Tetrahedron Letters 49 (2008) 6573–6574

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

An alternative and facile purification procedure of amidation and esterification reactions using a medium fluorous Mukaiyama reagent

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ARTICLE INFO

Article history:
Received 22 August 2008
Revised 3 September 2008
Accepted 5 September 2008
Available online 9 September 2008

ABSTRACT

A convenient methodology for the separation of a fluorous by-product using fluorous chemistry is described. A Mukaiyama coupling reagent bearing a medium fluorous tag, between 40% and 60% fluorine by weight, can be effectively separated from non-fluorous components by increasing the water content of the crude reaction mixture and subsequent filtration. Additional fluorous solid phase extraction is not necessary.

Organic molecules bearing small fluorous tags (C_6F_{13} and C_8F_{17}) are called light fluorous molecules. Light fluorous reagents,[1] scavengers[2] and catalysts[3] are especially convenient since they typically induce reactions of organic substrates under the same conditions as their non-fluorous counterparts, but are reliably removed from the crude reaction products by fluorous solid phase extraction.[4] In the field of amidation and esterification, some fluorous reagents have been developed, and these reagents are separable due to their fluorous properties in a fluorous biphasic system (FBS) and on fluorous silica gel supports.[5] Recently, we reported that the by-product derived from a light fluorous Mukaiyama coupling reagent[6] can be easily separated from the coupling products by fluorous solid phase extraction.[7] During our investigations into the scope and limitations for the coupling reagent, we discovered that a simple separation of the fluorous pyridone by-product, where fluorous solid phase extraction is not necessary, is possible when a medium weight fluorous version of Mukaiyama reagent is used. Herein, we report an alternative useful separation technique of the fluorous component from the reaction products.

The adjective 'medium' refers qualitatively to the weight of the fluorous tag. Representative light fluorous molecules have fluorine contents in the range of 30–40% of their molecular weight.[8] We prepared a Mukaiyama coupling reagent **1** bearing a $C_{10}F_{21}$ fluorous tag, giving it a fluorine content around 49% of its molecular weight, and accordingly named it 'medium fluorous Mukaiyama reagent'.[9] Upon completion of the coupling reaction, the reagent is converted to the corresponding fluorous pyridone **2**, with a concomitant reduction in the molecular weight. As a result, the fluorine content of **2** increases to 62% of its molecular weight, and loses its medium fluorous compound status and formally becomes a heavy fluorous compound. This feature provides a dual benefit in that the reagent behaves like a light fluorous compound during the reaction in terms of solubility and reactivity, and then the almost heavy fluorous nature of the product pyridone greatly facilitates purification. During our investigation to find the optimum conditions for the separation, we found that the medium fluorous Mukaiyama reagent **1**, which easily dissolved in *N,N*-dimethylformamide (DMF) during the coupling reaction, was insoluble in 20% aq DMF.[10] This observation suggested that the fluorous pyridone **2** could be separated effectively by increasing the water content in the crude product mixture when DMF is used as the solvent. In practice, compound **2** was effectively separated as a precipitate by adding water to the reaction mixture after the coupling reaction was complete and filtering. The purification did not require any further separation by fluorous solid phase extraction using expensive fluorous silica gel.[11] A typical procedure for the coupling reaction and purification is as follows: To a solution of benzoic acid (62.8 mg, 0.51 mmol), aniline (47 ml, 0.51 mmol), Et_3N (0.215 ml, 1.54 mmol) and DMAP (4-dimethylaminopyridine: 62.8 mg, 0.51 mmol) in dry DMF (8 ml: 16 volume/weight for **1**) was added the fluorous Mukaiyama reagent **1** (500 mg, 0.61 mmol) at room temperature. The reaction mixture was stirred for 1 h at ambient temperature. After the addition of H_2O (2 ml:4 volume/weight for **1**), the reaction mixture was stirred for an additional 5 min and then filtered (Scheme 1). After washing the precipitate with 20% aq DMF (10 ml), 1.0 M. HCl (10 ml) was added to the filtrate which was then extracted with diethyl ether. The organic layer was then washed again with 1.0 M HCl and brine. After drying the organic layer with Na_2SO_4, concentration of the organic phase provided the coupling product in quantitative yield (101 mg, in high purity (98.8%) (Table 1 entry 3)).

Signals corresponding to fluorous pyridone **2** were not observed in the ^1H NMR of the crude product after filtration. Interestingly,

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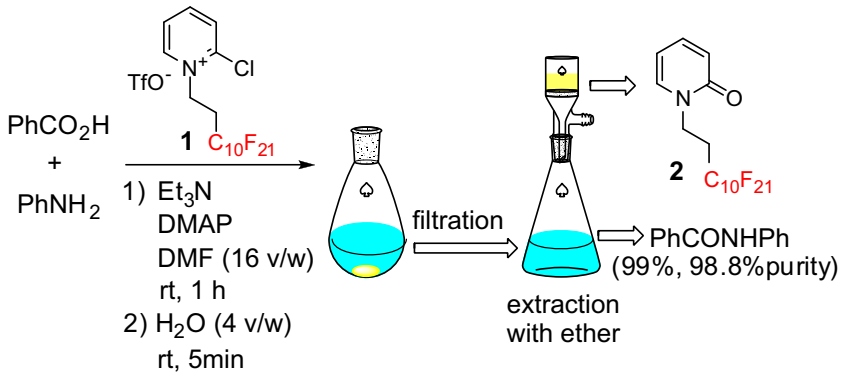
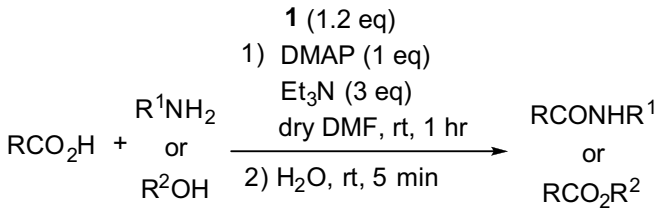
doi:10.1016/j.tetlet.2008.09.016



Scheme 1. A facile separation of fluorous pyridone **2**.

Table 1
Amide and ester forming reactions with the medium fluorous Mukaiyama reagent **1**



Entry	R	R^1	R^2	Yield (%)	Purity[a] (%)
Amidation					
1	Me	Ph	—	Quant.	98.2
2	Ph	Pr	—	98	95.6
3	Ph	Ph	—	99	98.8
4	Ph	L-Valine methyl ester[b]	—	Quant.	97.0
5	4-MeO-Ph	Ph	—	Quant.	96.2
6	4-NO_2-Ph	Ph	—	97	98.6
7[c]	4-NO_2-Ph	PhNHMe[d]	—	87	89.3
Esterrification					
8[e]	Ph	—	Bn	94	92.2
9	Ph	—	Butyl	99	90.1
10	Ph	—	Octyl	Quant.	92.0
11	4-Ph-Ph	—	Me	98	95.5
12	4-MeO-Ph	—	Me	96	96.0
13	4-NO_2-Ph	—	Me	Quant.	98.7
14	Boc-L-tryptophan[f]	—	Me	Quant.	91.3
15	Boc-L-tryptophan[f]	—	Ally	89	87.1

[a] Determined by HPLC.
[b] L-Valine methyl ester was used.
[c] The reaction was conducted for 2 h at rt.
[d] Phenylmethylamine was used.
[e] The reaction was conducted for 0.5 h at rt.
[f] Boc-L-tryptophan was used.

when the C_8F_{17} tagged Mukaiyama reagent (light fluorous variant) was used in the typical procedure outlined above, the reaction was successful, but the purification was not and slightly amounts of the pyridone were observed in the filtrate. Furthermore, no precipitation of the pyridone was observed in 20% aq DMF when original Mukaiyama reagent (non-fluorous-type) was used. These illustrate that it is essential to use $C_{10}F_{21}$ tag (medium fluorous type) for effective separation and purification. Table 1 shows the results of the purification for various coupling reactions employing reagent **1**. All reactions proceeded at room temperature and were complete in 2 h to give the target products in good yields and high purities.The esterification worked well even in the case of using Boc-L-tryptophan, which has indole ring in the molecule (Table 1 entries 14 and 15).

In summary, a new medium fluorous Mukaiyama reagent **1** was prepared and used in coupling reactions. We demonstrated that facile purification of the coupling products was possible by filtration without the need for fluorous solid phase extraction. We also conclude that a condensation strategy using reagent **1** is one of the most practical methods for various ester and amide forming reactions in terms of process chemistry.

Acknowledgements

This research was partially supported by the Ministry of Education, Science, Sports and Culture, Grant-in-aid for Scientific Research (C), 20580115. We thank Professor Dennis P. Curran, University of Pittsburgh, for the useful discussion. We also thank Wako Pure Chemical Industries, Ltd for funding this work.

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8. Light fluorous molecules typically contain **21** fluorines or fewer, and molecular weights can range from 400 to about 900 mu. They may exhibit little or even no solubility in fluorous solvents, so separations with fluorous solid phases are often the only practical methods; see Ref. 1.
9. *Preparation of medium fluorous Mukaiyama reagent* **1**: To a solution of 1*H*,1*H*,2*H*,2*H*-1-perfluorododecan-1-ol (25.0 g, 44.3 mmol), 2-chloropyridine (12.0 g, 53.2 mmol) in dry dichloromethane (80 ml) was added trifluoromethanesulfonic anhydride (15.0 g, 53.2 mmol) at 0 °C and the mixture was stirred at 45 °C for 30 h. Diethyl ether (100 ml) was added and the mixture was stirred for 0.5 h at room temperature. After filtration of the crude product, the recrystallization from ethyl acetate gave the **1** (29.9 g, 83.4%) as a white powder; mp 118.0–119.0 °C; ^{1}H NMR (270 MHz, DMSO-d_6) δ: 3.07 (2H, m), 5.02 (2H, t, J = 7.4 Hz), 8.19 (1H, m), 8.41 (1H, d, J = 7.4 Hz), 8.65 (1H, m), 9.26 (1H, d, J = 5.1 Hz); ^{19}F NMR (466 MHz, DMSO-d_6) ppm −125.7 (2F), −122.9 (2F), −122.4 (2F), −121.6 (4F), −121.4 (6F), −112.8 (2F), −80.2 (3F), −77.8 (3F).
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