Tetrahedron Letters 51 (2010) 133–135

Contents lists available at ScienceDirect

Tetrahedron Letters

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

Pronounced rate enhancements in condensation reactions attributed to the fluorous tag in modified Mukaiyama reagents

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ARTICLE INFO

Article history:
Received 5 September 2009
Revised 16 October 2009
Accepted 22 October 2009
Available online 27 October 2009

ABSTRACT

The observed rate enhancement for the condensation reaction between 2-phenyl benzoic acid and isopropanol mediated by fluorous Mukaiyama reagents is described. It is shown that Mukaiyama reagents bearing a fluorous tag increase the reaction rate considerably when compared to their non-fluorous tagged counterpart. Furthermore, it is observed that the longer the fluorous chain, the higher the activity of the Mukaiyama reagent.

The Mukaiyama condensation reagent (*N*-methyl-2-chloropyridinium iodide)[1] **1** is arguably one of the most useful reagents in organic synthesis with many reports of its use in a key ester or amide forming reaction in a synthetic sequence.[2] Nagashima et al. reported the first fluorous-tagged Mukaiyama reagent **2** and demonstrated its ability to successfully promote amide bond formation.[3] This Letter used a fluorous benzyl group as the fluorous tag and fluorous solid-phase extraction (FSPE)[4] of the reaction mixture efficiently removed the resultant fluorous pyridone by-product. Recently, we reported on light fluorous Mukaiyama reagents **3a** and **3b**,[5] which were more reactive than **2** and also that their by-products were more easily removed from the desired product using solvent tuning[6] in filtration or FSPE (Fig. 1). During our investigations into the scope and limitations of these modified Mukaiyama reagents, we discovered that the rate of the coupling reaction was greatly influenced by the length of the fluorous tag in these molecules. Herein, we delve deeper into the rate enhancement that fluorous tags in fluorous Mukaiyama reagents impart on the condensation reaction.

The fluorous Mukaiyama reagents **3a**–**3d** were prepared from 2-chloropyridine and the corresponding fluorous alcohols in a single step in yields ranging from 41% to 87%[2d] after recrystallization[7] as shown in Scheme 1.[8] The structures of salts **3a** and **3b** were all supported by ^{1}H NMR, ^{19}F NMR, and elemental analysis.[9] All of the modified Mukaiyama reagents are white powder and can be stored in desiccators for extended periods of time without decomposition. A non-fluorous Mukaiyama reagent **3e** was also prepared using the same method which is to serve as a control in the rate studies.[10]

The attractive feature of fluorous Mukaiyama reagents[5b] has been the simple product isolation from the reaction mixture and has served as the focus of previous studies. However, the effects on the rate of the condensation reaction for the fluorous Mukaiyama reagents have not been previously investigated. We began our investigation by comparing the reactivity of five Mukaiyama reagents **3a**–**3e** in an esterification reaction between 2-phenyl benzoic acid and isopropanol in $CDCl_3$ to allow for ^{1}H NMR monitoring of reaction aliquots. Five separate reactions were set up under identical conditions each with a different Mukaiyama reagent.

At given time points, the % conversion of the reaction was determined by recording ^{1}H NMR spectra of the reaction mixture and calculating the relative integration of the methine proton of the isopropyl ester and isopropanol.[11] A plot of % conversion versus time is shown in Figure 2 with the non-fluorous version of the Mukaiyama reagent bearing $C_{10}H_{21}$ tag **3e** shown in black, the $C_{10}F_{21}$ tag **3a** shown in blue, the C_8F_{17} tag **3b** shown in green, the C_6F_{13} tag **3c** shown in purple, and finally, the C_4F_9 tag **3d** shown in red. It is evident from Figure 2 that the reaction rate is greatly affected by the nature of the fluorous tag in the molecule. Interest-

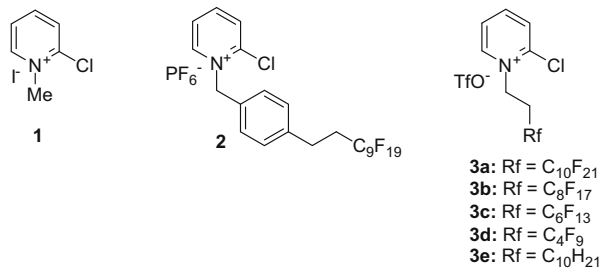

Figure 1.

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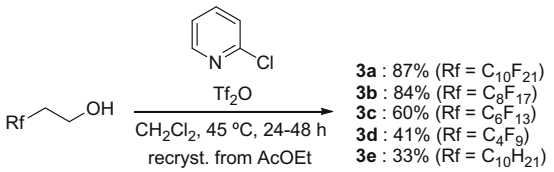
doi:10.1016/j.tetlet.2009.10.109



Scheme 1. Synthesis of fluoroalkylated Mukaiyama reagents.

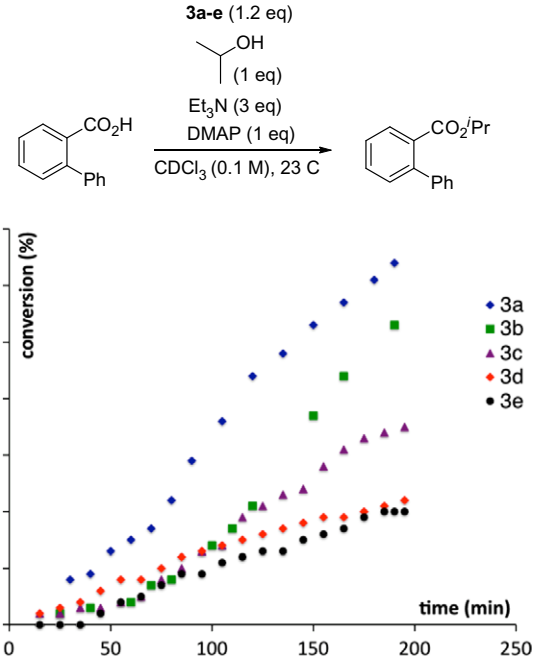


Figure 2. Comparison of conversion for ester formation in $CDCl_3$.

ingly, the relative rate enhancement effect of the different reagents directly correlates to the number of fluorines in the fluorous tag. We also found that the fluorous version of the Mukaiyama reagent promotes a faster reaction rate than the non-fluorous reagent bearing the same length of the carbon chain. (**3a** vs **3e**). The rate enhancement based on a fluorous tag was also observed in the esterification using isopropanol and non-substituted benzoic acid.

Figure 3 shows the calculation results for the atomic charge (NBO charge) and dipole moment of cationic part of **3a**, **3d**, and the corresponding non-fluorous reagent **3e** using GAUSSIAN 03 HF/6-31+G** method.[12] The result indicates that there is no significant difference, in terms of the atomic charge on the carbon atom where

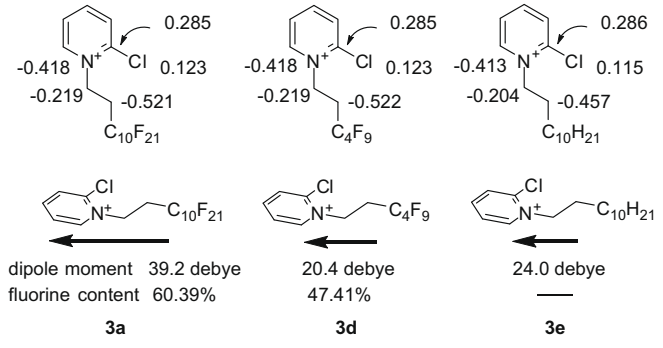


Figure 3. Calculation of atomic charge and dipole moment of cationic part of Mukaiyama reagent using GAUSSIAN 03 HF/6-31+G** method.

nucleophilic attack occurs, among the fluorous and non-fluorous reagents.[13] This can be explained by the ethylene spacer attenuating the electron withdrawing effect of the fluorous tag. On the other hand, a remarkable difference in dipole moment was calculated between **3a** and **3e**. Although it remains as a matter to be discussed and investigated further, it is quite likely that an aggregation state based on the fluorophilic effect of the fluorous tag in solution affects the reaction rate of this coupling reaction.

In summary, a rate enhancement is observed in a condensation reaction when using a fluorous chain containing Mukaiyama reagent when compared to a non-fluorous version. As the length of fluorous tag was increased, the reactivity of the reagent became higher. This is one of the rare examples where a fluorous tag changes the reactivity of the organic molecule.[14] Further investigation into the origin of this rate-enhancement is now in progress and will be reported in due course.

Acknowledgments

This research was partially supported by the Ministry of Education, Science, Sports and Culture, Grant-in-aid for Scientific Research (C), 20580115, and the fund for Agriomics project. We thank Professor Dennis P. Curran, University of Pittsburgh, for the useful discussion and Mr. Masahiko Bando, Otsuka Pharmaceutical Co. Ltd, for the elemental analysis of the fluorous Mukaiyama reagent **3a** and **3b**. We also thank Wako Pure Chemical Industries, Ltd for funding this work.

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7. A typical procedure for preparation of the fluorous Mukaiyama reagent **3a**: To a solution of 1*H*,1*H*,2*H*,2*H*-1-perfluorododecanol (15.0 g, 26.7 mmol), 2-chloropyridine (7.27 g, 64.0 mmol) in dry dichloromethane was added trifluoromethanesulfonic anhydride (9.03 g, 32.0 mmol) at 0 °C and the mixture was stirred at 45 °C for 48 h. Diethyl ether (80 ml) was added and the mixture was stirred for 1 h at room temperature. After filtration of the crude product, recrystallization from ethyl acetate gave **3a** (18.9 g, 87.4%) as a white powder.
8. There is a significant difference among isolated yields of the products due to the marked difference in crystallinity of the different reagents.
9. Compound **3a**: white powder; mp 118.0–119.0 °C; ^{1}H NMR (270 MHz, DMSO-d_6) δ: 3.02–3.22 (m, 2H), 5.06 (t, J = 7.4 Hz, 2H), 8.15–8.20 (m, 1H), 8.41 (dd, J = 8.6, 1.4 Hz, 1H), 8.63–8.69 (m, 1H), 9.27 (dd, J = 6.5, 1.6 Hz, 1H); ^{19}F NMR (466 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 $C_{18}H_8ClF_{24}NO_3S$: C, 26.70; H, 1.00; N, 1.73. Found: C, 26.58; H, 0.94; N, 1.65.Compound **3b**: white powder; mp 88.0–89.0 °C; ^{1}H NMR (270 MHz, DMSO-d_6) δ: 3.03–3.24 (m, 2H), 5.08 (t, J = 7.4 Hz, 2H), 8.16–8.22 (m, 1H), 8.45 (dd, J = 8.4, 1.1 Hz, 1H), 8.65–8.71 (m, 1H), 9.30 (dd, J = 6.3, 1.8 Hz, 1H); ^{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); 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.Compound **3c**: white powder; mp 83.0–85.0 °C; ^{1}H NMR (270 MHz, DMSO-d_6) δ: 3.04–3.25 (m, 2H), 5.08 (t, J = 7.4 Hz, 2H), 8.17–8.22 (m, 1H), 8.45 (dd, J = 8.1, 1.4 Hz, 1H), 8.64–8.71 (m, 1H), 9.30 (dd, J = 6.3, 1.8 Hz, 1H); ^{19}F NMR (466 MHz, DMSO-d_6) ppm −125.7 (2F), −123.0 (2F), −122.6 (2F), −121.6 (2F), −112.7 (2F), −80.2 (3F), −77.7 (3F).Compound **3d**: white powder; mp

68.0–69.0 °C; ^{1}H NMR (270 MHz, DMSO-d_6) δ: 2.94–3.24 (m, 2H), 5.08 (t, J = 7.4 Hz, 2H), 8.16–8.22 (m, 1H), 8.45 (dd, J = 8.4, 1.4 Hz, 1H), 8.64–8.70 (m, 1H), 9.30 (dd, J = 6.2, 1.6 Hz, 1H); ^{19}F NMR (466 MHz, DMSO-d_6) ppm −125.6 (2F), −124.0 (2F), −113.0 (2F), −80.5 (3F), −77.6 (3F).

10. Compound **3e**: white powder; mp 24.0–25.0 °C; ^{1}H NMR (270 MHz, DMSO-d_6) δ: 0.88 (t, J = 6.6 Hz, 3H), 1.25–1.46 (m, 18H), 1.92–2.03 (m, 2H), 4.81 (t, J = 7.8 Hz, 2H), 8.04–8.13 (m, 2H), 8.50–8.56 (m, 1H), 9.21 (dd, J = 6.1, 1.5 Hz, 1H).
11. The control experiments to confirm the relative integration of the isopropyl function were conducted. Isopropanol was mixed with **3a** and DMAP in $CDCl_3$ without 2-phenylbenzoic acid, and traced for 2 h by NMR. As the result, the integration from the isopropanol stayed the same. The same experiment with the ester was also conducted.
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