An Efficient DABCO-Catalyzed Ireland–Claisen Rearrangement of Allylic Acrylates

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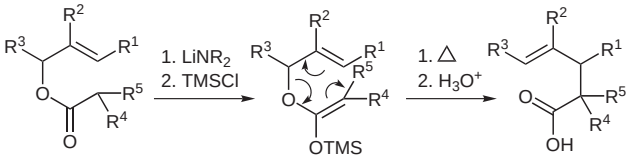
Abstract: A novel DABCO-catalyzed Ireland–Claisen [3,3]-rearrangement of allylic acrylates to give α-methylene-γ,δ-unsaturated carboxylic acids in the presence of an excess of TMSCl and DBU in refluxing acetonitrile was developed. The protocol provides an easy entry to α-methylene-γ,δ-unsaturated carboxylic acids from allylic alcohols in good yields.

Key words: DABCO, allylic acrylates, Ireland–Claisen rearrangement, α-methylene-γ,δ-unsaturated carboxylic acids

The thermal sigmatropic rearrangement of allyl vinyl ethers, referred to as the Claisen rearrangement,[1] provides an excellent route to γ,δ-unsaturated carbonyl compounds from allylic alcohols. Among numerous variants, the Ireland–Claisen rearrangement of allylic esters has attracted much attention since its discovery in 1972 by Ireland and Mueller.[2,3] Generally, the allylic ester is first deprotonated with a strong base like LDA to give the corresponding enolate. In order to avoid the possible aldol side reactions under these basic conditions, the enolates are usually transformed to silylketene acetals in the presence of a silylating agent prior to the rearrangement.[3] The subsequent Ireland–Claisen rearrangement proceeds to provide, after hydrolysis of the silyl ester, a γ,δ-unsaturated carboxylic acid (Scheme 1).



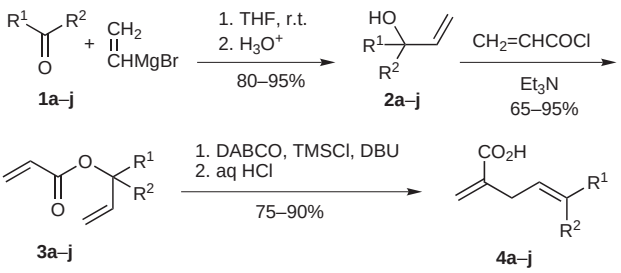
Scheme 1

In contrast to the classical Claisen rearrangement, the ester Ireland–Claisen rearrangement can be induced under much milder conditions, often at below ambient temperatures, thus allowing the reaction to convert acid-sensitive and thermally unstable molecules.[3] In fact, the Ireland–Claisen rearrangement has been frequently exploited as a key step in synthesis of many naturally occurring and/or biologically interesting compounds. Recent examples include the herbertane sesquiterpenes,[4] (–)-dactylolide,[5] Pro-Pro *E*-alkene dipeptide isostere,[6] anticancer agent roseophilin[7] and 1,22-dihydroxynitianes.[8]

By far the most frequently employed method for the stereoselective generation of either *Z*- or *E*-configured ester enolates has been the deprotonation using a strong base. Several other strategies have also been developed,[3] such as conjugate additions of organometallic nucleophiles to allyl acrylates and trapping the enolate intermediates as silylketene acetals,[3c] and dimerization of allyl acrylates to the dimeric silylketene acetals via electrochemical reduction.[9] All of these require stoichiometric quantities of reagents.

In 1993, Inanaga reported the first example of a tricyclohexylphosphine-catalyzed Ireland–Claisen rearrangement.[10] This provided an efficient entry to α-methylene-γ,δ-unsaturated carboxylic acids. Thomas and Smith successfully utilized this method as a key step in an approach to a synthesis of galbonolide B.[11]

Herein, we report the use of 1,4-diaza-bicyclo[2.2.2]octane (DABCO) as a nucleophilic catalyst in the Ireland-type [3,3]-rearrangement of a range of allylic acrylates. Being a moderately hindered weak base yet a nucleophile, DABCO has well been applied for catalyzing the Baylis–Hillman reaction[12,13] and N-methylation of indoles with dimethyl carbonate.[14] This novel method for effecting the Claisen rearrangement is of interest considering the fact that trialkylphosphines are generally very expensive and the use of them is often found to be rather inconvenient due to their propensity to oxidation.



Scheme 2

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The synthetic sequence is depicted in Scheme 2. The allylic alcohols **2** required for the generation of esters **3** were readily obtained from the Grignard addition reaction of vinylmagnesium bromide to the corresponding aldehydes or ketones **1** in THF, except for linalool (**2g**), which was commercially available. The synthesis of the corresponding acrylates **3** was accomplished by the reaction of acryloyl chloride with the alcohols **2** in the presence of catalytic amounts of triethylamine in moderate to high yields.[17]

The rearrangement of esters **3** were carried out with DABCO as the catalyst under conditions comparable to those described by Inanaga.[10] Thus, **3a** was treated with DABCO (0.2 equiv), trimethylsilyl chloride (TMSCl, 3.0 equiv), and DBU (2.0 equiv) in acetonitrile under reflux. The reaction was monitored by TLC and the rearrangement was complete after seven hours. Acidic work-up furnished the α-methylene-4-octenoic acid (**4a**) in 84% isolated yield.[15] We found also that the addition of DABCO was indispensable for the reaction, even though DBU is a comparable nucleophile.[16]

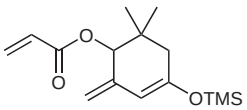
Several other organic bases, such as Et_3N, *i*-Pr_2NEt and DMAP as well as PPh_3 were also examined to promote the rearrangement. However, under a variety of different conditions, no or unacceptable yields of the desired products were obtained. This might be due to the decrease of nucleophilicity in comparison with DABCO.

This result encouraged us to explore the generality of our method. A range of allylic esters were then subjected to the Ireland–Claisen rearrangement according to our protocol, including the esters derived from secondary and tertiary allylic alcohols carrying aliphatic, olefinic and aromatic substituents. In general, all of the reactions tested worked well and the unsaturated carboxylic acid products were obtained in high yields after 7–15 hours. The results are summarized in Table 1. The configurations of compounds **4** were unambiguously determined either through data comparison with the literature reports or via analysis of ^{1}H NMR, ^{13}C NMR, and 2D NMR spectra.[17]

As shown in Table 1, the diastereoselective rearrangement delivered products with exclusive *E*-configuration in the case of secondary allyl esters (Table 1, entries 1–3), or, in the case of tertiary esters, preferentially *E*-configured acids (Table 1, entries 4, 6, 7). The predominance of *E*-products can be accounted for by a plausible chair-shaped transition state with the more sterically demanding group adopting the pseudo-equatorial position (see below).[18]

Worthy of note is that in the reaction of vinyl- and phenyl-substituted allyl esters **3i** and **3j** migration of the α-methyleno double bond to the aliphatic chain occurred under our conditions, affording the fully conjugated carboxylic acids **4i** and **4j**, respectively (Table 1, entries 9, 10).

To further test the applicability of the protocol, we examined the molecular transformation of **3k**, which was easily prepared from 4-hydroxy-3,5,5-trimethylcyclohex-2-enone. It can be envisaged that in the presence of large quantities of trimethylsilyl chloride **3k** would give the silyloxy diene **5** (Figure 1) with concurrent formation of the required structure for Ireland–Claisen rearrangement. Indeed, the rearranged product **4k** was formed after 24 hours by employing 0.3 equivalents of DABCO, 10.0 equivalents of TMSCl and 3.0 equivalents DBU. Apparently, the initial rearrangement product isomerized under the reaction conditions. However, the reaction proceeded to provide a low (15%) yield of the product with 85% conversion. Most of the substrate had suffered decomposition as indicated by the isolation of the starting alcohol in 55% yield (Table 1, entry 11). Instead of DABCO, tricyclohexylphosphine was found to be more active, leading to the formation of **4k** in 75% yield (Table 1, entry 12).



5

Figure 1

Table 1 DABCO-Catalyzed Ireland–Claisen Rearrangement of Allylic Acrylates[a]

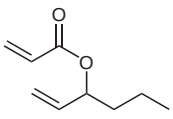
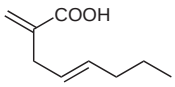
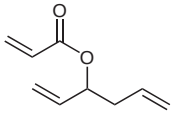
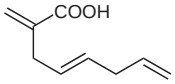
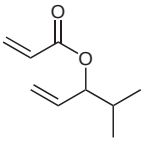
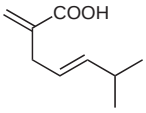
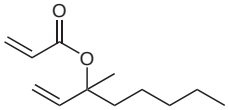
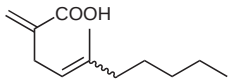
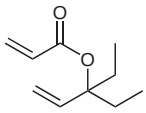
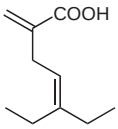
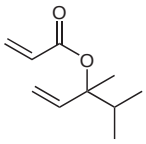
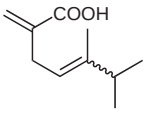
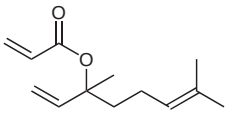
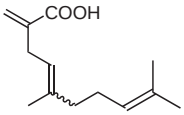
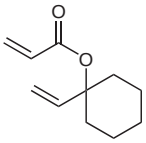
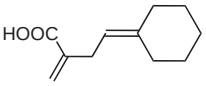
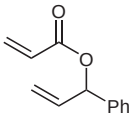
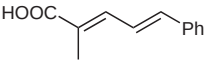
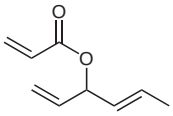
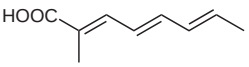
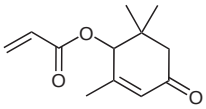
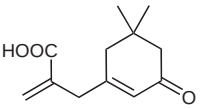
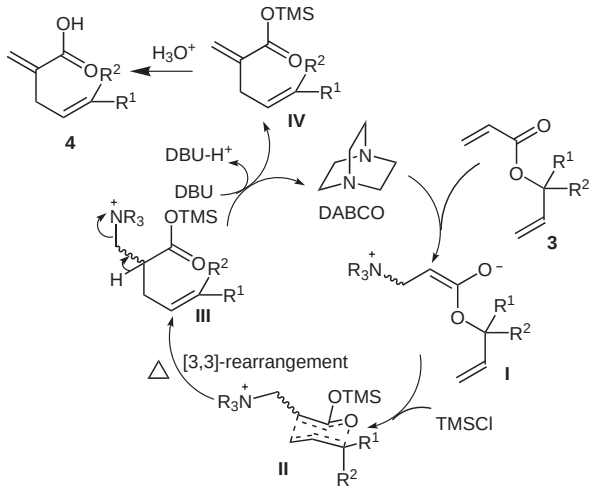
Entry	Substrate	Time (h)	Product	Yield (%)[b,c]	*E*:*Z* ratio[d]
1	 **3a**	7	 **4a**	84[b]	>99:1
2	 **3b**	7	 **4b**	80[b]	>99:1

Table 1 DABCO-Catalyzed Ireland–Claisen Rearrangement of Allylic Acrylates[a] (continued)

Entry	Substrate	Time (h)	Product	Yield (%)[b,c]	*E*:*Z* ratio[d]
3	 **3c**	7.5	 **4c**	86[b]	>99:1
4	 **3d**	12	 **4d**	75[b]	53:47
5	 **3e**	10	 **4e**	82[b]	
6	 **3f**	13	 **4f**	81[b]	80:20
7	 **3g**	15	 **4g**	79[b]	61:38
8	 **3h**	12	 **4h**	85[b]	
9	 **3i**	8	 **4i**	88[c]	>99:1
10	 **3j**	8.5	 **4j**	90[c]	>99:1
11[e]	 **3k**	12	 **4k**	15[b]	
12[f]	**3k**	12	**4k**	75[b]	

[a] The reaction was carried out in MeCN under reflux, using DABCO (0.2 equiv), TMSCl (3.0 equiv), and DBU (2.0 equiv).
[b] Isolated yield by chromatography.
[c] Isolated yield by recrystallization.
[d] The *trans*/*cis* ratio by GC.
[e] DABCO (0.3 equiv), TMSCl (10.0 equiv), and DBU (3.0 equiv) were used. Conversion reached 85%. 4-Hydroxy-3,5,5-trimethylcyclohex-2-enone was isolated in 55% yield.
[f] PCy_3 (0.2 equiv), TMSCl (10.0 equiv), and DBU (2.5 equiv) were used. Conversion reached 100%. 4-Hydroxy-3,5,5-trimethylcyclohex-2-enone was isolated in 5% yield.



Scheme 3 Reaction mechanism for the DABCO-catalyzed rearrangement of allylic acrylates

Like the trialkylphosphine as the catalyst,[10] the following mechanistic rationale for the DABCO-catalyzed Ireland–Claisen rearrangement of allylic acrylates was proposed (Scheme 3). In this reaction, DABCO functions as a nucleophile to first react with allyl acrylates and to generate the zwitterions **I**, which are intercepted by TMSCl to give intermediate ammonium allyl silyl ketene acetals **II**. In refluxing acetonitrile, **II** undergo [3,3]-sigmatropic rearrangement resulting in the formation of the silyl ester ammonium salt **III**. A chair conformation would be preferred for the cyclic transition state with the larger substituent R^1 in the less-hindered pseudoequatorial position. In the presence of the strongly hindered DBU, successive deprotonation of **III** occurs to regenerate DABCO as the catalyst and to furnish the silyl α-methylene-γ,δ-unsaturated carboxylates **IV**. Final hydrolytic desilylation of **IV** provides the α-methylene-γ,δ-unsaturated carboxylic acids **4**.

In summary, we have established a novel, DABCO-catalyzed Ireland–Claisen rearrangement leading to α-methylene-γ,δ-unsaturated carboxylic acids. The protocol accepts a wide range of allylic acrylates with good to high yields. The products feature densely functionalized compounds enabling easy further transformation. For example, they can be employed as precursors for the constructions of α-methylene-γ-butyrolactones,[10,19] a family that has created considerable attention over the years since this kind of ring is a ubiquitous subunit in a wide variety of biologically active natural products.[20] Our protocol is especially attractive since the reaction conditions are mild, and all of the reagents are inexpensive and oxygen-insensitive, hence without the necessity for rigorous solvent purification and degassing associated with the use of trialkylphosphines. We are currently investigating the scope and limitations of this DABCO-catalyzed process with respect to other unsaturated allylic esters as substrates. Promising results have been achieved and will be reported in the near future.

Acknowledgment

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(13) The unexpected superiority of DABCO over more basic tertiary amine catalysts in the Baylis–Hillman reaction between acrylamide and aldehydes has been reported. See: Faltin, C.; Fleming, E. M.; Connon, S. J. *J. Org. Chem.* **2004**, *69*, 6496.
(14) Shieh, W.; Dell, S.; Bach, A.; Repič, O.; Blacklock, T. J. *J. Org. Chem.* **2003**, *68*, 1854.
(15) **General Procedure of the Rearrangement.**
A reaction flask was charged with the allylic acrylate **3** (32.4 mmol), DABCO (0.73 g, 6.5 mmol), TMSCl (10.58 g, 97.4 mmol), DBU (9.90 g, 65.0 mmol) and MeCN (75 mL). The mixture was heated under reflux and the reaction was monitored by GC or TLC until the reaction was complete (reaction time as specified in Table 1). Then, the volatiles were removed under reduced pressure. The residue was suspended in Et_2O (100 mL) and stirred with 3 N HCl (40 mL) for a couple of minutes. The organic layer was separated, and washed sequentially with brine and H_2O, dried over anhyd $MgSO_4$ and concentrated in vacuo. The residue was purified by column chromatography or subjected to bulb-to-bulb distillation or recrystallization from EtOH to afford the pure compounds **4a**–**h** as a colorless oil and **4i**–**j** as a white solid (Table 1).
(16) Ghosh, N. *Synlett* **2004**, 574.

(17) All new compounds have been isolated in pure form and characterized by spectral data (NMR, IR and MS).
Selected Data for Compounds 4.
Compound **4c**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 12.23 (br, 1 H), 6.33 (s, 1 H), 5.67 (br s, 1 H), 5.52 (dd, *J* = 15.5, 6.1 Hz, 1 H), 5.42 (dt, *J* = 15.5, 6.1 Hz, 1 H), 2.99 (d, *J* = 6.1 Hz, 2 H), 2.30 (dsept, *J* = 6.1, 6.8 Hz, 1 H), 1.00 (2 d, *J* = 6.8 Hz, 6 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.0 (s), 140.5 (d), 139.5 (s), 127.3 (t), 123.0 (d), 34.1 (t), 31.1 (d), 22.4 (2q). IR (KBr): ca. 3000, 1698, 1436, 1289, 1158, 952 cm^{-1}. MS (EI): *m/z* = 154 $[M]^+$, 111 $[M - C_3H_7]^+$.
Compound **4e**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = ca. 11.1 (br, 1 H), 6.32 (s, 1 H), 5.68 (s, 1 H), 5.15 (t, *J* = 7.2 Hz, 1 H), 3.03 (d, *J* = 7.2 Hz, 2 H), 2.08 (br q, *J* = 7.5 Hz, 2 H), 2.07 (q, *J* = 7.5 Hz, 2 H), 1.03 (t, *J* = 7.5 Hz, 3 H), 0.97 (t, *J* = 7.5 Hz, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.1 (s), 145.6 (s), 139.5 (s), 126.9 (t), 118.2 (d), 29.2 (2 t), 23.2 (t), 12.1 (q), 12.8 (q). IR (KBr): ca. 3000, 1698, 1629, 1434, 1283, 1155, 954 cm^{-1}. MS (EI): *m/z* = 168 $[M]^+$, 139 $[M - C_2H_5]^+$.
Compound **4f** (major *trans*-isomer): ^{1}H NMR (300 MHz, $CDCl_3$): δ = ca. 11.0 (br, 1 H), 6.31 (s, 1 H), 5.65 (s, 1 H), 5.23 (t, *J* = 7.2 Hz, 1 H), 3.01 (d, *J* = 7.2 Hz, 2 H), 2.30 (sept, *J* = 6.8 Hz, 1 H), 1.60 (s, 3 H), 1.03 (2 d, *J* = 6.8 Hz, 6 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.1 (s), 144.1 (s), 139.1 (s), 126.8 (t), 117.6 (d), 36.8 (d), 29.4 (t), 21.4 (2q), 13.3 (q). IR (KBr,): ca. 3000, 1695, 1630, 1434, 1284, 1156, 952 cm^{-1}. MS (EI): *m/z* = 168 $[M]^+$, 125 $[M - C_3H_7]^+$.
Compound **4j**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.34 (d, *J* = 11.4 Hz, 1 H), 6.55 (dd, *J* = 14.7, 10.5 Hz, 1 H), 6.39 (dd, *J* = 14.7, 11.4 Hz, 1 H), 6.22 (dd, *J* = 14.1, 10.5 Hz, 1 H), 5.96 (dq, *J* = 14.1, 6.8 Hz, 1 H), 1.95 (s, 3 H), 1.85 (d, *J* = 6.8 Hz, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.7 (s), 141.0 (2 d), 135.0 (d), 131.6 (d), 125.2 (d), 125.0 (s), 18.6 (q), 12.3 (q). IR: (KBr): ca. 3000, 1678, 1601, 1427, 1316, 1268, 987, 929 cm^{-1}. MS (EI): *m/z* = 152 $[M]^+$, 107 $[M - CO_2H]^+$.
Compound **4k**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.47 (s, 1 H), 5.92 (s, 1 H), 5.75 (s, 1 H), 3.19 (s, 2 H), 2.24 (s, 2 H), 2.22 (s, 2 H), 1.05 (s, 6 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 28.3 (2 q), 33.7 (s), 39.6 (t), 43.8 (t), 51.0 (t), 125.8 (d), 130.3 (t), 136.0 (s), 161.1 (s), 171.1 (s), 200.6 (s). IR: (KBr): ca. 3000, 2929, 1720, 1667, 1372, 1160, 982 cm^{-1}. MS (EI): *m/z* = 208 $[M]^+$, 163 $[M - CO_2H]^+$.

(18) For a computational study on boat or chair preferences in the Ireland–Claisen rearrangements of cylohexenyl silyl ketene acetals, see: Khaledy, M. M.; Kalani, M. Y. S.; Khuong, K. S.; Houk, K. N. *J. Org. Chem.* **2003**, *68*, 572.

(19) For a review on this topic, see: Hoffmann, H. M. R.; Rabe, J. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 94.

(20) Cateni, F.; Zilic, J.; Zacchigna, M.; Bonivento, P.; Frausin, F.; Scarcia, V. *Eur. J. Med. Chem.* **2006**, *41*, 192; and references cited therein.