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One-pot sequential Baylis–Hillman and Michael reactions

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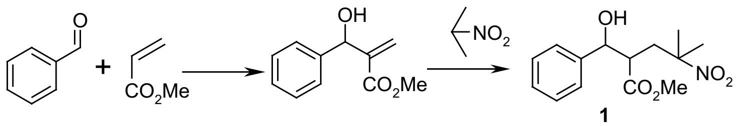
Abstract—A new one-pot procedure for the sequential Baylis–Hillman and Michael reactions has been developed to construct two carbon–carbon bonds with three components. This procedure has been applied to combine a variety of aromatic aldehydes, β-unsubstituted acrylates and activated methide nucleophiles to generate highly diversified and functionalized organic compounds.

Practical and efficient construction of highly functionalized and diversified molecules from readily available raw materials is a great challenge and highly desirable. Assembly of multiple components in a one-pot operation represents one of the possible avenues.[1] During our investigation for a practical synthesis of a developmental calcium receptor antagonist, we sought to transform the three readily available and inexpensive components of benzaldehyde, methyl acrylate and 2-nitropropane into molecule **1** (Scheme 1). We envisioned that the sequential Baylis–Hillman[2] and Michael reactions would represent a rapid and economical way to assemble these three components. To the best of our knowledge, there are no documented methods in the literature for one-pot, sequential Baylis–Hillman and Michael reactions to form two carbon–carbon bonds from three separate components. We report here our investigations on the one-pot, sequential Baylis–Hillman and Michael reactions and its application for the rapid construction of highly functionalized and diversified organic molecules from simple raw materials.

The Baylis–Hillman reaction is a superb example of an atom economic[3] and green[4] reaction. It has drawn considerable attention in the last few years due to its atom economy, potential catalytic nature, mild reaction conditions, toleration of oxygen and water as well as compatibility of diverse functionalities. In practice, the Baylis–Hillman reaction has several issues that have needed to be addressed, such as the use of stoichiometric instead of catalytic amounts of base, low yield and very long reaction times that range from days to weeks. More recent research on catalysts (Lewis base or Lewis acid), solvent systems and asymmetric catalysis has shined the light on the future development of this useful reaction.[5]

Aggarwal and Mereu[6] has demonstrated that 1,8-diazabicyclo[5.4.0]undec-7ene (DBU) is a far superior catalyst to the more commonly used base 1,4-diazabicyclo[2,2,2]-octane (DABCO). Fiftyfold rate accelerations were achieved when employing DBU instead of DABCO. Based on these observations, DBU was chosen as base catalyst for our studies.



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Scheme 1.

Keywords: Baylis–Hillman; Michael; Sequential; One-pot; DBU; Multi-component.

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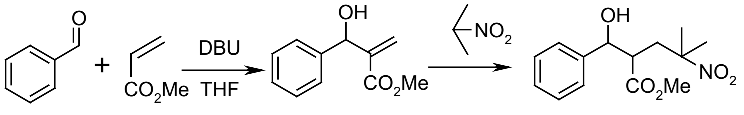
Considering the efficiencies of the Baylis–Hillman reaction, we reasoned that a catalytic, sequential Baylis–Hillman and Michael reaction without solvent would be an ideal atom economical and green process. To this end, we initially conducted our experiments at room temperature under solvent-free condition with DBU as the base catalyst. Thus, methyl acrylate was added to a mixture of aldehyde and DBU with evidence of a small exotherm and a formation of a viscous material. The Baylis–Hillman step proceeded smoothly and was complete in less than 5 h, as monitored by TLC and HPLC. Once complete, 2-nitropropane was added slowly to accomplish the subsequent Michael addition. Unfortunately, this step was highly exothermic and resulted in an even more viscous material which could not be properly stirred, thus causing local overheating. Although solvent-free conditions would be ideal, it was demonstrated to be unsafe and impractical. Simply adding a small amount of THF made the process more practical and eliminated the safety issues originating from the highly exothermic nature of the Michael reaction. However, addition of THF as solvent slowed the rate of the Baylis–Hillman reaction such that it now typically needed 2–24 h to achieve >95% conversion.[7] Even still, under our typical reaction conditions, the one-pot sequential Baylis–Hillman/Michael sequence afforded the desired product **1** in 60% isolated yield (Scheme 2).

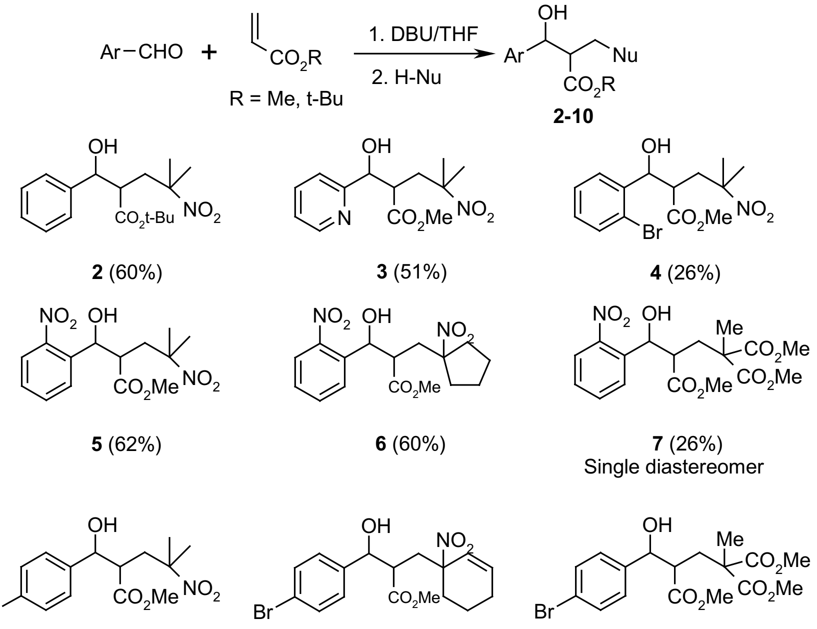
This multi-component procedure was successfully extended to a variety of functionalized aromatic aldehydes and nucleophiles. All reactions gave the desired products in good yields except for 2-bromo-benzaldehyde (26%), as shown in Scheme 3.[8] Roughly 50:50 mixtures of two diastereoisomers (*syn*/*anti*) were obtained in all reactions except for **9**, where an even mixture of all four diastereoisomers was produced, as determined by HPLC and LC–MS of the reaction mixture and ^{1}H NMR of the crude product. In addition, it was intriguing that one of the two diastereoisomers of molecules **7** and **10** was apparently unstable and disappeared during workup and silica chromatography. Only one pure diastereoisomer was obtained in 26% and 34% yield with **7** and **10**, respectively, although equal amounts of both diastereoisomers were detected while monitoring the reaction by HPLC, LC–MS and ^{1}H NMR. When 1-nitrocyclohexene was employed as the nucleophile, the Michael reaction proceeded by allylic deprotonation, followed by selective reaction at the α-carbon, to afford compound **9** as an even mixture of four diastereoisomers in 68% yield after silica chromatography.

It is worth pointing out that nucleophiles with more than one acidic proton, such as nitromethane and Meldrum's acid, gave complex reaction mixtures. With β-substituted acrylates, such as methyl crotonate, methyl



1 (60% isolated yield)

Scheme 2.



2 (60%)

3 (51%)

4 (26%)

5 (62%)

6 (60%)

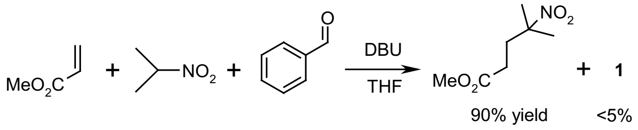
7 (26%)
Single diastereomer

8 (55%)

9 (68%)

10 (34%)
Single diastereomer

Scheme 3.



Scheme 4.

trans-cinnamate and ethyl 3,3-dimethyl acrylate, unfortunately, no Baylis–Hillman reaction occurred. Using the less reactive aldehyde 4-methoxybenzaldehyde gave, not surprisingly, no Baylis–Hillman product under these conditions. With DABCO as catalyst, only 2-nitro-benzaldehyde gave 60% yield of the desired Baylis–Hillman and Michael adduct; the other aromatic aldehydes stopped after the Baylis–Hillman reaction and afforded no Michael adducts. The reverse sequential sequence, Michael addition then Aldol condensation (i.e., DBU, methyl acrylate and 2-nitropropane were mixed first, and the aldehyde introduced later), gave no substantial desired product **1** (<5%). Instead, the Michael addition product was isolated in 90% yield (Scheme 4).

In conclusion, we have developed a new one-pot procedure to assemble an aromatic aldehyde, a β-unsubstituted acrylate and a methide nucleophile. With the numerous commercially available aldehydes, β-unsubstituted acrylates and activated methide nucleophiles, this one-pot procedure of sequential Baylis–Hillman and Michael reactions will be a useful tool for generating highly functionalized and diversified organic molecules.

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7. Typical procedure: To a solution of benzaldehyde (1 g, 1.0 equiv) in THF (2 mL) were added DBU (1.0 equiv) and methyl acrylate (1.1 equiv) subsequently. The resulting solution was stirred at ambient temperature for 16 h. 2-Nitropropane (1.2 equiv) was slowly introduced into the reaction solution and stirred for another 3 h. The reaction mixture was concentrated to dryness and purified by silica gel chromatography to afford the desired product as a diastereomeric mixture.
8. All compounds were charaterized spectroscopically. Compound **9** (four diastereoisomers): ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.5–7.4 (m, 2H, aromatic), 7.2–7.1 (m, 2H, aromatic), 6.1–5.9 (m, 1H, olefinic), 5.8–5.6 (two sets, m, 1H, olefinic), 4.8–4.6 (two sets, dd+d, 1H, CH–O), 3.6–3.5 (four peaks, s, 3H, CH$_3$–O), 3.1 (br, 1H), 2.85–2.65 (m, 1H, CH–CO$_2$), 2.6–1.5 (m, 8H, 4 × CH$_2$). ^{13}C NMR (400 MHz, CDCl$_3$): δ 174.6 (174.4), 140.3 (140.2, 140.1), 134.9 (134.8, 134.7, 134.6), 132.2 (131.9, 131.8), 128.5 (128.4, 128.2), 125.6 (125.4, 125.3, 125.1), 122.7 (122.3), 88.6 (88.5), 75.6 (74.1), 52.5 (52.4), 49.0 (48.7, 48.6), 39.8 (39.6, 37.8, 37.6), 32.4 (31.8, 31.7, 31.4), 24.9, 19.0. MS 420, 422 (M$^+$+23).