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CARBON-CARBON BOND FORMATION UNDER AQUEOUS REACTION CONDITIONS USING SULFONIUM AND SELENONIUM SALT ELECTROPHILES

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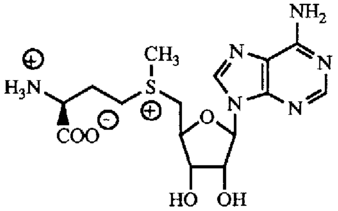
Abstract. *Methylation of relatively acidic (pK_a<13) carbon nucleophiles occurs at neutral pH in aqueous media using suitably substituted methyl sulfonium and selenonium salt electrophiles.*

S-adenosylmethionine, **1**, serves as a ubiquitous source of electrophilic methyl for both heteroatom and carbon nucleophiles in biological systems.[3] The "biomimetic" alkylation of heteroatom nucleophiles with sulfonium salt electrophiles in aqueous media has been described.[4] However, carbon-carbon bond formation via methyl transfer from a sulfonium salt to a carbon nucleophile has been limited to non-aqueous systems.[5,6] This difference can be attributed to the stabilization of the charged sulfonium salt by water, which attenuates its reactivity in aqueous media.[7] We report herein that, using suitably activated methyl sulfonium and selenonium salts, *the methylation of carbon nucleophiles (pK_a<13) can be achieved in aqueous media at neutral pH.*



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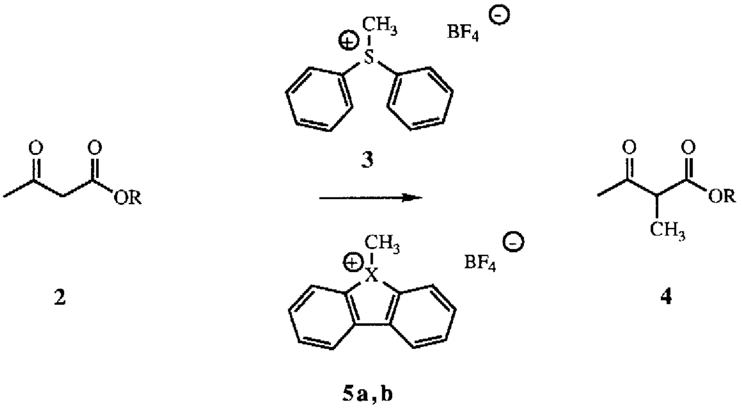
The alkylation of β-ketoesters (pK_a=11) with diphenylmethyl and trimethyl sulfonium salts in excellent yields *under aprotic conditions* has been independently reported by Julia[5] and Garst.[6] We have found that the reaction of ketoester **2** (R = p-*tert*-butylbenzyl) with diphenylmethylsulfonium tetrafluoroborate, **3**, is very sensitive to both solvent polarity and pH. Reaction of a 1.4 mM solution of **2** in a 15:85 50 mM pH 10 borate buffer[8]: acetonitrile mixture with 2 equivalents of **3** for one hour at 25°C leads to a modest 9% yield of **4**. If either the pH of the reaction mixture is even slightly lowered (below 9.7), or if the percentage of aqueous buffer in the reaction mixture is increased, no methylation of **2** is observed with **3**.



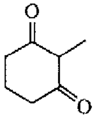
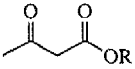
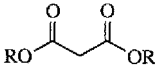
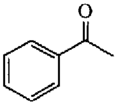
a: X = S; **b:** X = Se

We anticipated that dibenzothiophenium salt **5a**[9] should be a more reactive methylating agent than **3**, based on the aromatic stabilization which is gained on transferring methyl from the dibenzothiophenium salt, so that methylation with **5a** should be more tolerant of both lower pH and a more aqueous reaction medium. While the polarigraphic behavior[10] and the transfer of methyl to methanol[11] using **5a** have been reported, we are aware of no examples of the use of this reagent for carbon-carbon bond formation. *The reaction of **2** with **5a**, at pH 10, leads to the formation of **4** in 85% yield, an increase of an order of magnitude over that observed in the reaction of **2** with **3** under identical reaction conditions.* However, the yield of the methylation of **2** with **5a** depended critically on the pH of the reaction mixture, providing the mono-alkylated product **4** in 50% yield at pH 9, 30% yield at pH 8, and 5% yield at pH 7.

In an effort to increase the efficiency of the methylation at neutral pH, we next examined the reaction of **2** with the more electrophilic selenonium salt **5b**.[12,13] *The reaction of **2** with **5b** leads to the formation of **4** in 50% yield at neutral pH, an increase of an order of magnitude over that observed in the reaction of **2** with **5a** under identical reaction conditions.* The alkylation of other carbon nucleophiles with **5b** was also examined. The methylation of the more acidic (pK_a=9) 2-methyl-cyclohexane-1,3-dione using either **5a** or **5b** occurs in 70-80% yield at neutral pH, although a striking difference in the ratio of C- vs. O-alkylation was observed. In contrast to the methylation with sulfonium salt **5a**, which leads to the formation of a 1.8:1 mixture of C-/O-alkylated products, the reaction of the selenonium salt **5b** with 2-methyl-cyclohexane-1,3-dione leads to the exclusive formation of the C-alkylated product, a result which can be attributed to the greater propensity of the softer selenonium salt towards reaction on carbon.[12]

Less acidic nucleophiles are correspondingly less reactive. Alkylation of dibenzyl malonate (pK_a=13) with **5b** proceeds in 23% yield at pH 9 and 7% yield at pH 8. In contrast, methylation of dibenzyl malonate with dibenzothiophenium salt **5a** led to the formation of the monoalkylated product in 20% yield at pH 10 and 10% yield at pH 9. No reaction was observed with dibenzyl malonate and **5a** below pH 9. Finally, no reaction was observed with either **5a** or **5b** and acetophenone (pK_a=19) over the entire pH range examined (7-10). The relative rates for the alkylations of these nucleophiles with the dibenzoselenophenium salt **5b** are summarized in the Table.

RATE OF METHYLATION WITH SELENONIUM SALT 5b VS. pH (x 10^6mM/sec)

	pKa	pH 7	8	9
	9	510	1000	3200
	11	1.4	3.2	5.0
	13	0	0.69	1.8
	19	0	0	0

The efficient transfer of electrophilic methyl from sulfonium and selenonium salts **5a** and **5b** to carbon nucleophiles under aqueous conditions has now been achieved. The application of these results to the development of systems for transmethylation is currently underway in our laboratory.

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8. The methylation experiments were performed by reaction of a 1.4 mM solution of the carbon nucleophile in 15 to 70% 50 mM borate or phosphate buffer in acetonitrile, at pH values ranging from 7 to 10, with 10 equivalents of either diphenylmethyl sulfonium tetrafluoroborate **3**, 5-methyl dibenzothiophenium tetrafluoroborate **5a**, or 5-methyl dibenzoselenophenium tetrafluoroborate **5b** at 25^{o}C for one hour. Buffers were prepared according to procedures in the *Handbook of Analytical Chemistry,* cf. Bower and Bates, *J. Research National Bureau of Standards* **1955**, *55*, 197. Yields were determined by HPLC (reverse-phase C_{18} column using 70/30 acetonitrile/water as eluent and a uv detector at 253 nm) or capillary GC (OV-101). Preparative scale methylations of **2** with either **5a** or **5b** and isolation of the methylated product gave the same yields as those obtained by HPLC and/or GC analysis. The methylated products was characterized by NMR, IR and GC-MS.

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