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Tetrahedron Letters
Tetrahedron Letters 48 (2007) 4147–4150

# Preparation and condensation reactions of a new light-fluorous Mukaiyama reagent: reliable purification with fluorous solid phase extraction for esters and amides

Masato Matsugi,[a,*] Masakazu Hasegawa,[a] Daisuke Sadachika,[a] Sachina Okamoto,[a] Mami Tomioka,[a] Yoshimi Ikeya,[a] Araki Masuyama[b] and Yuji Mori[c]

[a]*Faculty of Agriculture, Meijo University, 1-501 Shiogamaguchi, Tempaku, Nagoya 468-8502, Japan*
[b]*Faculty of Engineering, Osaka Institute of Technology, 5-16-1 Omiya, Asahi, Osaka 535-8585, Japan*
[c]*Faculty of Pharmacy, Meijo University, 150, Yagotoyama, Tempaku, Nagoya 464-8606, Japan*

Received 19 February 2007; revised 19 March 2007; accepted 23 March 2007
Available online 6 April 2007

**Abstract**—A modified light-fluorous Mukaiyama reagent bearing a $C_8F_{17}$ tag was prepared and examined in ester and amide forming condensation reactions. Following the reactions, the desired product was effectively separated from the fluorous pyridone by-product using a simple fluorous solid phase extraction.


The Mukaiyama condensation reagent (*N*-methyl-2-chloropyridinium iodide)[1] **1** is one of the most useful reagents in organic synthesis and there are many reports of its use for the key ester or amide forming step of the synthetic route. Since the reagent was reported in 1975, various *N*-alkyl-2-halopyridinium salts have been developed, with the aim of achieving higher levels of efficiency.[2] Recently, fluorous-tagged 2-chloropyridinium hexafluorophosphate **2** was reported by Nagashima et al.[3] and shown to successfully promote amide bond formation (see Fig. 1). A fluorous benzyl group was used as the fluorous tag, and fluorous solid phase extraction (FSPE)[4] of the reaction mixture cleanly removed the corresponding fluorous pyridone by-product. In this protocol, the addition of 1-hydroxybenzotriazole (HOBT) is required to decrease the formation of the carboxylic anhydride by-product, so a resin-bound carbonate scavenger was used to remove excess HOBT.[5] Herein, we report a simple procedure for the condensation reaction using a new light-fluorous[6] Mukaiyama reagent **3**, which is more reactive than **2** and easily removable from the desired product using FSPE.

The light-fluorous Mukaiyama reagent **3** was easily prepared from 2-chloropyridine in a one step as shown in Scheme 1[2d] in 72% isolated yield after recrystallisation.[7] Elemental analysis as well as the $^1H$ and $^{19}F$ NMR spectra provide support for the salt structure **3**.[8] Compound **3** is a white powder that can be stored in the desiccator without decomposition for over one year. We chose the triflate as the counterion for the pyridinium salt because a triflate anion is reportedly a good counter anion for Mukaiyama-type reagents.[2c]

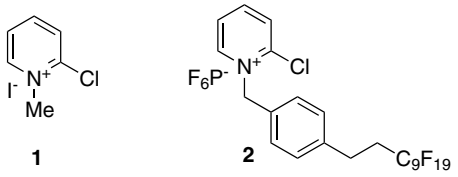
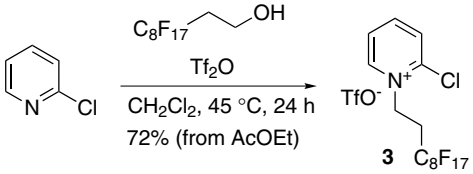



**Figure 1.**




**Scheme 1.** Synthesis of the fluoroalkyl Mukaiyama reagent.

* Corresponding author. Tel.: +81 52 832 1151; e-mail: matsugi@ccfms.meijo-u.ac.jp

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doi:10.1016/j.tetlet.2007.03.173

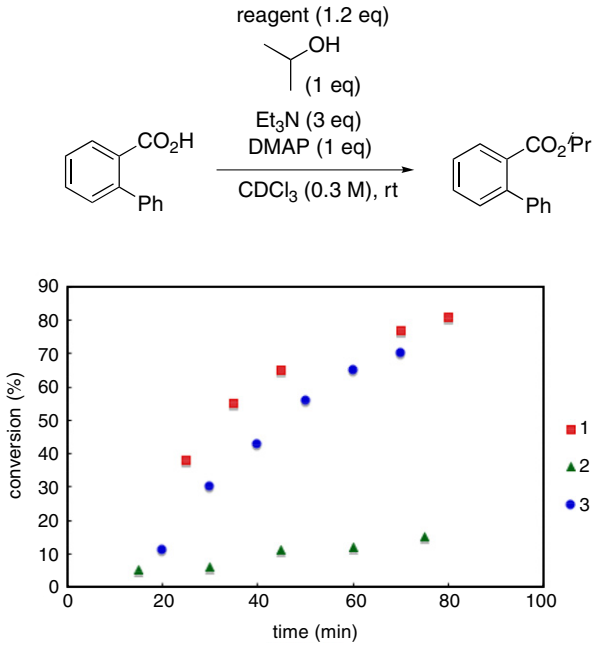



**Figure 2.** Comparison of conversion for ester formation in $CDCl_3$.

We expected that the fluorous Mukaiyama reagent with the ethylene spacer, **3**, to be more active in the condensation reaction than the ethylene benzyl spacer because the inductive effect of the fluorous tag should be stronger and because its fluorous tag is not bulky. To test this hypothesis, we compared the reactivity of the three Mukaiyama reagents in question **1**–**3** in an esterification reaction between 2-phenyl benzoic acid and isopropanol in $CDCl_3$ as the solvent to allow for $^1H$ NMR monitoring of reaction aliquots. Three separate reactions were

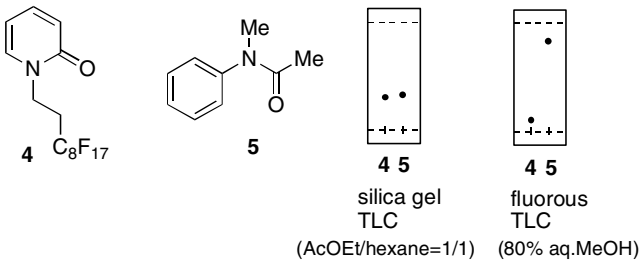
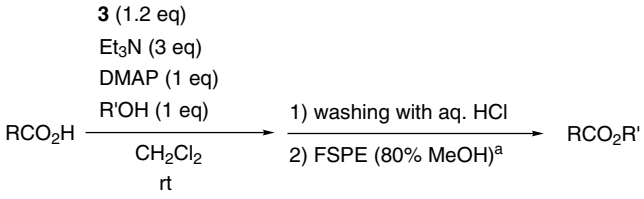
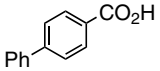
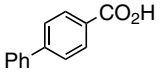
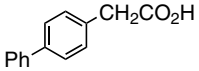
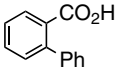
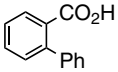
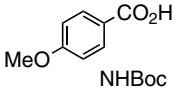
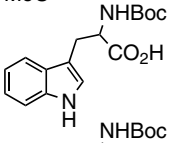
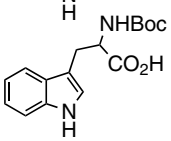
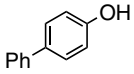



**Figure 3.** Comparison of TLC between FSPE conditions and regular conditions.

**Table 1.** Ester formation using **3** and FSPE




| Entry | Carboxylic acid | Alcohol | Time (h) | Yield[b] (%) | Purity[c] (%) |
|---|---|---|---|---|---|
| 1 |  | MeOH (10 equiv) | 1 | Quant. | 99.0 |
| 2 |  |  | 1 | 99 | 99.1 |
| 3 |  | MeOH (10 equiv) | 0.5 | Quant. | 97.4 |
| 4 |  | MeOH (10 equiv) | 1 | 87 | 98.9 |
| 5 |  |  | 2 | 80 | 92.0 |
| 6 |  | MeOH (10 equiv) | 1 | 94 | 99.8 |
| 7 |  | MeOH (10 equiv) | 1 | 71 | 99.0 |
| 8 |  |  | 1 | Quant. | 98.0 |

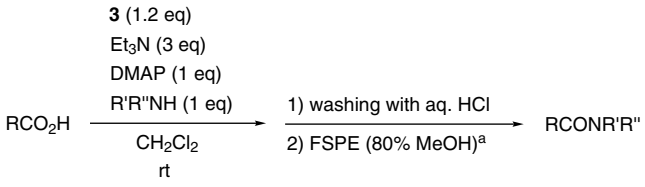
[a] The amount of fluorous silica gel used was 15 times the weight of **3**.
[b] Isolated yield.
[c] Determined by HPLC.

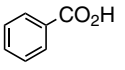
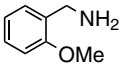
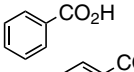
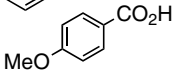
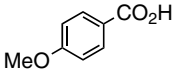
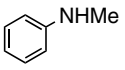
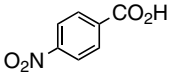
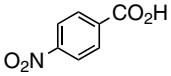
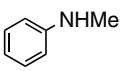
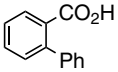
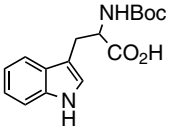
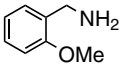
set up under identical conditions each with a different Mukaiyama reagent either **1**, **2** or **3**. At given time points the % conversion of the reaction was determined by recording $^1$H NMR spectra of the reaction mixtures and calculating the relative integrals of the methine proton of isopropoxy ester. A plot of % conversion versus time is shown in Figure 2 with the original Mukaiyama reagent **1** shown in red, the ethylene spacer version **3** shown in blue, and finally the ethylene benzyl derivative, **2**, shown in green. It is clear that fluorous reagent **3** has a higher reactivity than **2**, and almost the same reactivity as the original Mukaiyama reagent **1** in this particular ester forming reaction. Interestingly, the solubility of **2**, which showed the lowest activity, was the highest among these reagents.

Synthetically, we envisioned separating the target product from fluorous pyridone **4**, derived from the Mukaiyama reagent, via FSPE after the condensation reaction.[9] The ability of simple product purification is the most important feature of the fluorous Mukaiyama reagent. When the $R_f$ values of both the product and the pyridone by-product are similar to each other, it is difficult to separate these compounds effectively by the usual chromatography. For example, when acetic acid and *N*-methylaniline were used as the substrates with fluorous Mukaiyama reagent **3**, the target product could not be separated effectively from the corresponding pyridone **4** by standard column chromatography. The $R_f$ values (AcOEt/hexane = 1/1) of **4** and product **5** were 0.30, and 0.33, respectively, by regular TLC (Silica gel 60 $F_{254}$; MERCK) as shown in Figure 3. As a result complete resolution of adducts **4** and **5** by column chromatography was not trivial. On the other hand, there was a remarkable difference in $R_f$ values between **4** and **5** on fluorous TLC[10] (0.11 vs 0.83) when eluting with 80% MeOH as shown in Figure 3. This significant difference in $R_f$ enabled facile separation of fluorous pyridone **4** and amide **5** when the FSPE strategy was employed.

Table 1 shows the various ester formation reactions using **3** under mild basic conditions. The procedure of the condensation reaction was simple and easily carried out. All reactions proceeded at room temperature and were complete in under 2 h. Upon completion, the reaction mixture was washed with aq HCl to remove the TEA and DMAP and then subjected to FSPE eluting with 80% MeOH to give the target products in good yields and high purities.[11] Similarly, various amide forming reactions without HOBT were investigated and the results are shown in Table 2. Although the

**Table 2.** Amido formation using **3** and FSPE




| Entry | Carboxylic acid | Amine | Time (h) | Yield[b] (%) | Purity[c] (%) |
|---|---|---|---|---|---|
| 1 |  |  | 2 | 80 | 99.1 |
| 2 |  | $PhNH_2$ | 4 | Quant. | 99.8 |
| 3 |  | $PhNH_2$ | 2 | 86 | 95.1 |
| 4 |  |  | 5 | 77 | 98.9 |
| 5 |  | $PhNH_2$ | 2 | 76 | 99.7 |
| 6[d] |  |  | 2 | 91 | 95.8 |
| 7 |  | $PhNH_2$ | 2 | 84 | 99.8 |
| 8 |  |  | 2 | 84 | 98.9 |

[a] The amount of fluorous silica gel used was 15 times the weight of **3**.
[b] Isolated yield.
[c] Determined by HPLC.
[d] 0.2 equiv of DMAP was used.

by-products that did not move on TLC were slightly observed, moderate to good yields and easy purification were achieved in all cases.

In summary, a new fluorous Mukaiyama reagent **3** was prepared and it was found that the reactivity was higher than known fluorous Mukaiyama reagent **2**. Furthermore, we demonstrated that **3** is a useful reagent for condensation reactions when the $R_f$ values of both the product and the pyridone by-product are similar on regular TLC. We conclude that a condensation strategy using reagent **3** and FSPE is one of the most convenient methods for various ester and amide forming reactions.

## Acknowledgements

This work was supported by Grant-in-Aids for Creative Scientific Research (No. 14GS0214) from the Japan Society for the Promotion of Science. We thank Professor Dennis P. Curran, University of Pittsburgh, for the useful discussion and Professor Shuji Akai, Shizuoka Pharmaceutical University, for the elemental analysis of the fluorous Mukaiyama reagent **3**. We also thank Wako Pure Chemical Industries, Ltd, for funding this work.

## References and notes

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2. For examples: (a) Mukaiyama, T.; Aikawa, Y.; Kobayashi, S. *Chem. Lett.* **1976**, 57–60; (b) Kametani, T.; Sekine, H.; Honda, T. *Heterocycles* **1983**, *20*, 1577–1580; (c) Folmer, J. J.; Acero, C.; Thai, D. L.; Rapoport, H. *J. Org. Chem.* **1998**, *63*, 8170–8182; (d) Crosignani, S.; Gonzalez, J.; Swinnen, D. *Org. Lett.* **2004**, *6*, 4579–4582; (e) Donati, D.; Morelli, C.; Taddei, M. *Tetrahedron Lett.* **2005**, *46*, 2817–2819.
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5. (a) Zhang, W.; Curran, D. P.; Chen, C. H.-T. *Tetrahedron* **2002**, *58*, 3871–3875; (b) Lindsley, C. W.; Zhao, Z.; Leister, W. H. *Tetrahedron Lett.* **2002**, *43*, 4225–4228; (c) Lindsley, C. W.; Zhao, Z.; Leister, W. H.; Strauss, K. A. *Tetrahedron Lett.* **2002**, *43*, 6319–6323; (d) Zhang, W.; Chen, C. H.-T.; Nagashima, T. *Tetrahedron Lett.* **2003**, *44*, 2065–2068.
6. Curran, D. P. A User's Guide to Light Fluorous Chemistry. In *The Handbook of Fluorous Chemistry*; Gladysz, J., Horváth, I., Curran, D. P., Eds.; Wiley-VCH: Weinheim, 2004; pp 128–155, 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 solvent, so separations with fluorous solid phase are often the only practical methods.
7. Preparation of fluorous Mukaiyama reagent **3**: To a solution of 1*H*,1*H*,2*H*,2*H*-1-perfluorodecanol (68.4 g, 85.3 mmol), 2-chloropyridine (33.5 g, 171 mmol) in dry dichloromethane was added trifluoromethanesulfonic anhydride (50.0 g, 177 mmol) at 0 °C and the mixture was stirred at 45 °C for 24 h. Diethyl ether (100 ml) was added and the mixture was stirred for 0.5 h at room temperature. After the filtration of the crude product, the recrystallisation from ethyl acetate gave **1** (68.2 g, 72%) as a white powder.
8. Fluorous Mukaiyama reagent **3**: white powder; mp 131.0–132.0 °C; $^1$H NMR (270 MHz, DMSO-$d_6$) $\delta$: 3.04–3.29 (2H, m), 5.07 (2H, t, $J = 7.4$ Hz), 8.19 (1H, m), 8.45 (1H, d, $J = 8.2$ Hz), 8.64–8.70 (1H, m), 9.28 (1H, d, $J = 6.3$ Hz); $^{19}$F NMR (465 MHz, DMSO-$d_6$) ppm −125.7 (2F), −123.0 (2F), −122.5 (2F), −121.7 (4F), −121.4 (2F), −112.8 (2F), −80.2 (3F), −77.8 (3F); Anal. Calcd for $C_{16}H_8ClF_{20}NO_3S$: C, 27.08; H, 1.14; N, 1.97. Found: C, 26.68; H, 1.10; N, 2.11.
9. Curran, D. P. Separations with Fluorous Silica Gel and Related Materials. In *The Handbook of Fluorous Chemistry*; Gladysz, J., Horváth, I., Curran, D. P., Eds.; Wiley-VCH: Weinheim, 2004; pp 101–127.
10. The fluorous TLC is a TLC plate, which is coated with fluorous silica gel and commercially available from Fluorous Technologies Incorporated; <http://www.fluorous.com/>.
11. A typical procedure for amide formation and FSPE: To a solution of benzoic acid (71 mg, 0.58 mmol), *N*,*N*-dimethylaminopyridine (71 mg, 0.58 mmol) in dry dichloromethane (15 ml) were added triethylamine (0.24 ml, 1.74 mmol), aniline (0.053 ml, 0.58 mmol) and **3** (500 mg, 0.70 mmol) at room temperature, then the mixture was stirred for 4 h. After washing the organic layer with aq HCl and removal of the volatile components by evaporation, the mixture was submitted to separation by FSPE. A short column was packed with fluorous silica gel (7.5 g, 15 times weight for **3**) using 80% methanol as the solvent. The crude reaction mixture was then loaded onto this column and eluted with 20 ml of 80% methanol to give *N*-phenylbenzamide in quantitative yield (116 mg) as a white solid.