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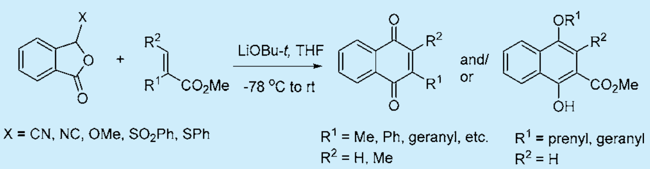
Synthesis of Vitamin K and Related Naphthoquinones via Demethoxycarbonylative Annulations and a Retro-Wittig Rearrangement

Dipakranjan Mal,* Ketaki Ghosh, and Supriti Jana

Department of Chemistry, Indian Institute of Technology, Kharagpur 721302, India

Supporting Information

ABSTRACT: Anionic annulations of 3-nucleofugal phthalides with α-alkyl(aryl)acrylates involving a demethoxycarbonylation provide a succinct synthesis of vitamin K and related naphthoquinones. Also reported is a new cascade reaction stemming from a Cope−retro-Wittig rearrangement. This cascade leads to direct formation of 1-hydroxy-4-prenyloxynaphthalene-2-carboxylates from the corresponding α-prenyl acrylate acceptors.



Vitamin K, a family of natural products, is of importance in many key biochemical processes of living systems, including blood coagulation, bone metabolism, and cell growth.[1,2] It is established that vitamin K is essential for proper formation of prothrombin which converts blood fibrinogen to fibrin that results in blood clots.[3] Vitamin K is also involved in a number of other biological processes, namely, maintenance of bone, early development of skeletal[4] and cellular growth.[5] In addition, vitamin K is shown to inhibit the growth of a number of tumor cell lines.[6] Structurally, the vitamin K series is menadione (**1**) with a divergent substitution at the C-3 position (Figure 1). For example, vitamin K_1 or phylloquinone (**3**) contains a 3-phytyl substituent, whereas vitamin K_2 or menaquinone (**2**) has repeating unsaturated isoprene units at C-3 position and they are denoted as MK-*n*, where *n* indicates the number of unsaturated isoprene units. In Figure 1 are presented the structures of the vitamin K series and some biologically important natural 1,4-naphthoquinones **4**−**7** which show antimicrobial,[7] anti-inflammatory,[8] antimalarial,[9] and cardiotonic activities. Vitamin K_3 (**1**) is a synthetic compound sometimes used as a nutritional supplement. It is widely used as a blood coagulating agent due to its *anti*-hemorrhagic effects and is a key intermediate in the synthesis of the other vitamins of group K. On an industrial scale, vitamin K_3 is produced by stoichiometric oxidation of 2-methylnaphthalene by CrO_3 in sulfuric acid. This method produces about 18 kg of toxic inorganic waste per 1 kg of target product.[10] Alternatively, a one-pot synthesis of vitamin K_2 from 3-phenylthioisobenzofuranone and alkenyl phenyl sulfone via anionic cycloaddition process lacks environmental efficiency as well as atom economy.[11] Direct coupling involving allylsilanes, allylstannanes, and stanylquinones was investigated in detail in the 1990s. More recently, Lipshutz et al. used a Ni(0)-catalyzed coupling between vinylalanes and chloromethylated 1,4-naphthoquinones as a route to vitamin K_1 and K_2.[12] Thus, the development of an environmentally friendly method for the production of substituted quinones continues to be a challenging goal.

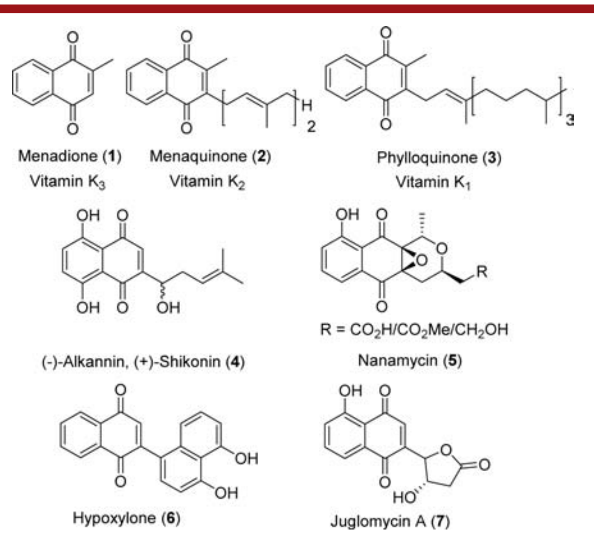


Figure 1. Vitamin K genre and some naturally occurring naphthoquinones.

In a recent report,[13] we described a demethoxycarbonylative annulation of α-substituted acrylates with phthalides for the regiocontrolled synthesis of polysubstituted 1-naphthols, wherein the demethoxycarbonylation occurred under base-promoted reaction conditions. In an extension of this study, we considered the use of a 3-nucleofugal phthalide (e.g., **8**) in the annulation for a direct entry to naphthoquinones. Since the nucleofugal group at C-3 increases the oxidation level, the resulting products would be 1,4-naphthoquinols, which, in turn, would be expected to yield 1,4-naphthoquinones on aerial oxidation. This study was

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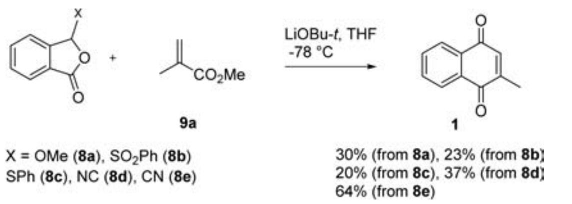
undertaken with the aim of achieving an efficient synthesis of vitamin K and similar naphthoquinones. Although the extension is perceptible in terms of tandem Michael−Dieckmann condensation, its success much depends on suppressing the competing reactions such as Michael addition and 1,2-addition that lead to dimerization. Sometimes, exceptional stability of the incipient carbanion of the phthalides leads to failure of the desired initial Michael addition.[14] Furthermore, the choice of bases and reaction conditions play crucial roles. For example, Brimble et al. and Donner et al. performed thorough studies to achieve successful annulations.[15] Initially, the reactivities of phthalides **8** with methyl methacrylate **9a** in the presence of LiOBu-*t* in dry THF at −78 °C (Table 1) were explored. The

Table 1. Bases Screened for the Annulation of 8e

entry	base/conditions (°C)	product	%yield
1	LiOBu-*t*/−60 to rt	1	64
2	LiHMDS/−78 to rt	1	20
3	LDA/−78 to rt	1	23
4	NaH/0 to rt		intractable mixture

reaction of readily accessible 3-methoxyphthalide (**8a**) with methyl methacrylate (**9a**) in the presence of LiOBu-*t* resulted in direct formation of the expected menadione (**1**) in 30% yield. As shown in Scheme 1, the reactions with phenylsulfonylphthalide

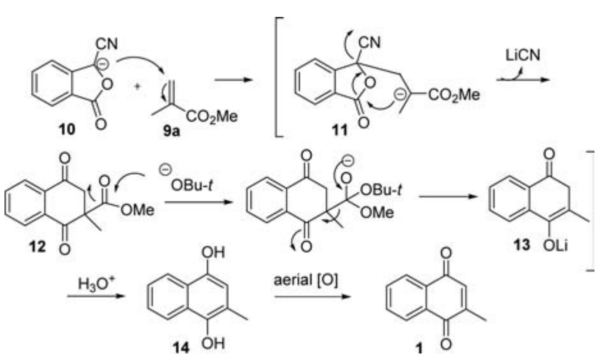
Scheme 1. Annulation Reaction of 3-Nucleofugal Phthalides with Acrylates and Base Screening



8b and phenylthiophthalide **8c** also gave menadione (**1**) in 23% and 20% yields, respectively. With the recently developed 3-isocyanophthalide (**8d**),[16] the yield of **1** was slightly higher. From the base screening study (Table 1), 3-cyanophthalide (**8e**) was found to be the best donor.

The formation of 2-methylnaphthoquinone (**1**) is explained by the electron-arrow mechanism shown in Scheme 2. At low temperature, the incipient phthalide anion **10** adds to the acrylate **9a** in Michael addition mode to form new anion **11**. This anion **11** then attacks at the phthalide carbonyl group resulting in

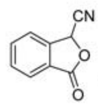
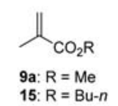
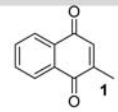
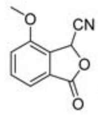
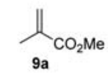
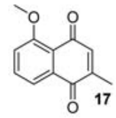
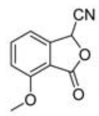
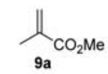
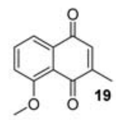
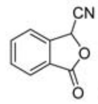
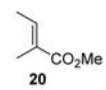
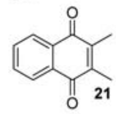
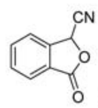
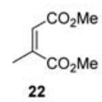
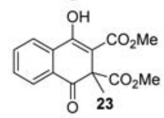
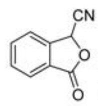
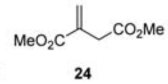
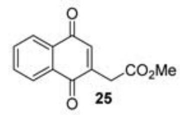
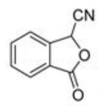
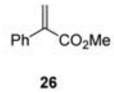
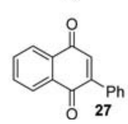
Scheme 2. Probable Mechanism for the Formation of 2-Methylnaphthoquinone



removal of lithium cyanide to produce dihydronaphthoquinone **12**. The nucleophilic attack of *tert*-butoxide anion at the ester carbonyl proceeds to effect demethoxycarbonylation and concomitant fragmentation to yield intermediate **13**. This then undergoes enolization to produce 1,4-naphthoquinol **14**, which transforms to quinone **1** via an aerial oxidation.

Enthused by our success in the above demethoxycarbonylative annulation (Scheme 1), we established the generality of the reaction with different phthalides and acrylates (Table 2). To

Table 2. Benzannulation of Substituted Acrylates with 3-Cyanophthalides[a]

entry	donor	acceptor	product	%yield
1	 8e	 9a: R = Me; 15: R = Bu-*n*	 1	64 (R = Me) 50 (R = Bu-*n*)
2	 16	 9a	 17	70
3	 18	 9a	 19	62
4	 8e	 20	 21	67
5	 8e	 22	 23	74
6	 8e	 24	 25	57
7	 8e	 26	 27	62

[a]Reaction conditions: LiOBu-*t*, dry THF, −78 °C to rt, 6−7 h. [b]10% 2-phenyl-3-cyanonaphthoquinone was obtained as a byproduct along with **27**.

evaluate the sensitivity of the dealkoxycarbonylation step to steric effects, we reacted butyl methacrylate (**15**) with 3-cyanophthalide (**8e**) (Table 2, entry 1). With LiOBu-*t* as base, it gave the desired menadione (**1**) in 50% yield. The lower yield suggests sensitivity of the annulation to steric effects. Under similar reaction conditions, cyanophthalide **16** underwent annulation with methyl methacrylate (**9a**) to produce methoxynaphthoquinone **17** in 70% yield (Table 2, entry 2).[17] Likewise, 2-methyl-8-methoxynaphthoquinone (**19**)[18] was formed in 62% yield when the annulation was carried out with 7-methoxycyanophthalide **18**[19] (Table 2, entry 3). When methyl tiglate **20** was reacted with 3-cyanophthalide **8e** in the presence LiOBu-*t*, dimethylnaphthoquinone **21** was formed in 67% yield (Table 2, entry 4). On the other hand, naphthoate **23** was formed in 74% yield when 2-methylmaleate **22** was subjected to annulation with cyanophthalide **8e**, and the corresponding demethoxycarbonylated product was not detected (Table 2, entry 5).

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Attempted demethoxycarbonylation of a purified sample of **23** with an excess amount of bases LiOBu-*t*, LiHMDS, or LDA was unsuccessful. A similar attempt, however, was successful when its *O*-methyl derivative was treated with LiOBu-*t*.[20] The contrasting reactivity of **23** and *O*-methyl derivative to LiOBu-*t*-promoted demethoxycarbonylation can be explained by the electrostatic repulsion of the oxyanion of **23** to addition of *tert*-butoxide anion to the ester carbonyl groups. With dimethyl itaconate (**24**), the desired naphthoquinone **25** was obtained in 57% yield (Table 2, entry 6). The reaction of 2-phenyl acrylate **26** with 3-cyanophthalide **8e** provided 2-phenylnaphthoquinone **27** in 62% yield (Table 2, entry 7).

For an entry to vitamin K structures, we developed a general synthesis of α-alkenyl acrylates **28a−f** in 2 steps starting from corresponding alkenyl bromides **29a−c**. Allylic bromides **29a−c** were treated with methyl 2-(diethoxyphosphoryl)acetate **30** in the presence of KOBu-*t* in dry DMF at 0 °C to rt for 20 h to give phosphonoacetates **31a−c** in 70−80% yields.

Wittig−Horner reaction of **31a−c** with paraformaldehyde or acetaldehyde in the presence of NaH furnished α-alkenyl acrylates **28a−f** in good yields (Scheme 3). When the simplest allyl acrylate **28a** was reacted with the 3-cyanophthalide **8e** in the presence of LiOBu-*t*, 2-allyl-1,4-naphthoquinone[21] (**33**) was obtained in 65% yield (Table 3, entry 1).

Scheme 3. Synthesis of α-Alkenylacrylates via Wittig−Horner Reactions

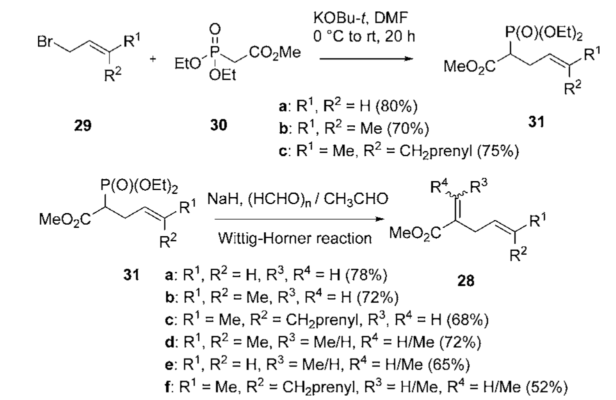
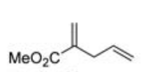
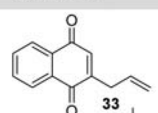
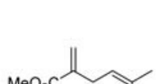
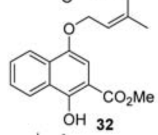
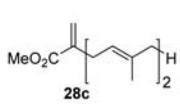
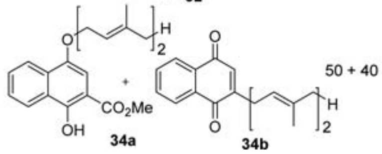


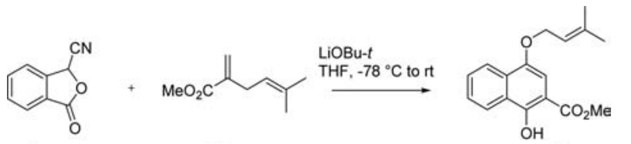
Table 3. Annulation of 8e with α-Allyl/Prenyl/Geranyl Acrylates 28a−c[a]

entry	acceptor	products	%yield
1	 **28a**	 **33**	65
2	 **28b**	 **32**	83
3	 **28c**	 **34a** + **34b**	50 + 40

[a]Reaction conditions: donor **8e**, base LiOBu-*t*, dry THF, −78 °C to rt, 6−7 h.

However, an interesting result emerged when α-prenyl acrylate **28b** was subjected to this annulation. 4-Prenyloxynaphthoate **32** (Scheme 4, Table 3, entry 2) was exclusively formed (83%) in place of the expected naphthoquinone. Similarly, the reaction of α-geranyl acrylate **28c** with phthalide **8e** under identical reaction conditions, produced 3-geranyloxynaphthoate **34a** and 2-geranyl-1,4-naphthoquinone **34b**[23] in a 5:4 ratio (Table 3, entry 3).

Scheme 4. Unusual Formation of 3-Prenyloxynaphthoate 32

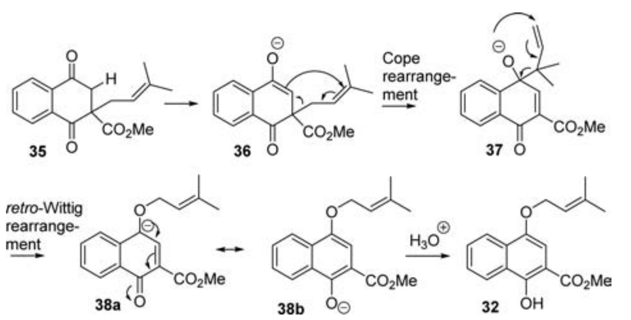


8e **28b** **32** (83%)[a,b]

[a]40% (with LDA); 52% (with LiHMDS); 32% (with NaHMDS); [b]Structure of **32** was confirmed by an independent synthesis. Methyl 1,4-dihydroxy-2-naphthoate was first synthesized[22] by Hauser annulation of **8e** and methyl acrylate. It was then selectively prenylated with prenyl bromide and K_2CO_3.

Formation of 3-prenyloxynaphthoate **32** can be explained by the mechanistic proposal in Scheme 5. Intermediate **35** is produced by the Michael addition followed by Dieckmann cyclization of 3-cyanophthalide **8e** and α-prenyl methacrylate **28b**. Thereafter, a Cope rearrangement of intermediate **36** occurs to form the oxy-anion **37**. A retro-Wittig rearrangement of anion **37** furnishes **32** after protonation. It appears that C-5 gem-substitution is one of the driving forces of the retro-Wittig rearrangement. The stability of the final product could be another.

Scheme 5. Plausible Mechanism for the Formation of 4-Prenyloxynaphthoate 32



The above rearrangement (Scheme 4) was prevented when an acrylate (**28d−f**) carried a β-methyl group. For all three cases studied, tetrahydronaphthoates (**39**, **41**, **43**) were intercepted. Under the reaction conditions, in situ demethoxycarbonylation did not occur. However, treatment of the tetrahydronaphthoates **39**, **41**, and **43** with LiOBu-*t* in refluxing THF furnished expected quinones **40**[24] and **42**[25] and vitamin K_2/menaquinone **2**,[26] respectively (Table 4, entries 1−3). For the naphthoquinone **40**, the yield was 45% and for prenyl analogue **42**, 55%. The overall yield of menaquinone (**2**) (5:3 mixture of *E* and *Z* isomer) was 26%.

In summary, we have shown that demethoxycarbonylative annulation of 3-nucleofugal phthalides with α-substituted acrylates produces a succinct route to 1,4-naphthoquinones, including vitamin K_2. This one-pot synthetic approach is

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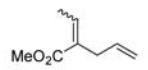
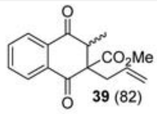
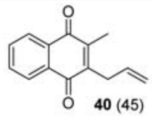
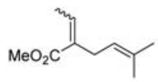
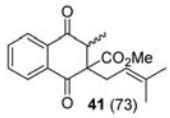
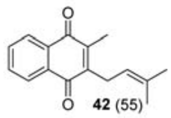
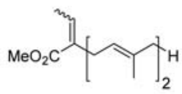
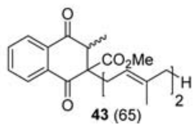
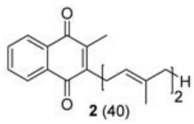
Table 4. Annulation of 8e with α-Allyl/Prenyl/Geranyl Acrylates 28d−f and Demethoxycarbonylation[a]

entry	acceptor	products (%yield)	demethoxy-carbonylation[b] (%yield)
1	 28e	 39 (82)	 40 (45)
2	 28d	 41 (73)	 42 (55)
3	 28f	 43 (65)	 2 (40)

[a]Reaction conditions: Donor **8e**, base LiOBu-*t*, dry THF, −78 °C to rt, 6−7 h. [b]2−3 equiv of LiOBu-*t*, dry THF, reflux, 3 h.

regiospecific. With further refinements, such a method would be industrially viable. More notably, *α*-prenyl/geranyl acrylates display an unprecedented cascade reaction involving Cope rearrangement and retro-Wittig rearrangement and lead to direct formation of 1-hydroxy-4-prenyl/geranyloxy-2-naphthoates.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02920.

Synthesis, analytical data, and NMR spectra (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: dmal@chem.iitkgp.ernet.in.

Notes

The authors declare no competing financial interest.

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