Conjugate Addition–Alkylations

Oxonitriles: Multicomponent Grignard Addition–Alkylations**

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Dedicated to Professor Edward Piers on the occasion of his retirement

Efficiently installing high molecular complexity is a fundamental pursuit in organic synthesis.[1] Several excellent strategies have emerged for installing multiple bonds in a single synthetic operation; bidirectional synthesis,[2] domino reactions,[3] biomimetic cascades,[4] and multicomponent reactions.[5] Each strategy exhibits complementary advantages, with multicomponent reactions benefiting from an inherent convergence that fulfills the synthetic criteria of assembling complex targets from fragments of similar size.[6]

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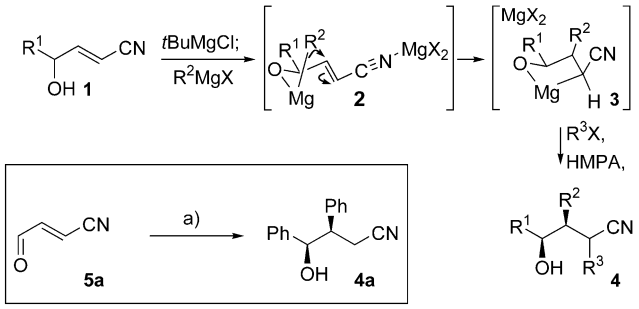
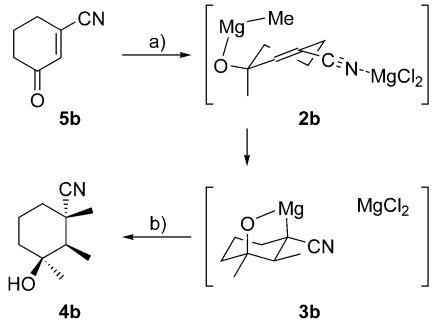
As a subclass of multicomponent reactions, conjugate addition–alkylation reactions install two new bonds and up to three stereocenters in a single synthetic operation.[7] Chelation-controlled conjugate addition–alkylations exhibit the additional advantage of promoting conjugate additions with less reactive Michael acceptors. The strategy is particularly effective for γ-hydroxyalkenenitriles (Scheme 1, **1**→**4**)[8] where chelation permits a facile conjugate addition–alkylation with a recalcitrant class of Michael acceptors that are unreactive toward many conventional nucleophiles.[9]



Scheme 1. Chelation-controlled conjugate additions to alkenenitriles. a) PhMgBr (3 equiv), THF, RT, 1.5 h, (58%).

The highly efficient chelation-controlled conjugate additions to γ-hydroxyalkenenitriles **1** stimulated a multicomponent variation with Grignard reagents and oxonitriles for potentially installing three new stereocenters in one operation (inset, Scheme 1). Conceptually, the addition of a Grignard reagent to the γ-oxonitrile **5a** was envisaged to directly generate an alkylmagnesium alkoxide intermediate **2**, which triggered conjugate addition and generated the dimagnesiated nitrile **3** for potential alkylation (Scheme 1). Addition of excess PhMgBr to oxonitrile **5a**[10] triggers sequential carbonyl and conjugate additions, generating **4a** as the sole stereoisomer.

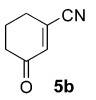
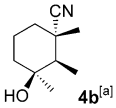
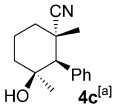
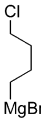
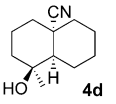
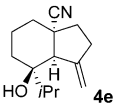
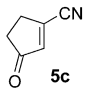
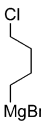
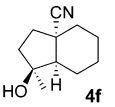
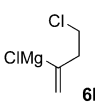
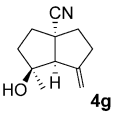
Although the formation of **4a** validates the multicomponent concept, optimizing the reaction was frustrated by the volatility and instability of **5a**.[10a] Attention was therefore redirected toward the more stable six-membered oxonitrile **5b**[11] (Scheme 2). Addition of excess methylmagnesium chloride to **5b** triggers the sequential carbonyl addition–conjugate addition affording the cyclic magnesiated nitrile **3b**.[8] Intercepting this formal dianion with methyl iodide installs a third stereocenter,[12] generating **4b** as a single stereoisomer.[13]



Scheme 2. Multicomponent addition–alkylation with oxonitrile **5b**. a) MeMgCl, THF, −78°C, 1 h; b) −78°C→RT, 2 h, MeI, 86%.

The efficient three-component addition–alkylation of **5b** is typical of the reactivity exhibited in a range of multicomponent reactions (Table 1). Grignard reagents react significantly faster with the carbonyl group than in the subsequent chelation-controlled conjugate addition, permitting the sequential addition of two different Grignard reagents, first to the ketone and second in the conjugate addition (Table 1, entry 2). Employing ω-haloalkyl Grignard

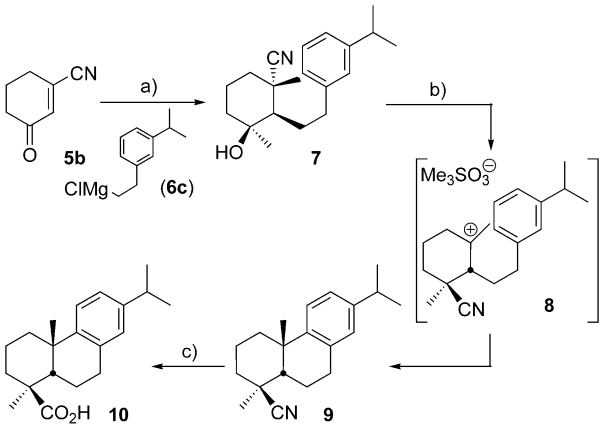
Table 1: Multicomponent oxonitrile conjugate addition–alkylations.

Entry	Oxonitrile	Reagents	Alkanenitrile	Yield [%]
1	 **5b**	MeMgCl, MeI	 **4b**[a]	86
2	 **5b**	MeMgCl, PhMgCl, MeI	 **4c**[a]	71
3	 **5b**	MeMgCl,  **6a**	 **4d**	53
4	 **5b**	*i*PrMgBr,  **6b**[b]	 **4e**	58
5	 **5c**	MeMgCl,  **6a**	 **4f**	53
6	 **5c**	MeMgCl,  **6b**[c]	 **4g**	50[b]

[a] Stereochemistry assigned by X-ray crystallography.[14] [b] Prepared by *i*PrMgCl exchange.[15] [c] An equivalent of *t*BuLi is added after addition of **6b** to promote conjugate addition through the ate complex.[16]

reagents, such as chlorobutylmagnesium bromide (**6a**) or the related Grignard reagent **6b**, for the conjugate addition allows a smooth annulation route to the *cis*-fused decalin **4d** and hydrindane **4e**, respectively (Table 1, entries 3 and 4, respectively). Similarly, carbonyl additions to the corresponding five-membered oxonitrile **5c**,[11] followed by addition of the ω-haloalkyl Grignard reagents **6a** and **6b**, generates nitrile-substituted hydrindane and octalin rings in one synthetic operation (Table 1, entries 5 and 6).

The rapid installation of three new stereocenters makes the multicomponent Grignard addition to oxonitriles ideally suited to terpenoid synthesis. Combining the multicomponent addition with cationic cyclization provides a particularly efficient entry to the dehydroabietic acid skeleton, several congeners of which exhibit antitumor, antibiotic, and cytotoxic actitvity.[17] Sequential addition of MeMgCl and Grignard **6c**[18] to **5b** followed by methylation with MeI installs the entire abietane carbon skeleton (Scheme 3).



Scheme 3. Multicomponent *epi*-dehydroabietic acid synthesis. a) MeMgCl, THF, 1 h; **6c**, −78 °C→RT; MeI, 2 h, 54%; b) Me_3SO_3H, $MeNO_2$, 0 °C, 1.5 h, 75%; c) NaOH, H_2O, diethylene glycol, 16 h, 170 °C; 6 h, 246 °C; HCl 90%.

Intramolecular Friedel–Crafts alkylation affords predominantly[19] the *cis*-abietane **9**, illustrating the advantage of the small, non-nucleophilic nitrile that permits arylation without prior interception of the carbocation intermediate **8** that occurs with the corresponding ester.[20] Nitrile hydrolysis completes the synthesis of *epi*-dehydroabietic acid **10**.[21]

Multicomponent Grignard addition–alkylations of oxonitriles rapidly assembles highly substituted mono- and bicyclic nitriles. Employing ω-haloalkyl Grignard reagents permits an efficient route to octalins, hydrindanes, and decalins with aryl-substituted Grignards being ideally suited for annulation by Friedel–Crafts alkylations. Collectively the strategy rapidly assembles a diverse array of cyclic nitriles, with complete control over the three stereogenic centers.

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