

Task specific onium salts (TSOSs) as efficient soluble supports for Zard radical addition to olefins

Julien Verron, Jean-Michel Joerger, Mathieu Pucheault and Michel Vaultier*

Université de Rennes 1, UMR CNRS 6510, Campus de Beaulieu, 263 Avenue du Général Leclerc, 35042 Rennes, France

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Abstract—Task specific onium salts (TSOSs), that is, functionalised ammonium salts, have been used as soluble supports to carry out intermolecular radical additions of xanthates to olefins and functional group interconversions. This methodology provides results by far superior to those reported with other soluble supports and allows for very easy purifications of reaction products. © 2007 Elsevier Ltd. All rights reserved.

Following pioneering Merrifield's work, solid-phase organic synthesis has developed enormously over the last 20 years.¹ Along with the heterogeneous nature of the polymeric supports arise a number of technical problems including slow and nonlinear reaction kinetics, reduced solvation, poor reaction sites accessibility, reactions monitoring and the low loading of these resins. Thus, soluble polymer supports such as polyethylene glycols, polyvinyl alcohol, soluble polystyrene² and dendritic polyglycerols³ allow performing reactions in solution and have been demonstrated to be possible alternatives to solid supports. Although purification of the functionalised supports, usually by precipitation and filtration, is still an easy process, low loading capacity, aqueous solubility and retention of solvent traces remain problematic. Fluorous tagged molecules and solvents have also been successfully used but are costly and specialised technologies.⁴ The arsenal of organic chemists still needs a valuable alternative to these soluble supports.

According to an exponentially growing literature, room temperature ionic liquids (RTILs) are a new category of solvents which have been shown to be a realistic substitute to volatile organic solvents for a large number of reactions.⁵ Within this new area, recently reported task specific ionic liquids (TSILs) are particularly promising. Defined as ionic liquids bearing a functional group

covalently tethered either to the cation, the anion or both, they have been conferred special properties/reactivities and behave as reagents or catalysts.⁶ In addition, we,⁷ then others⁸ thought to use functionalised onium salts (that is, task specific onium salts, TSOSs) as soluble supports for organic synthesis, whatever their melting point, provided that they are used as solutions either in molecular solvents or in ionic liquids. This basically led to the new concept of onium salts supported organic synthesis. This concept was successfully applied to a wide range of reactions such as cycloadditions,⁷ multi-component reactions,^{7b} palladium-catalyzed cross-coupling reactions^{7,8} or peptide synthesis^{8,9} to mention, but a few examples. Undoubtedly, applications will widen as they present convincing advantages over existing supports including (1) a very large number of possible combinations of functionalised cations and counter anions allowing a fine tuning of their properties (2) a facile reaction monitoring by using conventional analytical techniques such as routine NMR or HPLC, (3) easy separation of the supports from the target molecules after cleavage usually by simple extraction with a solvent or bulb-to-bulb distillation under vacuum (4) high loading capacity of both supports and solutions correlated to their low molecular weights and the use of highly concentrated solutions. Easy to prepare in large quantities at low cost, solutions of TSOSs can be pumped or canulated therefore making automation possible.

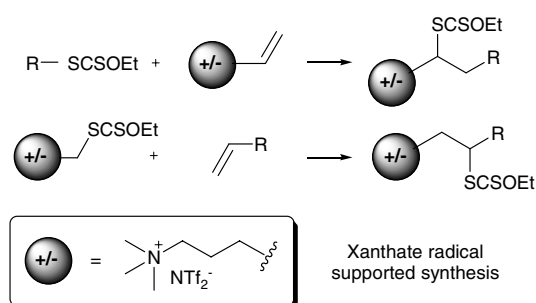
Radical reactions have become an important tool in organic synthesis¹⁰ albeit used with limited success in supported synthesis. Because reaction kinetics differ strongly from those observed under homogenous

Keywords: Task specific ionic liquids; Zard radical addition; Onium salts supported organic synthesis; Xanthate.

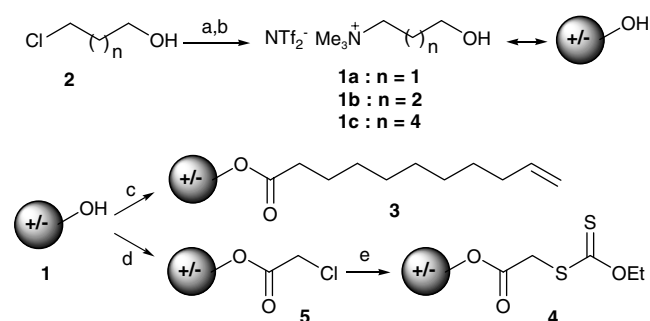
* Corresponding author. Tel.: +33 2 23 23 62 74; fax: +33 2 23 23 69 55; e-mail: michel.vaultier@univ-rennes1.fr

conditions, radical reactions are particularly disfavoured on solid supports leading to addition of large amounts of radical initiator and longer reaction times.¹¹ Therefore, soluble supports have been employed to attempt circumventing these difficulties. The use of soluble supports is hampered by hydrogen abstraction α to oxygens.¹² Zard and co-workers have studied intermolecular additions of radicals generated from xanthates precursors,¹³ on both insoluble and soluble supports under homogeneous conditions in that last case. We have used this elegant work as a reference to evaluate the efficiency of our TSOSs as soluble supports for the addition of radicals generated from a xanthate to an olefin and functional group interconversions of supported xanthates as well (Scheme 1). Radical polymerizations have been well investigated in RTILs,¹⁴ however, examples of radical reactions leading to non-polymeric molecules are scarce.¹⁵ Therefore, the compatibility of RTILs with xanthate-based radical reactions was first investigated by carrying out radical addition of methoxycarbonylmethylxanthate to allyl phthalimide induced by dilauroyl peroxide (DLP) in some conventional ionic liquids. We were pleased to observe the formation of the adduct in four different ionic liquids based on ammonium and imidazolium cations under homogeneous conditions. In all solvents, the product was isolated in good yields ([tmba][NTf₂], 71%) ([bmim][NTf₂], 69%; [bmim][PF₆], 68%; [bmim][BF₄], 61%) as compared to an 83% yield reported for the same reaction in 1,2-dichloroethane.¹³ DLP amount necessary for full conversion was higher (15–20 mol %) in the RTILs than for the same reaction in 1,2-DCE (5 mol % of DLP).¹³ This could be explained by the higher viscosity of RTILs which would prevent the formed radicals from diffusing out of the solvent cage and subsequently facilitating their recombination.^{14,16}

We next embarked on the TSOS's supported chemistry. Salts **1** were chosen as our starting platforms to support the reagents, either the xanthate or the olefin. The choice of the ammonium versus imidazolium salts was dictated by stability issues¹⁷ and some practical advantages; namely, a simplified ¹H NMR spectrum beyond 3.7 ppm allowing easy routine NMR reaction monitoring. **1a–c** were classically obtained as clear free flowing oils by quarternisation of trimethylamine with terminal chloroalkan-1-ol **2a–c**, followed by an anion metathesis with lithium triflimide in water (>95% yield for the two



Scheme 1. Radical reactions in onium salts supported organic synthesis.

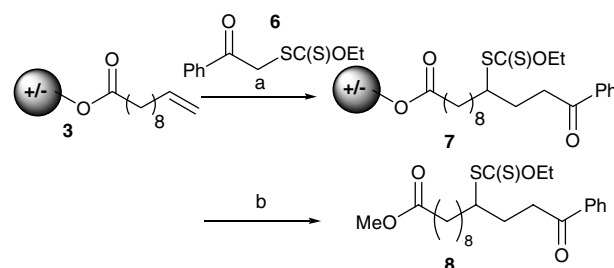


Scheme 2. Supports synthesis. Reagents and conditions: (a) NMe₃, H₂O/CH₃CN, 70 °C, 14 h; (b) LiNTf₂, H₂O, rt, overnight; **1a**, 95%; **1b**, 94%; **1c**, 84% (c) **1c**, ClCO(CH₂)₈CH=CH₂, K₂CO₃, CH₃CN, 0 °C then rt, 2 h, 91%; (d) **1**, ClCOCH₂Cl, K₂CO₃, 0 °C then 40 °C, 4 h, **5a**, 94%; **5b**, 99%; **5c**, 94%; (e) KSC(S)OEt, CH₃CN, rt, 2 h, **4a**, 86%, **4b**, 96%, **4c**, 98%.

steps) (Scheme 2).^{5d} Supported olefin **3** and xanthate **4a–c** were chosen for the sake of comparison with literature work¹³ and synthesised by small modifications of described procedures facilitating TSOSs purification (Scheme 2).

Noticeably, loading capacities of supports **1a–c**, (respectively 2.51, 2.43 and 2.27 mmol/g) are higher than the usual PEG or soluble polystyrene ones. Additionally, unlike these supports, concentrated solutions of **1a–c**, useful for xanthate chemistry¹⁰ can be used owing to **1**'s low molecular weight and good solubility in polar solvents. Intermolecular radical addition to the supported olefin **3c** was carried out in the presence of a 3-fold excess of xanthate **6** in 1,2-DCE at 80 °C in the presence of 13% molar of DLP as an initiator (Scheme 3).

Reaction monitoring by ¹H NMR showed complete conversion of **3c** after 4 h at 80 °C. Adduct **7c** was separated from excess starting xanthate **6** and non-supported impurities by washing several times with ether and then fully characterised (see Supplementary data) Cleavage from the support by transesterification in boiling acidic methanol led to the starting support **1c** and ester **8a–c** which could be easily separated by ether extraction and isolated pure in a 74% yield from **3c** after column chromatography.¹⁸ This is close to the 80% yield reported for the reaction between xanthate **6** and 10-



Scheme 3. Radical addition to supported olefin. Reagents and conditions: (a) DLP (13 mol %), 1,2-DCE, 80 °C, 4 h; (b) HCl, MeOH, reflux, overnight, 74% from **3c**.

undecenoate reported by Zard and co-workers¹³ Support **1c** could be recycled in a 92% yield and excellent purity. Interestingly, the same reaction with 10-undecenoic acid supported on a Wang resin and on Wang-like soluble polystyrene is reported to be sluggish with conversions below 80% even though higher xanthate/olefin ratios and more than 50 mol % of DLP have been used. Furthermore, a 9/1 mixture was obtained combining the linear adduct and a cyclic product arising from the cyclisation of the intermediate xanthate analogous to **7**.¹³ Noteworthy, this tetralone formation was not observed using TSOS **3c** owing to a conserved discrepancy between xanthate transfer and cyclisation rates mimicking closely non-supported reaction media.

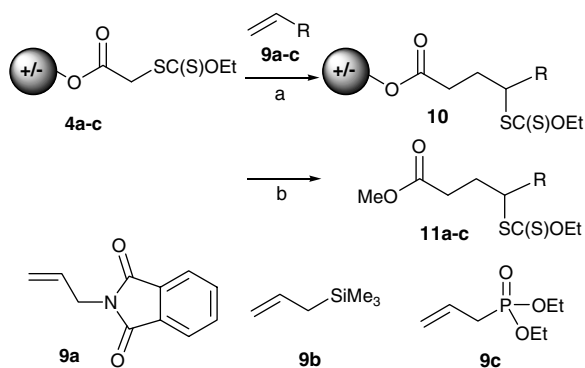
Reaction of **4a–c** with 1.3 equiv of olefin **9** in the presence of 10% of DLP was completed within 2 h leading to adducts **10aa–ac** in nearly quantitative yields (Table 1). These results are significantly better than using the same xanthate grafted on other soluble or insoluble supports¹³ and comparable to non-supported version. Indeed, on a soluble polystyrene, 3 equiv of olefin and 40 mol % DLP are required to obtain complete conversion and only 54% of adduct **11a** were obtained after cleavage. With Wang resin as a support, it was necessary to use 10 equiv of **9a** and 32 mol % of DLP to get a 26% isolated yield of **10aa**.

Reaction scope has been investigated. Structurally diverse supports have been used for this reaction leading to similar conversions (Scheme 4), and among olefins allylphthalimide (**9a**), allyltrimethylsilane (**9b**) and allyl-diethylphosphonate (**9c**) reacted equally well. Cleavage

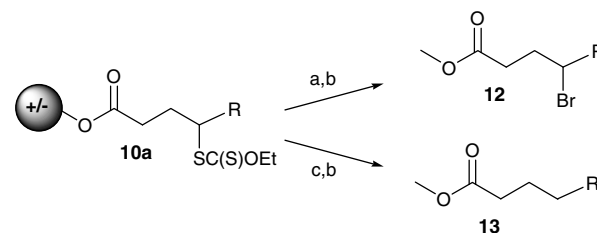
Table 1. Radical addition of the supported xanthate **4** to olefins **9**

Entry	4	Olefin	Addition (yield ^a %)	Cleavage (yield ^a %)
1	4a	9a	10aa (86)	11a (97)
2	4b	9a	10ba (86)	11a (47)
3	4c	9a	10ca (98)	11a (61)
4	4a	9b	10ab (90)	11b (80)
5	4a	9c	10ac (79)	11c (89)

^a Isolated yield after purification.



Scheme 4. Radical addition of supported xanthate. Reagents and conditions: (a) DLP 10 mol %, **9a–c** 1.3 equiv 1,2-DCE, 80 °C; (b) DIPEA, MeOH, reflux, overnight.



Scheme 5. Further functionalisation of supported xanthates. Reagents and conditions: (a) C(BrMe₂)COOEt (5 equiv), DLP (6 × 50 mol %), 1,2-DCE, 80 °C, 12 h; (b) HCl, MeOH, reflux, overnight; (c) DLP (13 × 10 mol %), isopropanol, 80 °C, 14 h.

from the support was completed after 16h in refluxing anhydrous MeOH in the presence of DIPEA (0.5 equiv) leading to methyl esters **11a–c**, which were isolated in good yields (Scheme 4, Table 1). Noticeably, cleavage from longer chain supports is slightly less efficient (entries 2 and 3) but with the 3-carbon chain linker, good conversions were obtained, regardless of substituents. The radical addition of supported xanthates to olefins is a particularly stringent test for the three different supports discussed above. It appears that TSOSs supports are superior to the others¹³ and might open the way to efficient supported radical chemistry allowing for very easy purification of products.

Xanthates are also useful for functional group interconversions via radical paths (Scheme 5).¹⁹ Namely, **10a** could be converted into the corresponding bromide by heating with DLP and ethyl 2-bromoisobutyrate as a source of bromine.^{19d} After cleavage with acidic methanol, product was isolated in a 41% yield over three steps from **4a** which is very good as compared to similar non-supported substrates.^{19d} Reduction of the C–S bond in **10a** can also be done in isopropanol in the presence of a stoichiometric amount of DLP^{19a} affording *N*-phthalimido methyl 4-aminobutanoate after cleavage in 56% isolated yield (two steps).

In addition to the use of ionic liquids as potential replacements for DCE in radical reactions, this study shows for the first time that task specific onium salts are efficient soluble supports to perform radical additions. Both the olefinic radical acceptor and the xanthate radical precursor can be supported by simple esterification of the ionic supports **1a–c**, easily prepared in two steps in high yields. Reactions are then carried out under homogeneous conditions in 1,2-DCE solutions, allowing easy ¹H NMR monitoring and separation of reactions products. This is also the first comparison reporting results obtained with TSOSs with those obtained from other supports such as Wang resins and soluble polystyrenes for a given reaction.

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Supplementary data

Supplementary data includes experimental procedure for addition and physical data for all adducts. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.04.024.

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