcohols would be desirable for the fact that much more alcohols are readily (and commercially) available than thiols. Moreover, inherent drawbacks of thiols, such as their tendency to lead to oxidative disulfide formation, their (often) bad odour and toxicity as well as their propensity to oxidize to give sulfones and sulfides in the final materials could be circumvented by using alcohols instead of thiols. The development of oxa-Michael reactions in general has received less attention compared to the addition of nucleophiles based on carbon, nitrogen or sulphur to electron-poor olefins, but received considerable attention in the past decade. In particular, the work by Bergman and Toste on phosphine-initiated hydroalkoxylation of α,β-unsaturated ketones paved the way for studying and using the oxa-Michael reaction in organic chemistry. The application of these findings in polymer and materials chemistry, however, is scarce.† We herein wish to report the nucleophile-mediated oxa-Michael addition reaction of divinyl sulfone and alcohols and the application of this reaction in polymerisations.

First, a series of potential nucleophiles for mediating the reaction was tested, employing the reaction conditions outlined in Scheme 1 and Table 1. 1-Methylimidazole (1-MIM) and 1,4-diazabicyclo[2.2.2]octane (DABCO) as well as triethylamine (NEt₃) gave hardly any conversion towards the desired oxa-Michael addition product (cf. Table 1, entries 1–3). 4-Dimethylaminopyridine (DMAP) performed better yielding roughly a 1:1 mixture of mono- and disubstituted products after 24 h (cf. Table 1, entry 4). Finally, triphenylphosphine (PPh₃) gave satisfactory results. After 2 h, 83% of the disubstituted product were already observed and full conversion towards this product was found after 24 h (cf. Table 1, entry 5). The PPh₃ loading could be reduced to 2.5 mol% without compromising the conversion too much (91% disubstituted product after 24 h). For comparison, a base-mediated reaction was carried out using 3 eq. (with respect to DVS) of Cs₂CO₃. Under these conditions, after 2 h, less than 2/3 of DVS were converted into the disubstituted

Scheme 1 Addition of benzyl alcohol (3 eq.) to divinyl sulfone (DVS) yielding the mono- (mono) and the diaddition (di) products initiated by various nucleophiles.

Institute for Chemistry and Technology of Materials, Graz University of Technology, NAWI Graz, Strenggasse 9, A-8010 Graz, Austria.

E-mail: slugovc@tugraz.at

† Electronic supplementary information (ESI) available: Experimental details and spectral data. See DOI: 10.1039/c5cy01527h
addition product and after 24 h, almost complete conversion was observed (cf. Table 1, entry 6). The reactivity order of the different nucleophiles could be rationalized with their corresponding methyl cation affinities (MCA, cf. Table 1). Based on these results, we selected PPh₃ as the nucleophilic mediator for further studies because PPh₃ is air-stable (in contrast to electron-richer alkylphosphines which exhibit higher MCA values and accordingly putatively a higher reactivity).

As the next step, the substrate scope of the reaction was investigated. Primary aliphatic alcohols (Table 2, entries 1–4) reacted faster than secondary alcohols (Table 2, entries 5 and 6). The simplest tertiary aliphatic alcohol, t-butanol, gave no reaction at all (Table 2, entry 7). Phenylmethanol is a better substrate than 2-propen-1-ol (Table 2, entry 9) and 2-propyn-1-ol is a particularly good substrate (Table 2, entry 13). Adding alkyl groups at the 3- or 1-position of 2-propyn-1-ol (Table 2, entries 14–16) resulted in lower conversion compared to that of the parent substrate, while the 

| Entry | Alcohol, R = | Nuc | MCA (kJ mol⁻¹) | Mono/diadduct (%) |
|-------|-------------|-----|---------------|------------------|
| 1     | R = CH₃Ph   | 1-MIM | 550           | 3/0              |
| 2     | R = CH₃Ph   | DABCO | 562           | <1/0             |
| 3     | R = CH₃Ph   | NEt₃ | 562           | 0/0              |
| 4     | R = CH₃Ph   | DMAP | 381           | 42/9             |
| 5     | R = CH₃Ph   | PPh₃ | 618           | 17/83            |
| 6     | R = CH₃Ph   | Cs₂CO₃ | 38/57       | 3/0              |

*Methyl cation affinity (MCA) according to ref. 8.

Conversion of DVS towards the mono- and disubstituted products as determined by ²H-NMR spectroscopy after reaction times of 2 h and 24 h. 

Additional products formed to about 17%.

**Table 2** Substrate scope of the oxa-Michael addition of DVS ([DVS] = 0.55 M) and alcohols (3 eq.) in dry dichloromethane at 40 °C in the presence of PPh₃ (10 mol% with respect to DVS)

| Entry | Alcohol, R = | pKₐ a | pKₐ b | Mono/diadduct (%) |
|-------|-------------|-------|-------|------------------|
| 1     | Me          | 15.20 | 15.17 | 1/99             |
| 2     | Et          | 15.50 | 15.24 | 23/77            |
| 3     | n-Bu        | 15.92 | 15.24 | 54/46            |
| 4     | n-Dodecyl   | 15.70 | 15.20 | 73/7             |
| 5     | i-Pr        | 15.70 | 15.31 | 64/10            |
| 6     | c-Hex       | 16.57 | 15.31 | 9/0              |
| 7     | t-Bu        | 16.84 | 15.38 | 0/0              |
| 8     | Water       | 15.7  |       | 31/9             |
| 9     | Benzyl      | 15.44 | 14.36 | 17/83            |
| 10    | α-Methyl benzyl | 14.43 |     | 77/4             |
| 11    | Allyl       | 15.52 | 14.43 | 19/81            |
| 12    | 1-Phenyl allyl | 13.61 |     | 73/27            |
| 13    | Propargyl   | 13.60 | 13.21 | <1/1>99          |
| 14    | 3-Methyl propargyl | 14.16 | 13.14 | 36/64            |
| 15    | 1-i-Pr propargyl | 13.14 |     | 48/52            |
| 16    | 1,1-Dimethyl propargyl | 13.34 | 65/14 | 67/33            |
| 17    | 1-Phenyl propargyl | 12.40 |     | <1/1>99          |
| 18    | 1,1-Diphenyl propargyl | 11.58 | 84/16 | 63/37            |
| 19    | Phenol      | 9.97  | 9.86  | 4/0              |

a According to ref. 4. b Calculated using Advanced Chemistry Development (ACD/Labs) Software V11.02, retrieved from SciFinder. c Conversion of DVS towards the mono- and disubstituted product as determined by ²H-NMR spectroscopy after reaction times of 2 h and 24 h; isolated yields of the diadducts range from 91 to 32% and are given in the ESI. d Additional products formed to about 17%.
forming the corresponding phosphonium alkoxide B. The conjugate addition of the generated alkoxide to DVS forms ion pair C. Protonation of the carbanion by another alcohol results in the formation of the β-alkoxy sulfone derivative and phosphonium alkoxide B to complete the catalytic cycle. The rate-determining step of the reaction is believed to be the proton transfer from the alcohol to carbanion A (statement based on mechanistic studies of related thiol-Michael reactions). The values of entropy of activation (measured in a related system) are very negative suggesting the necessity of a precise arrangement of PPh₃, the electron-deficient olefin and the proton donor for the reaction to occur. The following results support the briefly sketched mechanistic picture. Deuterium incorporation in α-position to the sulfone group was found upon performing the reaction with MeOH-d₄ or in CDCl₃ as the solvent (cf. ESI†), suggesting that a strong base is generated during the reaction. ³¹P-(H)-NMR monitoring of the reaction revealed that a phosphorus signal for zwitterion A is not observable. Only upon addition of the alcohol signals at 24.5 ppm and 24.4 ppm (relative to 85% H₃PO₄) tentatively assigned to the phosphonium-containing ion pairs B and C formed. The reaction becomes faster by (a) using more acidic alcohols forming alkoxides with sufficient nucleophilicity (cf. Table 2), (b) lowering the reaction temperature (optimum about 10 °C, cf. ESI†) and (c) increasing the concentration (cf. ESI†). The latter finding implies to carry out the reaction under solvent-free conditions. The reaction of DVS and 2-propanol is a good showcase. Under the conditions, as mentioned in Table 2 (entry 5), only 13% of the diadduct were formed after 24 h. Optimized reaction conditions (using 26 eq. of 2-propanol and 10 mol% PPh₃ at room temperature, cf. ESI†) gave the diadduct in 75% isolated yield after column chromatographic purification.

Switching to di- and trifunctional alcohols allowed for the preparation of polymers (cf. Fig. 1). Reacting an equimolar formulation of 4-(2-hydroxyethyl)phenol and DVS in water (5 eq.) upon adding 10 mol% PPh₃ (stock solution in CH₂Cl₂) at 25 °C gave a polymer characterized by a number average molecular mass (Mₙ) of 780 g mol⁻¹ and a polydispersity index (PDI) of 1.64. Similarly, using ethane-1,2-diol or but-2-yne-1,4-diol, polymers characterized by a Mₙ of 790 g mol⁻¹ and a PDI of 1.5 or a Mₙ of 3200 g mol⁻¹ and a PDI of 1.9 were obtained. In the case of but-2-yne-1,4-diol, a solution polymerisation reaction in THF/CH₂Cl₂ = 1 : 1 ([DVS] = 0.5 mol L⁻¹) was performed, yielding a polymer characterized by a Mₙ of 6400 g mol⁻¹ and a PDI of 1.7 in 70% yield (conversion was quantitative, cf. ESI†).

Multifunctional alcohols like propane-1,2,3-triol and 2-ethyl-2-(hydroxymethyl)propane-1,3-diol gave insoluble yet cross-linked polymer networks. In these cases, solvent-free conditions were applied resulting in fast and exothermic reactions, thus mixing of the three components is hardly possible (also because of the poor solubility of PPh₃ in the neat alcohols – ideally, the nucleophile should be dissolved in the alcohol and this solution should then be mixed with DVS†). Therefore, these reactions are preferably mediated with alcohol-soluble DMAP (0.05 eq.). Mixing of the DMAP/alcohol solution with DVS led to a somewhat retarded polymerisation reaction with a pot life of approx. 30 s. The formulation was transferred into Teflon moulds (22 × 5 × 3 mm) and specimens for dynamic mechanical analysis (DMA) were produced by curing for 4 h at 80 °C. The use of propane-1,2,3-triol resulted in stiff and brittle specimens which break upon mounting into the sample holder of the DMA machine. 2-Ethyl-2-(hydroxymethyl)propane-1,3-diol-based polymers gave specimens with a storage modulus of 3300 MPa at 10 °C and a T_g of 28 °C (determined to be the maximum of the loss modulus curve).

In conclusion, we demonstrated that the nucleophile-mediated oxo-Michael reaction between alcohols and divinyl sulfone is particularly fast and efficient under solvent-free conditions, allowing for the preparation of polymers. The reactivity of the alcohols decreases in the order primary > secondary > phenol > tertiary alcohols, and allylic, benzylic...
and propargylic alcohols exhibit distinctly higher reactivity than their saturated congeners.

Acknowledgements

The authors thank Isabel Hanghofer and Angelina Eder for the skillful synthetic work, Adriana Kovalcik for DMA analyses and Petra Kaschnitz for NMR analyses.

Notes and references

1 C. E. Hoyle and C. N. Bowman, Angew. Chem., Int. Ed., 2010, 49, 1540–1573.
2 (a) A. B. Lowe, Polym. Chem., 2014, 5, 4820–4870; (b) D. P. Nair, M. Podgorski, S. Chatani, T. Gong, W. Xi, C. R. Fenoli and C. N. Bowman, Chem. Mater., 2014, 26, 724–744.
3 (a) S. Chatani, D. P. Nair and C. N. Bowman, Polym. Chem., 2013, 4, 1048–1055; (b) J. W. Chan, C. E. Hoyle, A. B. Lowe and M. Bowman, Macromolecules, 2010, 43, 6381–6388; (c) W. X. Xi, C. Wang, C. J. Kloxin and C. N. Bowman, ACS Macro Lett., 2012, 1, 811–814.
4 (a) I. Ugur, A. Marion, S. Parant, J. H. Jensen and G. Monard, J. Chem. Inf. Model., 2014, 54, 2200–2213; (b) S. Takahashi, L. A. Cohen, H. K. Miller and E. G. Peake, J. Org. Chem., 1971, 36, 1205–1209.
5 C. F. Nising and S. Bräse, Chem. Soc. Rev., 2012, 41, 988–999.
6 I. C. Steward, R. G. Bergman and F. D. Toste, J. Am. Chem. Soc., 2003, 125, 8696–8697.
7 (a) Y. Yu and Y. Chau, Biomacromolecules, 2012, 13, 937–942; (b) S.-I. Matsuoka, S. Namera and M. Suzuki, Polym. Chem., 2015, 6, 294–301.
8 C. Lindner, R. Tandon, B. Maryasin, E. Larionov and H. Zipse, Beilstein J. Org. Chem., 2012, 8, 1406–1442.
9 H.-L. Liu, H. F. Jiang and Y.-G. Wang, Chin. J. Chem., 2007, 25, 1023–1026.
10 X.-G. Sun and C. A. Angell, Electrochem. Commun., 2005, 7, 261–266.
11 Y. C. Fan and O. Kwon, Chem. Commun., 2013, 49, 11588–11619.
12 C. Wang and C. Qi, Tetrahedron, 2013, 69, 5348–5354.
13 A. V. Salin, A. R. Faktkhutdinov, A. V. Il’in, V. I. Galkin and F. G. Shamsutdinova, Heteroat. Chem., 2014, 25, 205–216.
14 T. A. Albright, W. J. Freeman and E. E. Schweizer, J. Am. Chem. Soc., 1975, 97, 2942–2946.
15 S. Chatani, R. J. Sheridan, M. Podgorski, D. P. Nair and C. N. Bowman, Chem. Mater., 2013, 25, 3897–3901.