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Polymer-Supported Mukaiyama Reagent: A Useful Coupling Reagent for the Synthesis of Esters and Amides

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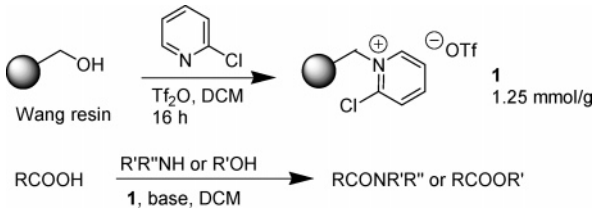
ABSTRACT



Polymer-supported *N*-alkyl-2-chloro pyridinium triflate was synthesized in one step from Wang resin. This reagent proved to be a very effective coupling reagent for the synthesis of esters or amides from carboxylic acids and alcohols or amines (primary and secondary).

N-Alkyl-2-halopyridinium salts have been extensively used for many years as activating agents for carboxylic acids.[1] In particular, *N*-methyl-2-chloropyridinium iodide (Mukaiyama reagent) has been used to convert carboxylic acids into esters,[2] amides,[3] lactones,[4] lactams,[5] and ketenes,[6] as well as thioureas into carbodiimides.[7] *N*-Ethyl-2-bromopyridinium tetrafluoroborate has been described as an excellent coupling reagent for peptide synthesis, showing both a high activity and a low level of racemisation.[8] However, chromatographic purification of the products obtained is generally needed to completely remove the byproducts.[9]

During the past decade, several techniques have been implemented with success to reduce the time spent for workup or purification processes during organic synthesis. One of the most successful of these techniques is certainly the use of polymer-supported reagents, which have been successfully employed both for the preparation of combinatorial libraries using solution-phase parallel synthesis and for the preparation of complex natural products such as Epothilone C.[10]

As such, a polymer-supported Mukaiyama reagent could represent a more user-friendly and efficient version of this common chemical.

The report from Convers et al.[11] of the first preparation of a polymer-supported Mukaiyama reagent and its use for the solution-phase preparation of guanidines prompts us to disclose our preliminary results on an alternative preparation

(1) Mukaiyama, T. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 707−708.
(2) Mukaiyama, T.; Usui, M.; Shimada, E.; Saigo, K. *Chem. Lett.* **1975**, 1045−1048.
(3) Bald, E.; Saigo, K.; Mukaiyama, T. *Chem. Lett.* **1975**, 1163−1166.
(4) Mukaiyama, T.; Usui, M.; Saigo, K. *Chem. Lett.* **1976**, 49−50.
(5) (a) Huang, H.; Iwasawa, N.; Mukaiyama, T. *Chem. Lett.* **1984**, 1465−1466. (b) Amin, S. G.; Glazer, R. D.; Manhas, M. S. *Synthesis* **1979**, 210−213. (c) Georg, G. I.; Mashava, P. M.; Guan, X. *Tetrahedron Lett.* **1991**, *32*, 581−584.
(6) Funk, R. L.; Abelman, M. M.; Jellison, K. M. *Synlett* **1989**, 36−37.
(7) Shibauma, T.; Shiono, M.; Mukaiyama, T. *Chem. Lett.* **1977**, 575−576.
(8) Li, P.; Xu, J. *Tetrahedron* **2000**, *56*, 8119−8131.
(9) Although sulfonic acid SPE columns could be used to scavenge both the residual Mukaiyama reagent and the byproduct (*N*-methyl-2-pyridone), this strategy is not compatible with molecules possessing basic sites, which represents a very serious limitation, especially for applications in medicinal chemistry.
(10) (a) Ley, S. V.; Baxendale, I. R.; Bream, R. N.; Jackson, P. S.; Leach, A. G.; Longbottom, D. A.; Nesi, M.; Scott, J. S.; Storer, R. I.; Taylor, S. J. *J. Chem. Soc., Perkin Trans. 1* **2000**, *23*, 3815−4195. (b) Storer, R. I.; Takemoto, T.; Jackson, P. S.; Ley, S. V. *Angew. Chem., Int. Ed.* **2003**, *42*, 2521−2525. (c) For a review covering polymer-supported coupling reagents, see: Katritzky, A. R.; Suzuky, K.; Singh, S. K. *ARKIVOC*, **2004**, *1*, 12−35.
(11) Convers, E.; Tye, H.; Whittaker, M. *Tetrahedron Lett.* **2004**, *45*, 3401−3404.

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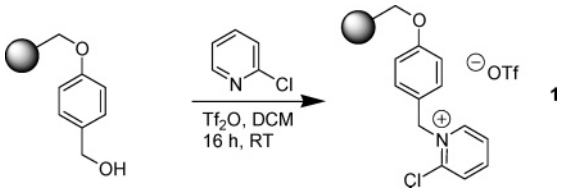
Scheme 1. Synthesis of Polymer-Supported Reagent **1**



of a series of polymer-supported *N*-alkyl-2-halo pyridinium salts and their use as coupling reagents for the synthesis of esters and amides.

The first strategy investigated for the preparation of the polymer-supported pyridinium salts involved the reaction of 2-chloropyridine with chloromethylpolystyrene (Merrifield resin). Various conditions were tested (from room temperature to refluxing THF, with or without the addition of equimolar NaI). Contrary to the results reported by Convers, all resins obtained had a very poor loading (ca. 10% from elemental analysis).

It was therefore decided to employ a resin bearing a better leaving group than a simple halide. Wang resin[12] was activated in situ with trifluoroacetic anhydride, forming a triflate ester, which was immediately substituted by the 2-chloropyridine present (Scheme 1).[13] The excess of 2-chloropyridine also acts as the base necessary for the formation of the triflate ester, so that the addition of another base is not necessary. The same reaction has been applied to 2-bromo and 2-fluoropyridine with excellent results.

Compared to the procedure reported by Convers, which gives yields of 33−72% depending on scale, mode of stirring, and loading of the starting Merrifield resin, this operationally simple one-pot protocol consistently gave complete conversion of the Wang resin to the halo-pyridinium salts, as judged by elemental analysis, on several 5-g batches.[14] It was also found that mass increase of the resin upon reaction (from 5.0 to 7.1 g starting from 1.7 mmol/g Wang resin) correlates well with the loading measured by elemental analysis and can be used as a quick and cheaper way to determine an approximate loading of the resin.

Another major advantage of the reported synthesis is that iodide-based additives are not needed. It is well-documented how the iodide anion can, in some circumstances, substitute the chlorine in the pyridinium salts and that the resulting 2-iodopyridinium salts do not activate carboxylic acids toward nucleophiles.[15] This could lead to lower and also more variable loadings. Therefore, the effective loading of the resin must be verified for each batch with an "end-use" test. With this improved synthesis, the counteranion is the non-nucleophilic triflate, circumventing this problem. The use of polymer-supported resin **1** was tested for the reaction between carboxylic acids and amines (Table 1). The reagent proved to be extremely effective at promoting these couplings, giving complete conversions (HPLC analysis) after short reaction times in most cases.

The reaction is operatively simple and does not require preactivation of the carboxylic acid. All reagents were just dissolved in DCM prior to addition of the resin. Very importantly, the required workup was very simple and easy to apply to parallel chemistry: a filtration on an amino-functionalized solid-phase extraction plug,[16] followed by washing with DCM and solvent evaporation afforded the products in high purity (HPLC, HPLC-MS, and NMR). A very slight excess of carboxylic acid (1.05 equiv) was employed to ensure complete reaction of the amine reagent, the excess of acid being trapped either on resin **1** or on the SPE column.[17]

The reaction gave very good results, especially with sterically hindered or other unactivated amines. For example, couplings of proline or valine methyl ester with Boc-tryptophan proceeded with good yields (Table 1, entries 2, 3, and 6). The coupling between Boc-protected tryptophan and valine methyl ester was shown to proceed with very little racemization, giving a de of 99% (HPLC). The reaction is relatively insensitive to steric bulk on the carboxylic acid partner: (4-nitro)-phenylalanine methyl ester could be efficiently coupled to pivalic acid in just 2 h (entry 9). However, the coupling of a C-terminal dipeptide (Cbz-Gly-PheOH) with valine methyl ester gave poor isolated yields (entry 7).

N-Methylaniline, poorly nucleophilic because of both steric and electronic effects, coupled very efficiently with acetic acid (entry 11). The reaction with the more sterically hindered pivalic acid (entry 13) required harsher reaction conditions: using 3 equiv of acid and heating the reaction mixture under microwave irradiation for 10 min at 100 °C gave a product containing only ca. 10% of starting amine, which could be easily removed by filtration on a sulfonic acid derivatized SPE column.[18]

Formamides were obtained in good yield and excellent purity without requiring the use of an excess of formic acid (entry 14).

(12) Hydroxymethylphenoxymethyl polystyrene (cross-linked with 1% divinylbenzene) 150−300 μm, loading 1.7 mmol/g, from Polymer Laboratories.

(13) **Experimental Procedure.** Wang resin (5.00 g, 8.5 mmol) was suspended in dry DCM (50 mL). 2-Chloropyridine (4.0 mL, 42.5 mmol, 5 equiv) was added, and the mixture was cooled with an ice bath. Trifluoromethanesulfonic anhydride (2.0 mL, 11.9 mmol, 1.4 equiv) was added dropwise, and after 5 min the ice bath was removed. The mixture was stirred overnight at room temperature. The resin was collected by filtration and washed with DCM, DMF, and DCM and dried under vacuum.

(14) Elemental analysis of the resin gave 1.83% N, 4.22% S, and 5.85% Cl, which corresponds to a loading of 1.3 mmol/g (nitrogen and sulfur analyses) or 1.6 mmol/g (chlorine analysis, probably due to ca. 1% w/w DCM still trapped in the resin).

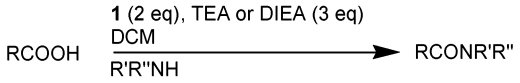
(15) (a) Folmer, J. J.; Acero, C.; Thai, D. L.; Rapoport, H. *J. Org. Chem.* **1998**, *63*, 8170−8182. (b) Bradlow, H. L.; Vanderwerf, C. A. *J. Org. Chem.* **1951**, *16*, 1143−1152. (c) Sutherland, J. K.; Widdowson, D. A. *J. Chem. Soc.* **1964**, 4650−4651.

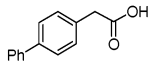
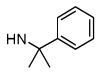
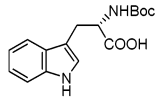
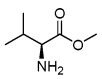
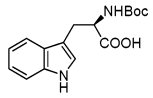
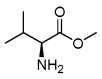
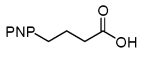
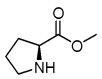
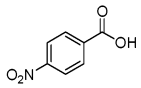
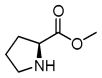
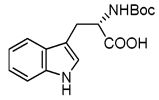
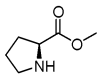
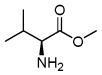
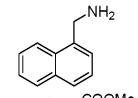
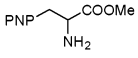
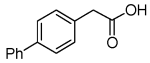
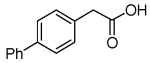
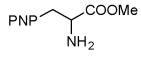
(16) Isolute NH_2 SPE column, 2 g, part no. 470-0200-D.

(17) **Typical Experimental Procedure.** The carboxylic acid (0.16 mmol, 1.05 equiv), the alcohol or amine (0.15 mmol, 1 equiv), and TEA (0.45 mmol, 3 equiv) were dissolved in anhydrous DCM (3 mL). When needed, PS-DMAP was added (20 mg, 0.03 mmol, 0.2 equiv). Resin **1** (240 mg, 0.3 mmol, 2 equiv) was added, and stirring was continued until completion of the reaction (HPLC). The resin was removed by filtration, and the filtrates were passed through an amino-functionalized SPE column (2 g). The resin and SPE column were washed with 10 mL of DCM, and then the combined filtrates were evaporated under vacuum to afford the desired ester or amide.

(18) Isolute SCX SPE column, 2 g, part no. 530-0200-D.

Table 1. Synthesis of Amides Using **1**[g]

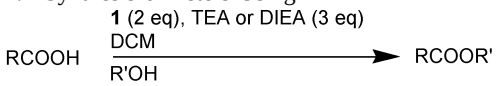


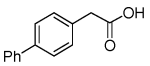
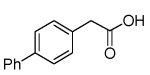
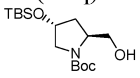
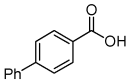
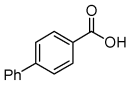
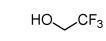
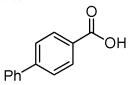
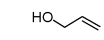
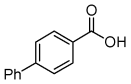
	Acid	Amine	Time (h)	Yield (%)[a]	Purity (%)[b]
1			0.25	69	97
2			16	88	99[c]
3			16	80	92[c]
4			3	86	99
5			16	93	92
6			2	99	96
7	Cbz-GlyPheOH		16	<15%	nd
8			1	85	90
9			2	76	88
10		 R= 3-(9*H*-carbazol-9-yl)propyl	0.5	77	97
11			16	94	>95[d]
12			1	100	97
13			10 min[e]	80	98[f]
14			16	68	94

[a] Isolated yield. [b] HPLC and NMR. [c] 99% de (HPLC). [d] NMR. [e] 100 °C under microwave irradiation, 3 equiv of pivalic acid was used. [f] After filtration on SCX resin. [g] All reactions were conducted using 1 equiv of amine and 1.05 equiv of carboxylic acid. PNP = *p*-nitrophenyl.

It is interesting to notice that α-aryl carboxylic acids such as biphenylacetic acid tend to react faster compared to other

Table 2. Synthesis of Esters Using **1**[e]



	Acid	Alcohol	Time (h)	Yield (%)[a]	Purity (%)[b]
1		MeOH (2 eq)	0.25	100[c]	99
2			1	94	89
3		MeOH (2 eq)	2	94	99
4			1	70	98
5			1	92	98
6		 10 eq	16	84	92
7			1	92	90
8			1	92	94
9			2	97	94
10			1	98	98
11		MeOH (2 eq)	1	99	99[d]
12			16	81	99
13			16	45	98
14			2	74	89
15			16	84	91

[a] Isolated yield. [b] HPLC and NMR. [c] PS-DMAP was not added for this experiment. [d] 98% ee (chiral HPLC). [e] All reactions were conducted using 1 equiv of alcohol and 1.05 equiv of carboxylic acid except when noted otherwise. PNP = *p*-nitrophenyl.

acids, even the less sterically hindered ones such as acetic acid (compare entries 11 and 12).

Reagent **1** also proved to be effective for the synthesis of esters (Table 2). Most simple esters were formed with very high isolated yields and high purities in less than 1 h. In one of the first tests using an aromatic carboxylic acid, it was realized that important amounts of symmetrical anhydride were being formed, which was fairly stable in the reaction conditions. For this reason, polymer-supported (dimethylamino)pyridine (PS-DMAP) was added to catalyze the reaction of these anhydrides with the alcohols. The carboxylic acid thus generated would in turn react with the excess of resin, yielding the desired ester. To ensure shorter reaction times, PS-DMAP (0.2 equiv) was always added for all subsequent ester-forming reactions.

Some of the most important protecting groups for carboxylic acids (methyl, allyl, trimethylsilylethyl, *p*-methoxybenzyl, and *p*-nitrobenzyl esters) could be prepared very easily using this strategy, using a very small excess of carboxylic acid (1.05 equiv), even when tertiary acids were employed. The sterically hindered Mosher ester of benzoin could also be prepared in only 3 h, giving easy access to these derivatives very useful for NMR determination of the enantiomeric excess of chiral alcohols (entry 9). Esterifications performed using the less nucleophilic trifluoroethanol gave somewhat lower but still acceptable yields, always with very good purities (entries 4 and 13). The reaction of phenols with carboxylic acids was investigated and shown to proceed satisfactorily (entries 14 and 15). In particular, synthetically useful pentafluorophenol esters could be prepared in high yield and purity. In this case a basic aqueous workup had to be employed instead of the SPE extraction to prevent reaction of the activated ester with the amino groups present on the polymer.

The reaction of Boc-tryptophan with methanol was used to evaluate the degree of racemization of α-chiral acids in the esterification reactions (entry 11): a gratifying 98% ee was observed by chiral hplc.

Finally, the synthesis of *tert*-butyl esters was investigated. Our first attempt was very successful with *tert*-butyl 4-(phenyl)benzoate being obtained with 84% yield and 92% purity using 10 equiv of *tert*-butyl alcohol at room temperature overnight (entry 6). However, the behavior of this reaction proved to be extremely erratic. Although the preparation of *tert*-butyl 4-(phenyl)benzoate could be successfully reproduced, similar carboxylic acids (e.g., 4-phenoxybenzoic acid) could not be efficiently converted into the corresponding *tert*-butyl esters, giving instead complex mixtures of products. Given the importance of *tert*-butyl esters as protecting group for acids, this reaction is still under investigation with the aim to provide an easier and automatable entry to these species.

In conclusion, a polymer-supported version of the popular Mukaiyama reagent has been prepared in one step from commercially available Wang resin. This polymer-supported reagent proved to be an excellent coupling reagent for the synthesis of both amides and esters, in particular when poorly nucleophilic amines are used. The products could be obtained in high purity and high yield with a very simple and easily automated workup.

Supporting Information Available: Experimental details for the preparation of all compounds and characterization data for all products. This material is available free of charge via the Internet at http://pubs.acs.org.

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