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Synthesis of Cyclopentenones from Cyclopropanes and Ynol Silanes

 Xiangbing Qi and Joseph M. Ready^[*]

Keywords

Cycloaddition; cyclopentenone; ynol; cyclopropane

Five-membered carbocyclic rings appear in all classes of organic materials including pharmaceutical agents, polymers, natural products and catalysts. Accordingly, their preparation has challenged synthetic chemistry since the inception of the field.[1] In this regard, [3+2] cycloadditions - both concerted and stepwise - represent convergent strategies for the construction of the cyclopentane nucleus.[2] Dipolar cycloadditions, in particular, have proven especially successful, and of the various all-carbon dipoles available, donor-acceptor cyclopropanes (**1**) have proven especially versatile.[3] In the presence of Lewis acids, these materials undergo ring-opening to yield 1,3-dipoles. Pursuing a general interest in the reactivity of electron-rich alkynes,[4] we envisioned a cycloaddition between such dipoles and ynol ethers (**2**, Scheme 1). In analogy to Diels-Alder reactions involving Danishefsky's diene[5] we postulated that the intermediate vinylogous acetal **3** might decompose to the cyclopentenone **4** during the reaction. While donor-acceptor cyclopropanes have been shown to combine with indoles,[6] enol ethers[7] and aryl acetylenes,[8] a condensation with ynol derivatives has not been documented. Indeed, these alkynes have hardly been explored in the context of [3+2] cycloadditions.[9]

Exploratory studies examined the reaction of cyclopropane **1a** ($R^1, R^2 = H$) with ynol ether **2a** ($R^3 = n\text{-Bu}$) which is prepared in a single step from *n*-hexyne.[10] Several Bronsted and Lewis acids, including Me_3SiOTf ($\text{Tf} = \text{SO}_2\text{CF}_3$), $\text{HN}(\text{Tf})_2$ and BBr_3 , promoted the formation of cyclopentadiene **5aa** and cyclopentenone **4aa** in moderate yield. Despite substantial efforts to optimize the reaction conditions, however, we were never able to develop a protocol that returned the cycloadducts in synthetically useful yield. Our early experiments suggested similarly mediocre performance with Me_2AlCl ; therefore, when we reinvestigated this Lewis acid several months after our initial experiments, we were surprised to find that it promoted the cycloaddition cleanly and rapidly.[11] Our hope that the increase in yield reflected improved technique was quickly dispelled when we discovered substantial differences in reactivity between aged and freshly opened bottles of reagents.

Reactions involving Me_2AlCl from a new bottle required >24h to go to completion (Table 1, entry 1). Under otherwise identical conditions, reagent drawn from bottles that had been used for several months displayed markedly superior reactivity (entry 2). Reasoning that this observation could be accounted for by evaporation (solutions of Me_2AlCl in hexanes were used) or adventitious air or water, we performed a series of control experiments. Modest changes to the charge of Me_2AlCl had little effect on the rate of the reaction (not shown), and neither did small amounts of water (entry 3). In contrast, when dry air was bubbled through

[*]Mr. X. Qi, Prof. J.M. Ready, Department of Biochemistry, University of Texas Southwestern Medical Center at Dallas, Dallas, TX 75390-9038 (USA), Fax: (+1) 214-648-0320, joseph.ready@utsouthwestern.edu, <http://www.swmed.edu/readylab/>

solutions containing the Lewis acid, we could recapitulate the phenomenon observed with aged bottles of reagent, and isolate **4aa** in good yield (entry 4).[12]

Under optimized reaction conditions, air was bubbled through a solution of the Al reagent (1 equiv) at room temperature. At -78 °C, cyclopropane (1.3 equiv) and ynol ether (1 equiv) were added, and the solution was stirred until the reaction was complete (2-24 h). HF·pyridine was added, and, after aqueous workup, cyclopentenone **4** was purified by flash chromatography. In this way, a series of substituted donor-acceptor cyclopropanes combined with a range of ynol ethers to yield enones in generally good yields (Table 2). Silyl ynol ethers bearing olefins, alkynes, ethers, halides and aromatic rings all functioned effectively in the transformation (entries 1-12). Unfortunately, the ynol derived from phenyl acetylene was a poor substrate (entry 13). Cis- and trans-disubstituted cyclopropanes appear to behave equivalently (entry 1-2). Likewise, substitution at C3 (entries 14-16), C1 (entry 17), or both (entries 18-19) is accommodated in the cycloaddition. Thus, tri-, tetra-, and even penta-substituted cyclopentenones can be formed in good yields and in a convergent manner. Furthermore, both partners in the cycloaddition can be accessed in a single operation from readily available materials.

The NMR spectrum of anaerobic solutions of Me₂AlCl revealed one singlet at -0.31 ppm (CDCl₃). After oxygenation, the same solution displays two upfield singlets at -0.39 and -0.43 ppm and two downfield resonances suggestive of a methoxide (3.87 and 3.85 ppm). We interpret these signals as arising from (MeO)AlMeCl, the product of aerobic oxidation of one methyl-aluminum bond. The two sets of signals (ca. 1:2 ratio) likely correspond to diastereomeric cyclic trimers.[13] Indeed, addition of 1 equiv of methanol to Me₂AlCl yields a substance with substantially the same spectrum, and the reagent thus produced is a better Lewis acid for the cycloaddition than Me₂AlCl (Table 1, entry 5). Interestingly, while the major products formed upon addition of methanol or air to Me₂AlCl are the same, the reaction of methanol is noticeably messier: an unidentified precipitant is formed, and the ¹H NMR spectrum of the filtrate contains several minor products. Perhaps as a consequence, the cycloadditions using this reagent are lower yielding and generate more side products. Thus aerobic oxidation of dialkyl alanes constitutes a clean and efficient method to generate a strong but selective Lewis acid. Finally, it is important to note that we observe no difference between the (MeO)AlMeCl generated from new versus aged bottles of Me₂AlCl (Table 1, entries 4 vs. 6).

With respect to the utility of the methodology described here, comparisons to two standard syntheses of cyclopentenones are appropriate. This cycloaddition is more direct than the Nazarov cyclization, and, in contrast to that cyclization, yields a single olefin positional isomer. [14] Likewise, while the Pauson-Khand reaction is generally limited to intramolecular cyclizations, the reactivity described above functions efficiently in an intermolecular context. [15]

While (MeO)AlMeCl has been characterized previously, it has found infrequent use as a Lewis acid.[16] In the present transformation, it appears strong enough to activate the cyclopropane towards ring-opening and to mediate the decomposition of the vinylogous acetal (**3**), but mild enough to coexist with the ynol ether and the cyclopentenone. Whether this favorable reactivity profile extends to other classes of dipolar cycloadditions and, more broadly, other Lewis-acid promoted reactions remains the subject of future investigations.

Experimental Section

A dried test was charged with anhydrous dichloromethane (1 mL) and Me₂AlCl (0.5 mL of 1M solution in hexanes, 1 equiv). Dry air (20 mL) was bubbled through the solution at room

temperature. The resulting solution was cooled to $-78\text{ }^{\circ}\text{C}$. Cyclopropane (0.65 mmol, 1.3 equiv) and silyl ynol ether (0.5 mmol, 1 equiv) were added sequentially into the reaction solution. The reaction was stirred at $-78\text{ }^{\circ}\text{C}$ and monitored by TLC. Upon completion, the reaction was quenched by adding 0.5 mL of 30% HF-pyridine solution. After stirring at $-78\text{ }^{\circ}\text{C}$ for 5 minutes, the reaction mixture was diluted with ether and water. The aqueous layer was washed with 30 mL ether. The combined organic layers were washed with 50 mL of brine and dried with anhydrous MgSO_4 , concentrated and purified by flash chromatography on silica gel.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

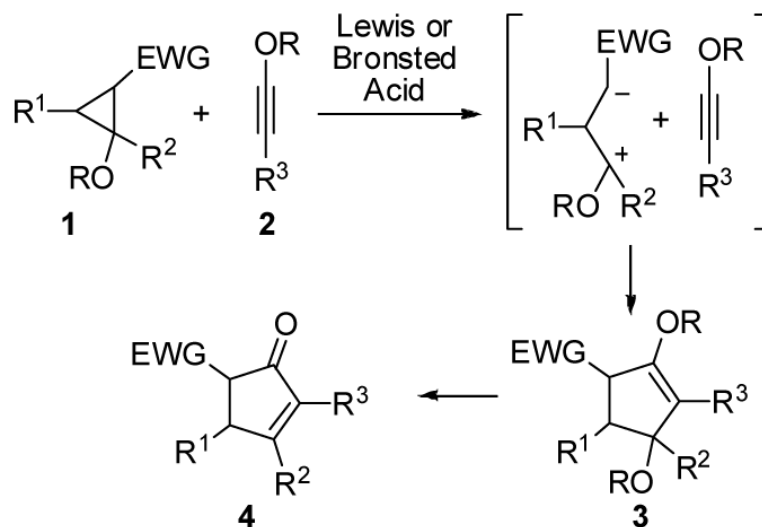
Acknowledgments

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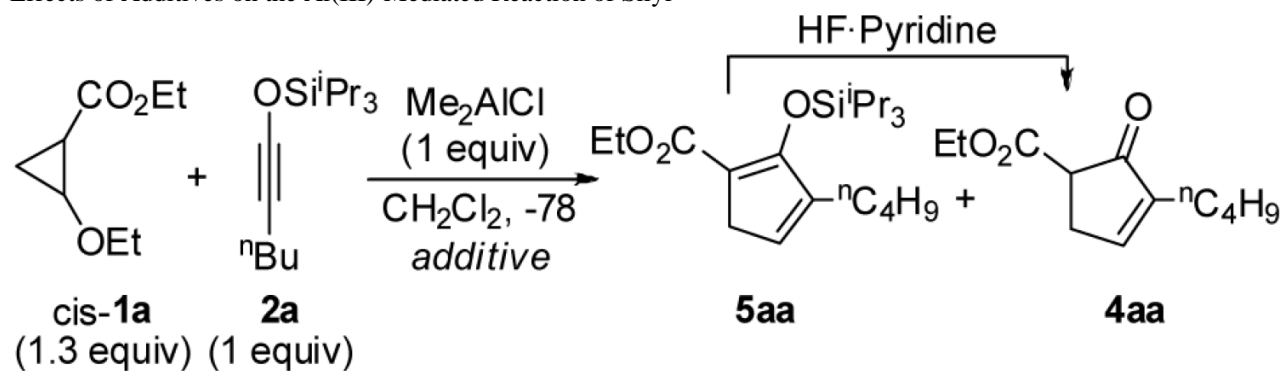
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- [11]. MeAlCl₂: 34% **4aa**; MAO: 11%; Et₂AlCl: 53%; Me₃Al, AlCl₃ and (EtO)₃Al: traces.
- [12]. Additional notes: a) The isolation of minor quantities of **A** from the reaction mixture indicates that the cycloaddition is stepwise. b) Lower yields were obtained with *tert*-butyl-diphenylsilyl ethers while *tert*-butyl-dimethylsilyl ethers could not be prepared in satisfactory yields. c) Similar yields are observed in dichloroethane. Substantially reduced yields are observed in chloroform. No reaction occurs in ether or THF.
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Scheme 1. Cycloaddition of ynoles with 1,3-dipoles derived from opening of donor-acceptor cyclopropanes. EWG = electron-withdrawing group.

Table 1

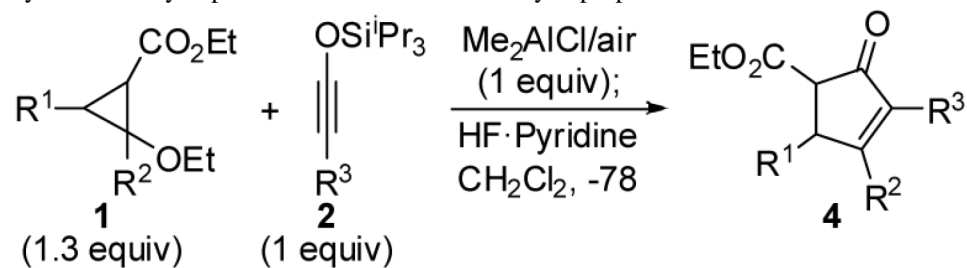
Effects of Additives on the Al(III)-Mediated Reaction of Silyl

Ynol Ethers with Cyclopropanes.^[a]

Entry	Me ₂ AlCl ^[b]	Additive	Time (h)	Yield (%) ^[c]
1	Freshly opened	None	28	74
2	Aged ^[d]	None	6	76
3	Freshly opened	H ₂ O (10 mol %)	24	64
4	Freshly opened	Air ^[e]	5	77
5	Freshly opened	MeOH (1 equiv)	3	70
6	Aged	Air ^[e]	5	74

^[a] 0.33M in **2**. Reactions carried out on 0.5 mmol scale.^[b] 1M solution in hexanes.^[c] Isolated yield of **4aa**.^[d] Opened several months prior to use^[e] 20 mL dry air bubbled through the reaction solution at 23 °C.

Table 2

Synthesis of Cyclopentenones from Ynolates and Cyclopropanes.^[a]

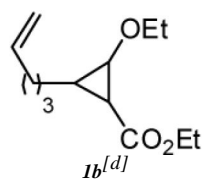
Entry	Cyclopropane	Ynolate
1	<i>cis-1a</i>	2a
2	<i>trans-1a</i>	2a
3	<i>cis-1a</i>	2b
4	<i>cis-1a</i>	2c
5	<i>cis-1a</i>	2d
6	<i>cis-1a</i>	2e
7	<i>cis-1a</i>	2f ^[c]
8	<i>cis-1a</i>	2g
9	<i>cis-1a</i>	2h
10	<i>cis-1a</i>	2i
11	<i>cis-1a</i>	2j
12	<i>cis-1a</i>	2k
13	<i>cis-1a</i>	2l

Entry

Cyclopropane

Ynolate

14

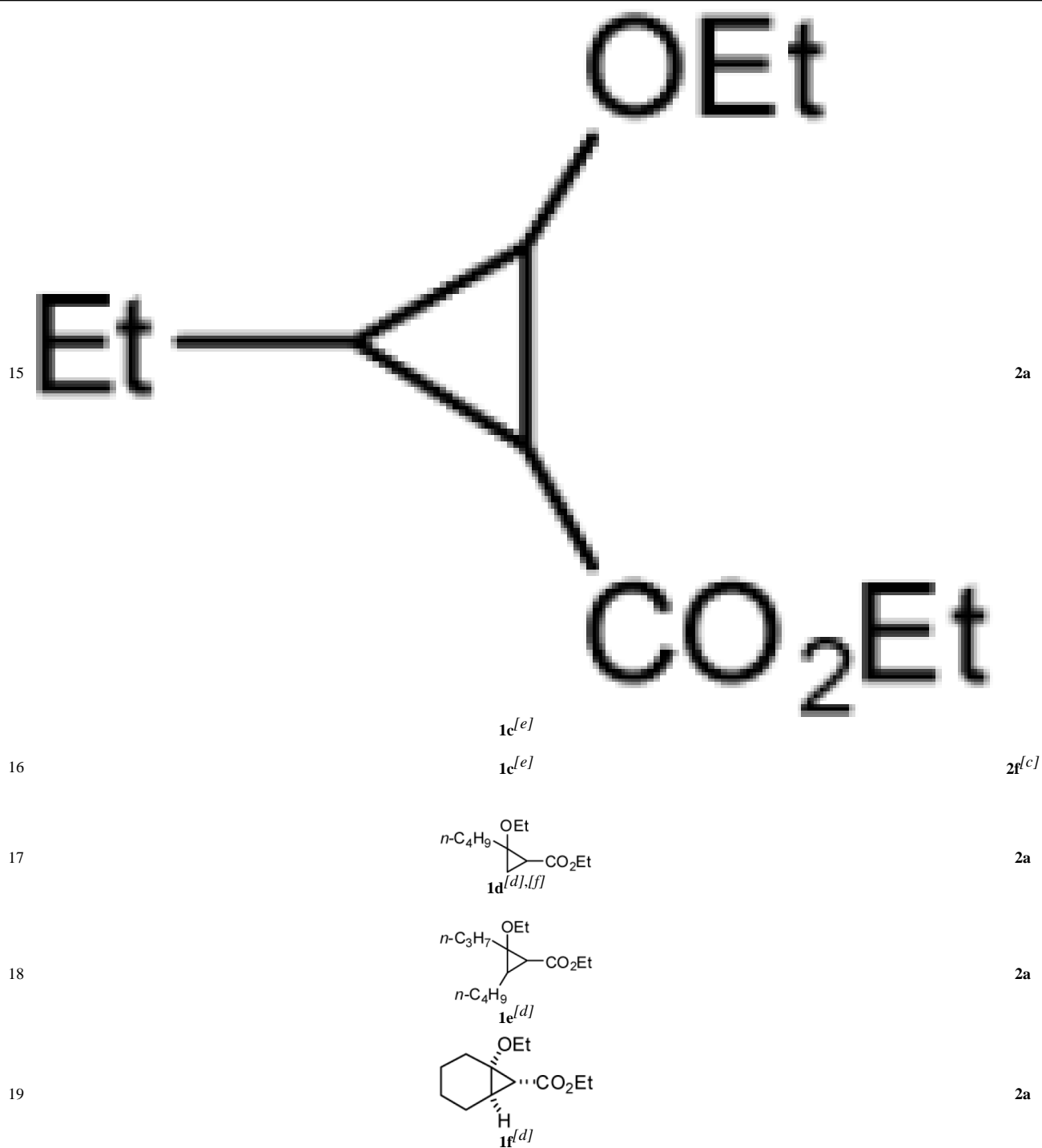


2a

Entry

Cyclopropane

Ynolate



[a] Reactions carried out on 1.0 mmol scale. Dry air (40 mL) bubbled through solution of Me₂AlCl at 23 °C prior to use. See supporting information for complete experimental details.

[b] Isolated yields.

[c] Ynolate **2f** was the bis-*(i*Pr)₃Si-ether.

[d] Single unassigned diastereomer.

[e] Mixture of diastereomers.

[f] 2.5 equiv **1d**.

[g] d.r. > 20:1.