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Solid supported active esters as linkers: modification of reactivity using iron carbonyl complexes

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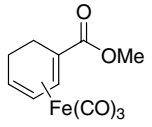
Abstract—The reactivity of three polymer-bound cyclohexadienoic acid active esters was modified by complexation with iron tricarbonyl in order to evaluate their potential use as linker systems for solid phase chemistry. The best results were obtained with the tetrafluorophenol ester, which was slowly cleaved when 1 equiv of amine was used, but could be rapidly cleaved with up to 94% yield when the amount of nucleophile was increased.

Solid supported active esters have been used as intermediates for amide formation on solid phase for over four decades, initiated by Merrifield's pioneering work on solid phase peptide synthesis.[1] Early examples of polymer-bound active esters include the various *o*-nitrophenol systems developed by Patchornik and co-workers,[2] as well as the polymer-bound 1-hydroxybenzotriazole derivatives from the same group.[3] A safety-catch system, where a phenolic ester is activated via oxidation of an adjacent sulfide to the corresponding sulfone, has been reported by Marshall and Liener,[4] and the Kenner safety-catch linker, while based on attachment via a sulfonamide moiety rather than an ester, can also be applied towards amide formation.[5] More recent examples include the tetrafluorophenol resins developed by Salvino et al.,[6] isomeric varieties of the nitrophenol linker employing different solid supports reported by Chang and co-workers,[7] a modified polymer-supported 1-hydroxybenzotriazole derivative with high reactivity prepared by Tartar and co-workers,[8] as well as a solid-supported chlorotriazene functioning as an active ester, as described by Masala and Taddei.[9] However, apart from the Kenner sulfonamide system, the use of active esters as *linkers* for solid phase synthesis has been rather limited. This is not surprising as the esters have been chosen for their high intrinsic reactivity and are designed to function as activating-reagents, rather than for more robust attachment of acids. We were interested to see if the reactivity of some of these active esters could be modified, in order to render them stable enough to be used as linkers under nucleophilic conditions, while still remaining reactive enough to be cleavable by amines under more vigorous conditions. Birch and co-workers have reported the enhanced stability of iron tricarbonyl complexed cyclohexa-1,3-dienecarboxylic acid methyl ester (**1**) towards hydrolysis.[10]



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We reasoned that this stabilizing effect could possibly be exploited to modify the reactivity of polymer-bound active esters of cyclohexadienoic acids. This would be of particular interest for iron carbonyl mediated reactions, as iron carbonyl stabilised cations have been used extensively in reactions with different nucleophiles, enabling the formation of both carbon–carbon and carbon–heteroatom bonds using the same type of conditions,[11] but could also be of more general interest as a way of linking dienoic acids in the form of active esters, allowing further transformations before cleavage. Oxidation of the dienoic system to the corresponding aromatic moiety has also been reported,[12] which could

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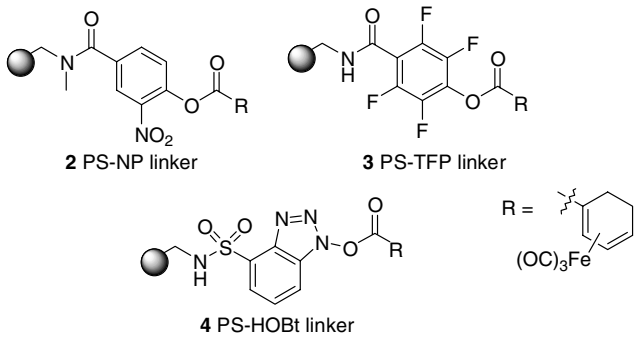
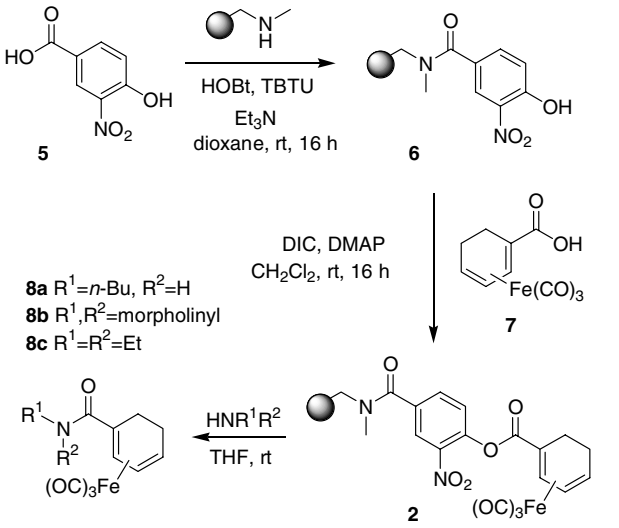


Figure 1. Active esters **2**–**4** used for cleavage studies.

extend the applicability to the formation of benzamide derivatives, although this aspect has not been investigated in this study.

Three different polymer-bound active esters (Fig. 1) were prepared and investigated regarding their stability towards different amines in THF at ambient temperature.

Polymer-bound *ortho*-nitrophenol resin **6** was prepared by coupling of **5** to aminomethyl polystyrene, using a protocol adapted from Berteina and de Mesmaeker,[13] and was reacted with an excess of iron tricarbonyl cyclohexadienoic acid (**7**) in the presence of DIC and DMAP to yield the corresponding polymer-bound ester **2** (Scheme 1). Analysis by IR showed vibrations at 1974 and 2050 cm^{-1} for the $Fe(CO)_3$ moiety and at 1722 cm^{-1} for the ester carbonyl group. The PS-TFP and PS-HOBt linkers, both commercially available, were esterified using the same protocol to form **3** and **4**.



Scheme 1. Preparation of polymer-bound active ester **2** and its cleavage with amines.

The esters were subsequently cleaved with three different amines under three different concentrations at ambient temperature, as exemplified for the polymer-bound active ester **2** (Scheme 1). The reaction was followed by HPLC using *N*,*N*-dimethylbenzamide as an internal standard. Amide products **8a**–**c** were also prepared in solution for reference purposes. The results from the cleavage studies are displayed in Tables 1–3.

Cleavage of polymer-bound esters **2** and **3** with the primary amine *n*-butylamine (Tables 1 and 2, entries 1–3) was rapid in all cases, yielding a substantial amount of

Table 1. Results from cleavage studies using active ester **2** (PS-NP linker)

Entry	R^1	R^2	Equiv	Conversion/% (time/h)	Isolated yield/%[a]
1	*n*-Bu	H	1	24 (1.5)	69
2	*n*-Bu	H	4	37 (1.5)	83
3	*n*-Bu	H	16	62 (1.5)	68
4	Morpholinyl		1	13 (4)	62
5	Morpholinyl		4	36 (4.5)	68
6	Morpholinyl		16	46 (4.5)	70
7	Et	Et	1	12 (46)	47
8	Et	Et	4	17 (46)	31
9	Et	Et	16	29 (46)	42

[a] When no further reaction occurred according to HPLC.

Table 2. Cleavage of ester **3** (PS-TFP linker)

Entry	R^1	R^2	Equiv	Conversion/% (time/h)	Isolated yield/%[a]
1	*n*-Bu	H	1	35 (1.5)	70
2	*n*-Bu	H	4	40 (1.5)	79
3	*n*-Bu	H	16	85 (1.5)	88
4	Morpholinyl		1	10 (4)	64
5	Morpholinyl		4	46 (4)	94
6	Morpholinyl		16	70 (4)	91
7	Et	Et	1	11 (46)	44
8	Et	Et	4	17 (46)	53
9	Et	Et	16	46 (46)	80

[a] When no further reaction occurred according to HPLC.

Table 3. Cleavage of ester **4** (PS-HOBt linker)

Entry	R^1	R^2	Equiv	Conversion/% (time/h)	Isolated yield/%[a]
1	*n*-Bu	H	1	81 (2.5)	85
2	*n*-Bu	H	4	94 (3)	94
3	*n*-Bu	H	16	97 (3)	99
4	Morpholinyl		1	47 (2)	96
5	Morpholinyl		4	92 (2.5)	92
6	Morpholinyl		16	77 (2.5)	82
7	Et	Et	1	46 (2)	52
8	Et	Et	4	70 (2.5)	94
9	Et	Et	16	96 (2.5)	99

[a] When no further reaction occurred according to HPLC.

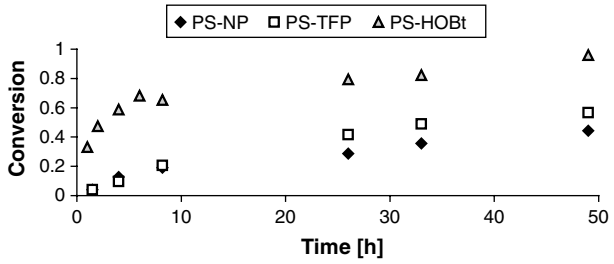


Figure 2. Conversion versus time (h) using 1 equiv of morpholine (followed by HPLC).

amide **8a** after 1.5 h even when only 1 equiv of nucleophile was used, indicating that the deactivation of the dienoic ester achieved via iron carbonyl complexation was not sufficient to convert the active ester moiety into a viable linker system in this case.

Reaction with secondary amines gave more interesting results however. Treatment of **2** or **3** with morpholine (Fig. 2) gave a substantially slower reaction as compared to cleavage with a primary amine, demonstrating the effect of steric hindrance of the incoming nucleophile in the aminolysis step. Only 10–13% of the polymer-bound substrate was cleaved after 4 h using 1 equiv of nucleophile (Tables 1 and 2, entries 4), while yields of up to 94% could be obtained within 24 h with active ester **3** by using an excess of nucleophile, although isolated yields for system **2** were slightly lower (68% for 4 equiv and 70% for 16 equiv). This could be due to steric hindrance from the nitro group in the *ortho* position or by a lesser activation of the ester bond.

Reactions of **2** and **3** with diethylamine (Tables 1 and 2, entries 7–9) followed the same trend, that is when 1 equiv of diethylamine was used, the yields were low in comparison with the other two nucleophiles for all three polymers, and the reaction was much slower than when morpholine was used as the nucleophile. Even when using 4 equiv of diethylamine, only 17% of **8c** was formed after 46 h for both linkers.

The third linker system examined, that is the HOBt linker (ester **4**), was by far the most reactive and the ester was aminolysed in a few hours with all three amines (Table 3), indicating that this active ester is better suited for direct amide formation rather than application as a linker in solid phase synthesis.

All three activated esters were effective and gave the expected amides in all cases. Although the PS-HOBt linkage gave the highest yields, the reaction rates were too rapid for its use as a linker. However, the PS-HOBt activated ester **4** would be the best choice for direct amide formation using iron tricarbonyl cyclohexadienoic acids. The PS-NP (**2**) and PS-TFP (**3**) systems showed similar reactivity towards amine nucleophiles, although the final isolated yields for the PS-TFP system were generally higher. The fact that PS-TFP is also commercially available makes the active ester 3 more suitable as a linker system. Nevertheless, amine nucleophiles react very rapidly with cationic complexes[14] making this a useful approach even for less sterically hindered amines. The application of ester **3** in cationic iron carbonyl mediated nucleophilic substitution reactions is currently being studied and the results will be presented in due course.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2005.11.132.

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