Thermal Retro-Aldol Reaction Using Fluorous Ether F-626 as a Reaction Medium

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Abstract: A high-boiling, fluorous–organic hybrid ether, F-626, was tested for use in thermal retro-aldol reactions and found to be an excellent reaction medium in view of the ease of separation from the product by fluorous/organic biphasic treatment. The recovered F-626 can be readily reused for subsequent runs.

Key words: retro-aldol reaction, fluorous ether, F-626, biphasic system

The emergence of new solvents in synthesis has stimulated renewed interest in traditional organic synthesis normally based on conventional organic solvents.^{1,2} We are interested in the use of F-626 (Figure 1), which is a fluorous-organic hybrid ether that was originally developed by Kao Corporation,³ as a solvent for green organic synthesis.⁴ The unique characteristics of F-626 include its good potential use as a substitute for organic solvents, and its thermomorphic nature when treated with organic substrates and reagents.⁵ Despite its relatively high boiling point (214 °C/760 mmHg), F-626 is nevertheless easily recoverable by fluorous/organic biphasic treatment. We previously reported on the use of F-626 as a solvent in a variety of synthetic reactions, such as the Vilsmeyer formylation reaction,^{4a} the Wolff-Kishner reduction,^{4a} the Diels–Alder reaction,^{4a} fluorous tin hydride based radical reactions,^{4a} and the Mizoroki-Heck reaction.^{4b}

The thermal retro-aldol reaction is a well-known reaction that is thought to proceed through a concerted mechanism.^{6,7} The retro-aldol products can be used as useful synthetic intermediates to prepare analogues of natural products or for structure confirmation.⁷ Typically, the reaction is carried out in a sealed tube because the use of high-boiling organic solvents often requires cumbersome procedures to separate them from the products. In this work, we report that F-626 is an excellent reaction medium for thermal retro-aldol reactions that is easily separable from the products.

We examined the thermally induced retro-aldol reaction using 2-hydroxymethyl-1-phenyl-1-hexanone (1a) as a model compound. The results are summarized in Table 1. Heating 1a at 200 °C for four hours without solvent gave a 75:25 mixture of the desired product 1-phenyl-1-hexanone (2a) and 2-methylene ketone 3a, which is formed as



Figure 1 F-626 (1*H*,1*H*,2*H*,2*H*-perfluorooctyl 1,3-dimethylbutyl ether)

a by-product through dehydration, in 47% total yield (entry 1). The use of the ionic liquid [bmim]NTf₂ as a solvent under similar conditions gave an even worse result: a 50:50 mixture of **2a** and **3a** (entry 2). We found that F-626 worked quite well for the thermal retro-aldol reaction. Whereas the fluorous ether solvent, F-626, does not dissolve **1a** at room temperature, upon heating, one layer resulted (Figure 2). After cooling, biphasic workup using acetonitrile and FC-72 (perfluorohexanes), followed by purification using silica gel chromatography, gave a 98% combined yield of **2a** and **3a** in a ratio of 95:5 (entry 3). For this retro-aldol reaction, heating to 200 °C is critical, since lowering the temperature to 180 °C resulted in a sluggish reaction (entry 4).



Figure 2 Pictures of the retro-aldol reaction using F-626. (A) Before heating. 1a is floating on F-626; (B) One layer upon heating at 200 $^{\circ}$ C for 10 min; (C) After the reaction.

We then examined the thermal retro-aldol reaction of several aldol compounds using F-626 as reaction medium. The results are summarized in Table 2. With the exception of *p*-hydroxyl-substituted phenone derivative **1d**, retroaldol products were obtained with high selectivity in preference to the dehydration products. In the case of **1d**, the acidic proton arising from the phenol portion, may catalyze the dehydration reaction (entry 5); consistent with this rationale, the corresponding *p*-methoxy substrate **1e** gave the retro-aldol product **2e** with high selectivity (entry 6). Aldol substrate **1f**, having a secondary alcohol moiety, underwent the retro-aldol reaction in a shorter reaction time (entry 7). Aliphatic α -hydroxymethyl ketone also worked well to give a good yield of ketone **2g** (entry 8).

SYNLETT 2010, No. 14, pp 2193–2196 Advanced online publication: 16.07.2010 DOI: 10.1055/s-0030-1258501; Art ID: U04110ST © Georg Thieme Verlag Stuttgart · New York

Table 1 Thermal Retro-Aldol Reaction and Reaction Media^a



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^a Reaction was carried out on 0.5 mmol scale for 4 h.

F-626 (4 mL)

^b Isolated yields after silica gel chromatography.

^c Determined by ¹H NMR analysis of the crude reaction mixture.

^d NMR yield.

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The workup procedure^{4a} is outlined in Scheme 1.⁸ Thus, treatment of **1a** with F-626 at room temperature gave two layers that became homogeneous upon heating. After cooling, the product **2a** was extracted into acetonitrile (4 mL) and the resulting acetonitrile layer was separated and washed with FC-72 (2 mL) to extract the remaining F-626. The FC-72 solution was combined with the separated F-626. After evaporation, 98% of F-626 was recovered that was essentially clean as judged by NMR analysis; recovered F-626 could be used for subsequent experiments without reducing the yield of **2a** (Table 2, entry 2).



Scheme 1 Separation and solvent recycling

We previously reported on a ruthenium hydride-catalyzed reaction that gave α -hydroxymethyl ketones as principal products.^{9,10,11} The combined procedures – the ruthenium hydride-catalyzed reaction and the thermal retro-aldol reaction – would give a new protocol for the synthesis of ketones. As outlined in Scheme 2, one-pot synthesis of 6-undecanone (**2g**) and 1-phenyl-1-hexanone (**2a**) was attained starting from 2-hexene-1-ol¹² or benzyl alcohol, respectively, upon reaction with 2-hexenal.





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Scheme 2 One-pot protocol for the synthesis of ketones by RuHcatalyzed coupling reaction and subsequent retro-aldol reaction using F-626

In summary, thermal retro-aldol reactions can be successfully carried out using the high-boiling fluorous–organic hybrid solvent, F-626, as a reaction medium in which both separation of the product and recycling of the solvent are easy to carry out. The procedure was successfully combined with RuH-catalyzed coupling reactions to give aldol-type products in a one-pot procedure that can be used for the synthesis of ketones.

 Table 2
 F-626-Mediated Retro-Aldol Reaction^a



 $^{\rm a}$ The reaction was performed with 1 (0.5 mmol) and F-626 (4 mL) at 200 $^{\circ}{\rm C}$

^b Isolated yield after silica gel column chromatography.

^c Determined by ¹H NMR analysis.

^d Recovered F-626 was used.

Acknowledgment

T.F. and I.R. acknowledge JSPS and MEXT Japan for funding. We appreciate the generous gift of F-626 from the Kao Corporation.

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- (8) General procedure for retro-aldol reactions using F-626: α-Hydroxymethyl ketone 1a (0.5 mmol, 104.7 mg) and F-626 (4 mL, 5.64 g) were placed in a 5 mL two-necked roundbottom flask, and heated at 200 °C for 4 h under nitrogen. After cooling to room temperature, the reaction mixture was poured into a separation funnel, and MeCN (4 mL) was added. The MeCN layer was separated, and extracted with FC-72 (6 × 0.33 mL). The combined fluorous layers were evaporated to give F-626 (5.53 g, 98%). The crude reaction mixture obtained from the MeCN layer was purified by silica gel chromatography (hexane–EtOAc, 98:2) to give a mixture of 2a and 3a (87.6 mg; 2a/3a = 95:5)
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