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Nucleophilic Partners in the Tandem Conjugate Addition−Dieckmann Condensation Reaction: 1. Synthesis of 1,2,3-Trisubstituted Naphthalenes

Aaron D. Martinez, Jay P. Deville, Joel L. Stevens, and Victor Behar*

Department of Chemistry MS-60 Rice University, Houston, Texas 77251-1892

behar@rice.edu

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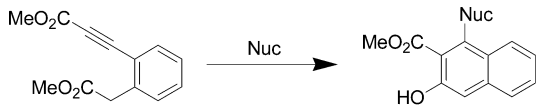
Abstract: The scope and limitations of the tandem conjugate addition−Dieckmann condensation for the construction of 1,2,3-trisubstituted naphthalenes is defined. Viable nucleophilic partners in this methodology include organocuprates, active methylenes, and a variety of heteroatom initiators.

Since the formal introduction of the Michael-induced ring-closing (MIRC) reaction concept by Little in 1980,[1] numerous accounts have appeared related to the utility of tandem reactions initiated by Michael addition to construct multicyclic arrays with remarkable atom economy.[2−5] We previously described the tandem conjugate addition−Dieckmann condensation strategy to access type II polyketide structures tetracenomycin A_2[6] and the lactonamycin ABCD-ring system.[7] The applicability of this reaction sequence to the construction of highly substituted naphthalenes was immediately recognized. Aside from traditional synthetic sequences to substituted naphthalenes such as the Stobbe condensation/Friedel−Crafts cyclization,[8] a recent method employing an anion-accelerated electrocyclization to construct 1-naphthols has been reported.[9] The general approach to substituted naphthalenes described herein involves the addition of a nucleophile to an appropriately substituted phenyl alkynyl ester with an ortho-disposed carbomethoxymethylene group (Figure 1). Dieckmann condensation and tautomerization affords fully aromatized 3-naphthol products.

With the promise of generating unnatural analogues of these polyketide structures, it was deemed necessary to define the scope and limitations of this tandem sequence.

TABLE 1.



1 **2a-n**

entry	nucleophile	time (h)	product	yield (%)
1	Me_2CuLi	1	**2a**	87
2	Bu_2CuLi	2.5	**2b**	80
3	$(Bu_3Sn)_2CuLi$	4	**2c**	recovered starting material
4	$NaCH(CO_2Me)_2$	4	**2d**	70
5	$NaCH_2NO_2$	3	**2e**	62
6	NaOPh	3	**2f**	65
7	*p*-MeOPhONa	4	**2g**	36
8	*p*-ClPhONa	2.5	**2h**	53
9	CH_2CHCH_2ONa	4	**2i**	complex mix
10	NaOAc	4	**2j**	recovered starting material
11	**$HCCCH_2ONa$**	**1.5**	**2k**	**75**
12	NaN_3	3	**2l**	53
13	PhSNa	12	**2m**	67
14	$(CuH{\cdot}Ph_3P)_6$	3.5	**2n**	84

The model substrate, diester **1**, has been previously described and was considered appropriate for studying the scope of the method. Initial experiments focused on the addition of carbon-based nucleophiles. As seen in Table 1, simple Gilman cuprate reagents[10] (entries 1 and 2) participate quite well in the reaction. Unfortunately, the corresponding stannyl cuprate reagents (entry 3) failed to give the desired cyclization product. Indeed, complete recovery of the starting material even under forcing conditions led to the conclusion that such nucleophiles were too hindered to participate in the reaction. In general, however, soft nucleophilic partners such as active methylene compounds add in smoothly as exemplified by addition of the anion of dimethylmalonate (entry 4) as well as the anion derived from nitromethane (entry 5).

Oxygen-based nucleophiles presented a significant challenge (entries 6−11). Phenolic anions initiate the cyclization in modest yields (entries 6−8). Access to biaryl ether structures by this method provides an interesting mild alternative to traditional Ullmann-type methods.[11] Harder oxygen nucleophiles (allyloxy anion, entry 9) failed to initiate the reaction presumably due to competing enolization of the benzylic ester and also in part due to active transesterification processes. Acetate (entry 10) was also a poor nucleophile for affecting cyclization. Success was finally achieved utilizing the alkoxide of a propargyl alcohol anion[12] (entry 11), and this reaction proceeded remarkably cleanly to afford cyclization adduct **2k** in 75% yield. Presumably the greater acidity of propargyl alcohol relative to its allyl counterpart provides

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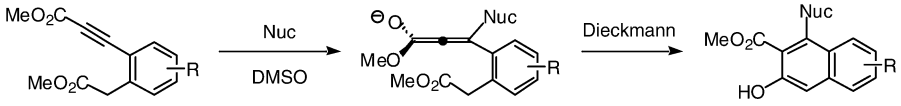

FIGURE 1. Tandem conjugate addition.

the softer nucleophilic character in its alkoxide required for desired conjugate addition rather than to compete with enolization. Confident in a method to introduce an oxygen-based nucleophile to gain access to phenolic structures, our attention turned to nitrogen nucleophilic sources. Addition of azide (entry 12) provides access to nitrogen-substituted naphthalenes in modest isolated yield. Compromised yields are observed due to the instability of the azide product upon silica gel chromatographic purification. As expected, thiolate (entry 13) adds in quite well as does the hydride-donating Stryker reagent (entry 14).[13]

The utility of this sequence in the construction of highly diverse naphthalene systems is realized by the ready conversion of the 3-substituted phenolic products to the corresponding triflate, which allows one to enter the manifold of a variety of palladium-catalyzed cross-coupling reactions.[14−24] Additionally, the resultant ester functionality at the 2-position gives access to a variety of latent functional groups. Finally, in addition to generating type II polyketide analogues by this methodology, the expansion of the tandem sequence to access a variety of substituted heteroaromatic systems, including indoles, quinolines, benzofurans, and benzothiophenes, is under investigation. The results of this work will be reported in due course.

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Supporting Information Available: Genereal procedures and preparation of all compounds **2a**,**b**,**d**−**h**,**k**−**n,** as well as copies of ^{1}H and ^{13}C NMR. This material is available free of charge via the Internet at http://pubs.acs.org.

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