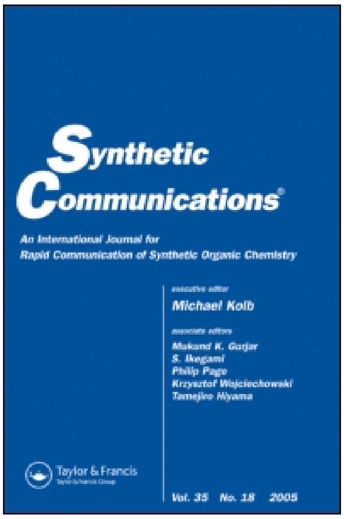

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# TANDEM CONSTRUCTION OF CARBON-CARBON AND CARBON-OXYGEN BONDS IN THE BAYLIS-HILLMAN CHEMISTRY: SYNTHESIS OF FUNCTIONALIZED *dl-BIS*-ALLYL ETHERS

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# TANDEM CONSTRUCTION OF CARBON–CARBON AND CARBON–OXYGEN BONDS IN THE BAYLIS-HILLMAN CHEMISTRY: SYNTHESIS OF FUNCTIONALIZED *dl-BIS*-ALLYL ETHERS

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## ABSTRACT

Tandem coupling between acrylonitrile and aryl aldehydes under the catalytic influence of DABCO involving the construction of two carbon–carbon bonds and one carbon–oxygen bond leading to the synthesis of *dl*-functionalized *bis*-allyl ethers has been described.

Synthesis of molecules with symmetry and functionalities in a meticulous manner has been one of the major sources for the success and growth of the present day organic synthesis.[1–3] Stereoselective construction of carbon–carbon and carbon–hetero atom bonds has been and continues to be one of the most fundamental reactions in organic chemistry and hence

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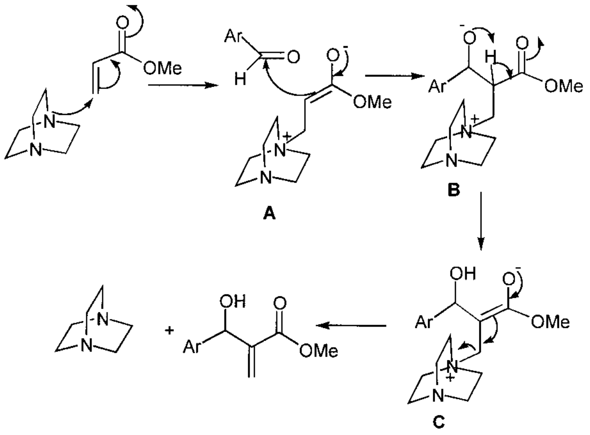
represents a forefront of research in synthetic organic chemistry.[4–10] We herein report tandem construction of two carbon–carbon bonds and one carbon–oxygen bond via the DABCO induced tandem coupling between acrylonitrile and aryl aldehydes under the extended Baylis-Hillman reaction conditions thus providing a simple synthesis of functionalized *dl*-*bis*-allyl ethers with C-2 symmetry.

The Baylis-Hillman reaction is an emerging carbon–carbon bond forming reaction producing synthetically useful molecules containing chemospecific functional groups, whose applications in a number of stereoselective transformations have been well documented in the literature.[11–23] The mechanism of this reaction is believed to proceed through the initial Michael type addition of DABCO to the activated alkene followed by the aldol type reaction of the resultant zwitterion enolate (**A**) to aldehyde to produce the zwitterion (**B**) which suffers a proton migration and subsequent elimination of the catalyst (DABCO) provides the desired densely functionalized molecules (Scheme 1).

It occurred to us that if we can use the oxygen anion (**B** in Scheme 1) in further controlled reaction with the product there will be also the formation of C–O bond in the Baylis-Hillman conditions leading to the generation of an interesting class of molecules with more functionalities. A careful literature survey reveals that ethers are formed as side products in the Baylis-Hillman reaction of methyl acrylate and formaldehyde (Equation 1).[24,25] However, to the best of our knowledge there is no report in literature on a similar reaction with other aldehydes leading to the formation of *bis*-allyl ethers. We have therefore undertaken this



*Scheme 1.*

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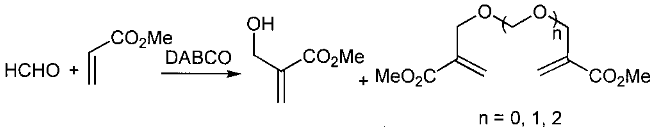
project of examining the reaction between aryl aldehydes and acrylonitrile under the Baylis-Hillman conditions with a view that *bis*-allyl ethers can be synthesized in one-pot operation and if possible they can be isolated in stereochemically pure form.



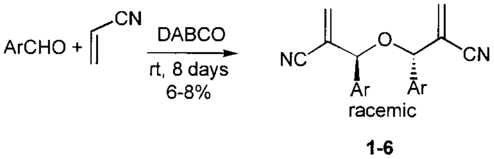
(1)

During our studies in this direction we have carried out number of experiments. We have obtained a very fascinating result when we have carried out the Baylis-Hillman coupling reaction of acrylonitrile with benzaldehyde for longer time i.e., eight days at room temperature, thus providing *bis*(2-cyano-1-phenylprop-2-en-1-yl) ether (**1**) in 8% isolated yield as a racemic mixture (Equation 2) along with the usual Baylis-Hillman adduct i.e., 3-hydroxy-2-methylene-3-phenylpropanenitrile (≈40%) and some other unidentified products.

The structure of this *bis*-allyl ether **1** was also confirmed by single crystal X-ray data (Figure 1). Though the yield of this molecule is low, this reaction has fascinated us because, this reaction constructs two carbon–carbon bonds and one carbon–oxygen bond leading to the isolation of *dl-bis*-allyl ether (**1**) with five functional groups. This success led us to examine the generality of this reaction.

Accordingly, we have carried out the reaction of a variety of aromatic aldehydes with acrylonitrile in the presence of DABCO for longer time i.e., 8 days thus leading to the isolation of functionalized *dl-bis*-allyl ethers (**2–6**) in 6–7% yields (Equation 2, Table 1) along with the usual Baylis-Hillman adducts (≈40%) and some other unidentified products.

In fact, we have also examined all these molecules on HPLC using chiral column, chiralcel OD, which showed two peaks of equal intensity



**1-6**

Ar = phenyl, 2-methylphenyl, 4-methylphenyl, 4-ethylphenyl, 4-isopropylphenyl, 2,4-dichlorophenyl

(2)

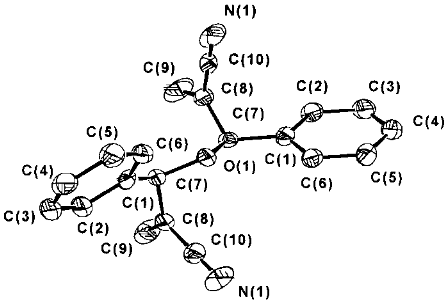


***Figure 1.*** ORTEP diagram of compound **1**.

***Table 1.*** Synthesis of Functionalized *dl*-*bis*-Allyl Ethers[a,b,c]

| Aldehyde Ar= | Product | Yield (%) | M.P. (°C) |
|---|---|---|---|
| Phenyl | **1**[d] | 8 | 92 |
| 2-Methylphenyl | **2** | 7 | 109–110 |
| 4-Methylphenyl | **3** | 7 | 96–97 |
| 4-Ethylphenyl | **4** | 6 | 103 |
| 4-Isopropylphenyl | **5** | 7 | 132 |
| 2,4-Dichlorophenyl | **6** | 6 | 149–150 |

[a] All the reactions were carried out on 20 mM scale of the aldehyde, with acrylonitrile (30 mM) in presence of DABCO (15 mol%) at room temperature for 8 days.

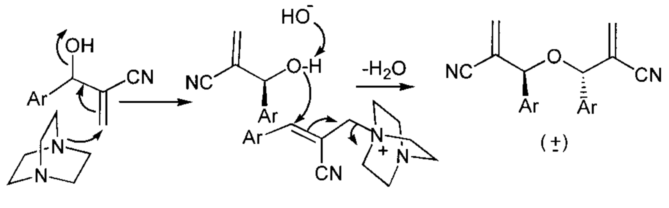
[b] All products gave satisfactory IR, $^1$H NMR (200 MHz), $^{13}$C NMR (50 MHz) and elemental analyses.

[c] Yields of the pure products obtained after silica gel column chromatography (5% ethyl acetate in hexanes).

[d] Structure was also confirmed by single crystal X-ray data.

(in each case) corresponding to both (*R*,*R*)- and (*S*,*S*)-enantiomers thus further confirming *dl* nature of these molecules. However, our attempts to use hexanal for a similar coupling reaction with acrylonitrile in the presence of DABCO were unsuccessful.

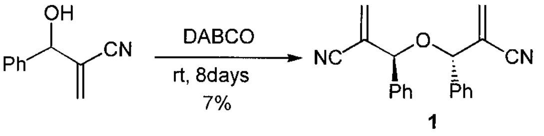
A possible mechanism for the formation of *bis*-allyl ethers **1–6** has been described in Scheme 2. This mechanism has been confirmed to some extent by treating 3-hydroxy-2-methylene-3-phenylpropanenitrile (the Baylis-Hillman adduct derived from benzaldehyde and acrylonitrile) with DABCO for eight days at room temperature which provided the



*Scheme 2.*

desired racemic *bis*-allyl ether (**1**) in 7% isolated yield (Equation 3) along with the starting material i.e., 3-hydroxy-2-methylene-3-phenylpropanenitrile (≈40%) and some other unidentified products.

In conclusion, this methodology describes, though the yields are low, an interesting construction of two carbon–carbon bonds and one carbon–oxygen bond via the tandem coupling of acrylonitrile and aryl aldehydes under the Baylis-Hillman conditions thus leading to the synthesis of *dl*-*bis*-allyl ethers in one-pot operation.



(3)

## EXPERIMENTAL

**Crystal structure analysis:** The X-ray diffraction measurements were carried out on automated Enraf-Nonius MACH 3 diffractometer at 293 (2) K using graphite monochromated Mo-K$\alpha$ ($\lambda = 0.71073$ Å) radiation. Refinements based on $F^2$ were carried out with SHELXL 97. The compound **1** was crystallized from ethyl acetate–hexane mixture (1 : 9) to provide the desired single crystals. Detailed X-ray Crystallographic data are available from the Cambridge Crystallographic Data Center, 12 Union Road, Cambridge, CB2, 1EZ, UK (for compound **1** CCDC #145718).

**Crystal data for $C_{20}H_{16}N_2O$ (1):** $M = 300.34$, Colorless crystal, Crystal dimensions 0.6 × 0.6 × 0.28 mm. Monoclinic, Space group C2/c, $a = 21.972\,(6)$, $b = 6.087\,(3)$, $c = 13.756\,(3)$ Å, $\alpha = 90.00°$, $\beta = 117.00°\,(19)$,

$\gamma = 90.00^\circ$, $V = 1639.3\,(10)\,\text{Å}^3$, $Z = 8$, $d_{\text{calcd}} = 1.217\,\text{g cm}^{-3}$, $\mu = 0.076\,\text{mm}^{-1}$, $F(000) = 632$, index ranges $0 \le h \le 30$, $0 \le k \le 8$, $-19 \le 1 \le 17$. The $\theta$ range = 2.08–29.98°, 105 variables and 0 restraints were refined for 1735 independent reflections with $I \ge 2\sigma(I)$ to $R = 0.0486$, $wR^2 = 0.1351$, GOF = 1.088.

All melting points were recorded on a superfit (India) capillary melting point apparatus and are uncorrected. IR spectra were recorded on JASCO-FT-IR model 5300 or Perkin-Elmer model 1310 spectrometer using samples as KBr plates. $^1$H NMR (200 MHz) and $^{13}$C NMR (50 MHz) spectra were recorded in deutero-chloroform ($CDCl_3$) on a Bruker-AC-200 spectrometer using tetramethylsilane (TMS, $\delta = 0$) as internal standard. Elemental analyses were recorded on Perkin-Elmer 240C-CHN analyzer. Mass spectra were recorded on a micro-mass VG7070H instrument. HPLC analysis were carried out on Shimadzu LC-10AD instrument using chiral column, chiralcel OD (7% 2-propanol in hexanes (for molecules **1**, **3–6**) and 2% 2-propanol in hexanes (for molecule **2**)).

**Typical representative procedure for synthesis of *dl-bis*[2-cyano-1-aryl-prop-2-en-1-yl] ethers:** A mixture of aryl aldehyde (20 mmol), acrylonitrile (1.97 ml, 30 mmol) and DABCO (0.336 g, 3 mmol, 15 mol%) was kept at room temperature for 8 days. Then the reaction mixture was diluted with ether (15 ml) and washed with water (2 × 10 ml). Aqueous layer was extracted with ether (3 × 10 ml). Combined organic layer was dried over anhydrous sodium sulfate. Solvent was evaporated and the residue was subjected to careful column chromatography (silica gel, 5% ethyl acetate in hexanes). The desired *bis*-allyl ethers (**1–6**) (the most non-polar molecule in the product mixture) were obtained either as crystalline solids (**2–5**) or viscous liquids (**1** and **6**) (along with the usual Baylis-Hillman adduct (≈40%) and some other unidentified products). However, subsequent crystallization of **1** and **6** (viscous liquids) from 10% ethyl acetate in hexanes provided the products **1** and **6** also as crystalline solids.

***dl-bis*[2-Cyano-1-phenylprop-2-en-1-yl] ether (1):** Colorless crystals. Yield: 8%; m.p.: 92°C; IR (KBr): 2229, 1620 cm$^{-1}$; $^1$H NMR: $\delta$ 4.80 (s, 2H), 5.94 (s, 2H), 6.01 (s, 2H), 7.28–7.51 (m, 10H); $^{13}$C NMR: $\delta$ 78.15, 116.62, 124.44, 127.52, 129.08, 129.43, 130.76, 135.68; Analysis calcd for $C_{20}H_{16}N_2O$: C, 79.98; H, 5.37; N, 9.33; Found: C, 79.76; H, 5.39; N, 9.29.

***dl-bis*[2-Cyano-1-(2-methylphenyl)prop-2-en-1-yl] ether (2):** Colorless crystals. Yield: 7%; m.p.: 109–110°C; IR (KBr): 2227, 1620 cm$^{-1}$; $^1$H NMR: $\delta$ 2.02 (s, 6H), 5.00 (s, 2H), 5.86 (d, 2H, $J = 1.50$ Hz), 6.00 (s, 2H), 7.14–7.46 (m, 8H); $^{13}$C NMR: $\delta$ 18.72, 74.57, 116.84, 124.03, 126.97, 127.90, 129.28, 130.51, 131.12, 133.30, 136.86; MS ($m/z$): 328 ($M^+$); Analysis calcd for $C_{22}H_{20}N_2O$: C, 80.46; H, 6.14; N, 8.53; Found: C, 80.38; H, 6.12; N, 8.56.

***dl-bis*[2-Cyano-1-(4-methylphenyl)prop-2-en-1-yl] ether (3):** Colorless crystals. Yield: 7%; m.p.: 96–97°C; IR (KBr): 2231, 1618 cm$^{-1}$; $^1$H NMR: δ 2.39 (s, 6H), 4.76 (s, 2H), 5.94 (d, 2H, $J = 1.4$ Hz), 5.99 (d, 2H, $J = 1.4$ Hz), 7.18–7.33 (m, 8H); $^{13}$C NMR: δ 21.22, 77.76, 116.84, 124.76, 127.61, 129.81, 130.42, 132.70, 139.40; MS (*m*/*z*): 328 (M$^+$); Analysis calcd for $C_{22}H_{20}N_2O$: C, 80.46; H, 6.14; N, 8.53; Found: C, 80.60; H, 6.11; N, 8.58.

***dl-bis*[2-Cyano-1-(4-ethylphenyl)prop-2-en-1-yl] ether (4):** Colorless crystals Yield: 6%; m.p.: 103°C; IR (KBr): 2226, 1620 cm$^{-1}$; $^1$H NMR: δ 1.27 (t, 6H, $J = 7.6$ Hz), 2.69 (q, 4H, $J = 7.6$ Hz), 4.78 (s, 2H), 5.94 (s, 2H), 5.99 (s, 2H), 7.18–7.31 (m, 8H); $^{13}$C NMR: δ 15.31, 28.64, 77.81, 116.93, 124.87, 127.72, 128.65, 130.43, 132.96, 145.71; MS (*m*/*z*): 356 (M$^+$); Analysis calcd for $C_{24}H_{24}N_2O$: C, 80.87; H, 6.79; N, 7.86; Found: C, 81.20; H, 6.78; N, 7.82.

***dl-bis*[2-Cyano-1-(4-isopropylphenyl)prop-2-en-1-yl] ether (5):** Colorless crystals. Yield: 7%; m.p.: 132°C; IR (KBr): 2226, 1619 cm$^{-1}$; $^1$H NMR: δ 1.28 (d, 12H, $J = 6.8$ Hz), 2.95 (sept, 2H, $J = 6.8$ Hz), 4.79 (s, 2H), 5.95 (s, 2H), 5.99 (s, 2H), 7.19–7.36 (m, 8H); $^{13}$C NMR: δ 23.89, 33.94, 77.79, 116.96, 124.86, 127.22, 127.67, 130.43, 133.08, 150.28; MS (*m*/*z*): 384 (M$^+$); Analysis calcd for $C_{26}H_{28}N_2O$: C, 81.21; H, 7.34; N, 7.29; Found: C, 81.00; H, 7.36; N, 7.25.

***dl-bis*[2-Cyano-1-(2,4-dichlorophenyl)prop-2-en-1-yl] ether (6):** Colorless crystals. Yield: 6%; m.p.: 149–150°C; IR (KBr): 2226, 1622 cm$^{-1}$; $^1$H NMR: δ 5.33 (s, 2H), 5.95 (s, 2H), 6.07 (s, 2H), 7.32–7.74 (m, 6H); $^{13}$C NMR: δ 75.17, 115.95, 122.38, 128.51, 129.68, 129.85, 132.01, 132.39, 134.30, 136.27; Analysis calcd for $C_{20}H_{12}N_2OCl_4$: C, 54.83; H, 2.76; N, 6.39; Found: C, 54.99; H, 2.74; N, 6.41.

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