

A RAPID ENTRY TO FUNCTIONALIZED CYCLOHEXANES AND CYCLOPENTANES VIA A ONE-POT, MULTICOMPONENT ANNULATIONS

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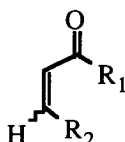
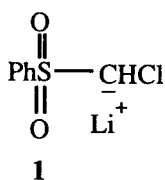
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ABSTRACT

Lithio chloromethyl phenyl sulfone has been demonstrated to be a good Michael donor for triggering a one-pot multicomponent cyclization involving enones, α, β -unsaturated ester and nitrile.

A one-pot multiple carbon-carbon bond formation both through ionic and radical processes has become an important methodology for a quick and efficient construction of complex organic molecules. Polycyclic structures possessing three-, five- and six-membered rings have been assembled by this approach. Eventhough the methodology is still evolving, it is evident that many natural products could be synthesized by this technology¹⁻¹⁸. As part of our program to develop the synthetic utilities of α -halomethyl aryl sulfoxides and sulfones^{19,20}, we had investigated the reaction of lithio α -chloromethyl phenyl sulfone **1** with a number of α, β -unsaturated compounds **2** and crotononitrile. Our results summarized in Table 1 indicate that the species **1** is a useful Michael donor for triggering a multicomponent annulation culminating in the formation of functionalized five- and six-membered carbocyclic compounds.



2: R₁, R₂ = -(CH₂)₂- ; -(CH₂)₃- ; Me, H ; OMe, Me

Typical procedure

Lithio chloromethyl phenyl sulfone **1** (5 mmol, in THF 15 ml) was generated by the reaction of chloromethyl phenyl sulfone with LDA at -78 °C. HMPA (1:10 v/v) was added and stirring was continued before the addition of α, β -unsaturated carbonyl compound (15 mmol, in THF 10 ml). The reaction mixture was stirred at -78 °C for 3 hr and then allowed to warm to room temperature overnight. The usual work up and purification by PLC (hexane:ethyl acetate) gave the product as a mixture of diastereomers.

It is evident that the carbanion **1** can initiate diverse reactions with different Michael acceptors. The highly significant feature (Scheme 1) of all the examples reported is the ability of the second Michael addition (pathway a) to compete successfully with the 1,3-substitution reaction (pathway b) (entropywise, this step is much more favourable).

The Michael reaction of the carbanion **1** with cyclohexenone and cyclopentenone (entries 1 and 2; 3 equivalents) gave the products **3** (37% yield) and **4** (14% yield) respectively^{1-4, 21-24}. In the case of the reaction with cyclohexenone, the 1,3-substitution product **8** was also isolated in 19% yield. The reaction with cyclopentenone using a 1:1 ratio of the reagents gave the cyclopropane **9** deriving from the 1,3-substitution reaction as the sole product. These results represent very few examples of sequential reaction which involving S_N2 reaction as the final ring closure step in the cascade yielding product with ring larger than the three-membered²⁵.

Scheme 1

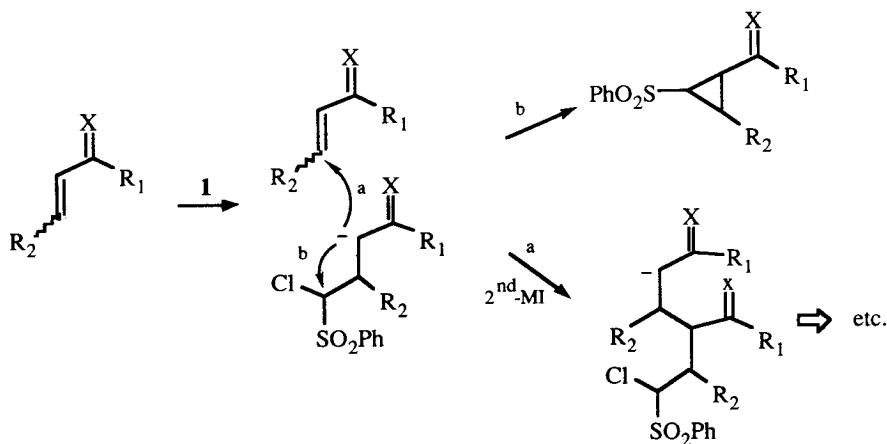
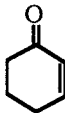
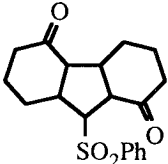

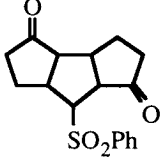
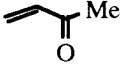
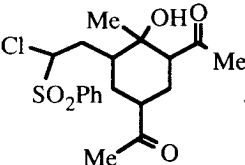
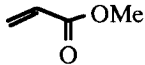
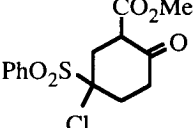

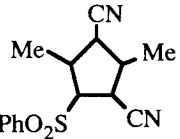
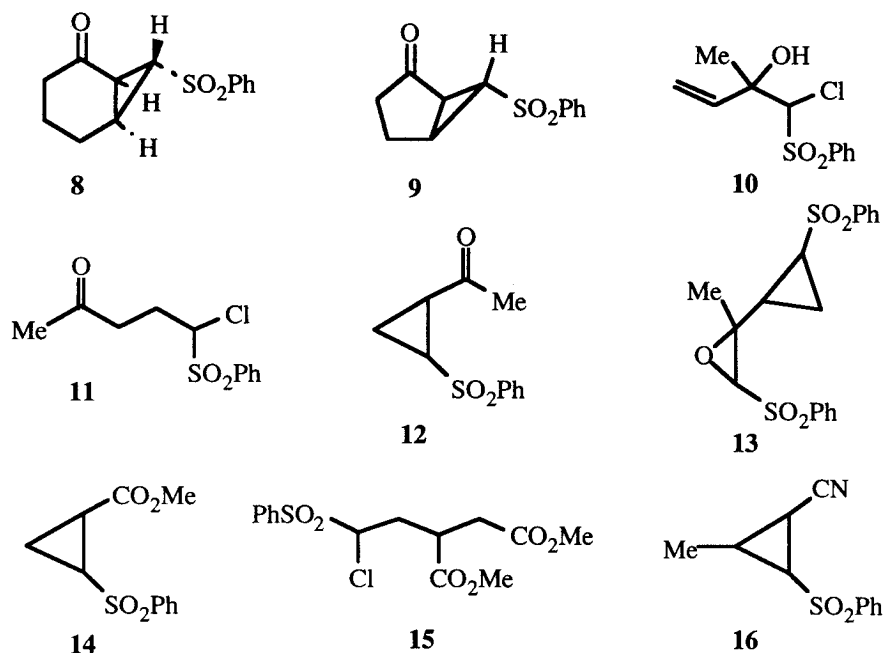


TABLE 1. Yields of Multicomponent One-Pot Annulation Products.

Entry	Substrate (3 equiv.)	Product ¹ (% yield)	Type of Reaction
1.		 3 (37%)	MI-MI-RC (S _N 2) (1+2+2)
2.		 4 (14%)	MI-MI-RC (S _N 2) (1+2+2)
3.		 5 (71%)	MI-MI-MI-RC (Aldol) (1+2+2+2)
4.		 6 (14%)	MI-MI-RC (Dieckman) (1+2+2)
5.		 7 (40%)	MI-MI-RC (S _N 2) (1+2+2)

¹Products were characterized by spectral data and elemental analyses. MI= Michael Reaction.

The reaction of the carbanion **1** with methyl vinyl ketone (3 equivalents) led to the cyclohexane derivative **5** in 71% yield^{1-4, 26-29}. This process represents one of very few examples of this type involving four-component coupling yielding six-membered ring^{1-4, 30-31}. Other minor products from this reaction are a small amounts of the 1,2 addition product **10** (3% yield) and the 1,4-adduct **11** (4% yield). When equimolar of the reagents was used, no compound **5** was detected, instead the cyclopropyl products **12** (15% yield) and **13** (12% yield) deriving initially from a 1,4-addition reaction of **1** to the methyl vinyl ketone followed by 1,3-S_N2 cyclopropane formation were the only identifiable products.



The Michael-Michael Dieckman sequential reaction³²⁻³⁵ of **1** with methyl acrylate gave the product **6** in 14% yield accompanying by the cyclopropane **14** (22% yield) and the acyclic double Michael product **15** (36% yield). The formation of product **15** reflects the comparable acidities of α -chlorophenyl sulfonyl and α -ester protons. The reaction of **1** with crotononitrile occurs in a slightly different pathway. The five-membered ring product **7** was isolated in 40% yield together with a small amount of the cyclopropane **16** (8%)^{21-24, 36-44}.

The results shown in Table 1, eventhough the yield of the cyclic compounds are moderate, the studies have demonstrated the synthetic utility of the simple carbanion **1** in the synthesis of complex molecules. Examples given contribute significantly to the emerging chemistry of tandem reactions. Further exploratory work is in progress.

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