Ethyl Vinyl Ether as a Synthetic Equivalent of Acetylene in a DABCO-Catalyzed Microwave-Assisted Diels–Alder–Elimination Reaction Sequence Starting from 2*H*-Pyran-2-ones

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Dedication to Professor Branko Stanovnik, University of Ljubljana, Slovenia, on the occasion of his 70th birthday.

Abstract: We present a study of the Diels–Alder reaction between various electron-deficient 2*H*-pyran-2-ones and ethyl vinyl ether. This microwave-accelerated sequence of a cycloaddition followed by a retro-Diels–Alder reaction (the elimination of CO_2) and a second elimination step of EtOH yields substituted aniline derivatives. The reaction sequence is greatly accelerated by the application of DABCO as a suitable base.

Key words: Diels–Alder reactions, arenes, catalysis with bases, anilines, microwave reactions

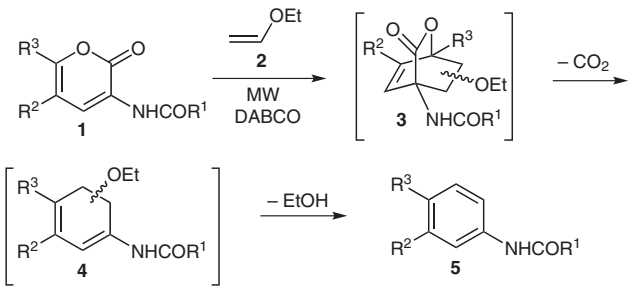
Acetylene is not a very suitable dienophile for Diels–Alder reactions.[1] First of all, it has no substituents that could confer some polarization on its multiple bond and, secondly, under standard conditions it is a gaseous compound, thus greatly limiting its possible usefulness. It is well known that for Diels–Alder reactions the partners should have complementary electronic properties (one molecule should be electron rich, the other electron deficient). Regardless of the problems described, an acetylene fragment might often be a desirable part for inclusion in a carbon scaffold when building larger molecules containing aniline or related aromatic moieties. Therefore, it is of interest to find suitably masked alternative reagents that contain the appropriate substituent(s), so conferring polarization on the multiple bond of acetylene and, at the same time, possessing a certain proclivity for the elimination of these groups in the final step(s).

In the literature[2] there are some reports on the use of different synthetic equivalents of acetylene, like phenyl vinyl sulfoxide,[2b–2d] fluoroalkyl vinyl sulfoxides,[2e] phenyl vinyl sulfide,[2f] ethynyl *para*-tolyl sulfone,[2g] and 1-benzenesulfonyl-2-trimethylsilylacetylene.[2h] However, we thought that ethyl vinyl ether might also be a molecule that would satisfy the above-mentioned conditions and act as a masked acetylene in the Diels–Alder reaction with 2*H*-pyran-2-ones. Based on literature examples[3] and our previous research[4] on Diels–Alder reactions with 2*H*-pyran-2-ones, we were well aware that the electron-rich double bond of ethyl vinyl ether will preclude its reaction with electron-rich 2*H*-pyran-2-ones, although it should be well suited to the reaction with electron-poor 2*H*-pyran-2-ones.

There are some previous reports[5] on the use of ethyl vinyl ether as a dienophile with different cyclic dienes, including derivatives of 1,2,4,5-tetrazines and 2*H*-pyran-2-ones. However, in all the cases described so far, it seems that the reaction times when 2*H*-pyran-2-ones were applied were rather long (up to 10 days),[5c] that the yields were relatively low, the reactions were not comprehensively investigated, and that no attempt was made to use catalysts. Ethyl vinyl ether, with its low boiling point (33 °C), can present a certain problem with the classical (reflux) conditions; therefore, the reactions described in the literature so far often used the 'sealed vessel' protocol. To avoid any problems in connection with this and also to conduct the reactions under defined conditions, we decided to use focused microwave-irradiation conditions[6] in a closed vessel, a well-established and useful way of carrying out reactions.

We envisaged the reaction sequence starting with a Diels–Alder cycloaddition of ethyl vinyl ether (**2**) on 3-acylamino-2*H*-pyran-2-ones **1**[7] substituted with suitable electron-withdrawing groups. In the first step an oxabicyclo[2.2.2]octene system **3** would be produced. If the reaction conditions applied would be appropriate, intermediate **3** would spontaneously eliminate a molecule of CO_2 in a retro-Diels–Alder reaction. This step is well known (also from our previous research)[4a,c,d] and should be facilitated by heating. The cyclohexadiene system **4** thus produced would probably not be stable and the elimination of a molecule of EtOH would take place, yielding the desired substituted aniline derivative **5** (Scheme 1).

Preliminary research has shown that the reaction between 2*H*-pyran-2-one **1a** (R^1 = Ph, R^2 = CO_2Me, R^3 = CH_2CO_2Me) and ethyl vinyl ether (**2**) can be carried



Scheme 1

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out in a solution of DMF under microwave-irradiation conditions (at 160 °C) without using any catalyst, yielding the aniline derivative **5a** (Table 1, entry 1) with complete conversion. However, using water or MeCN as the solvent at lower temperature (120 °C) without a catalyst did not yield any product **5a** (Table 1, entries 2 and 3). These data show that a high temperature is indeed needed for this transformation to proceed toward **5a**. But the rather harsh conditions in DMF also cause some decomposition of the starting compounds and thus decrease the purity of the product and its yield.

Table 1 Effect of Different Reaction Conditions and Bases on the Transformation between 2*H*-Pyran-2-one **1a** and Ethyl Vinyl Ether (**2**) Yielding **5a**

Entry	Base (mol%)	Time (min)	Conversion (%)
1	–[a]	120[b]	100
2	–[c]	120[d]	0
3	–[e]	120[d]	0
4	Pyridine (10)[e]	90[d]	38
5	Et_3N (10)[e]	90[d]	71
6	DABCO (10)[e]	90[d]	72
7	DABCO (20)[e]	90[d]	100
8	DABCO (10)[e]	120[d]	100
9	DABCO (10)[c]	90[d]	91
10	DBU (5)[e]	90[d]	71
11	DBU (10)[e]	90[d]	87
12	DBU (10)[e]	120[d]	100
13	DBN (10)[e]	90[d]	80
14	DMAP (10)[e]	90[d]	82
15	DMAP (10)[e]	120[d]	95
16	DMAP (10)[c]	90[d]	93

[a] DMF as solvent.
[b] MW irradiation, temperature set to 160 °C.
[c] Distilled H_2O as solvent.
[d] MW irradiation, temperature set to 120 °C.
[e] MeCN as solvent.

Therefore, we decided to embark on a search for an appropriate catalyst that would make a lower reaction temperature possible (around 120 °C). First, we employed pyridine (10 mol%) as a standard base catalyst for the reaction between **1a** and ethyl vinyl ether (**2**) in MeCN as the solvent under microwave irradiation conditions (at 120 °C, Table 1, entry 4). However, the ^{1}H NMR analysis of the crude mixture obtained after 90 minutes of irradiation showed a very low conversion (only around 38%). We decided to test some other bases, for example Et_3N, DMAP, DABCO, DBU, and DBN.[8] The results show (Table 1, entries 5–16) that there are no great differences between the sterically hindered bases; however, classical bases like pyridine and Et_3N show appreciably reduced catalytic activity.

We have also found that water might be a suitable reaction medium (Table 1, entries 9 and 16), as the conversions observed in water are comparable or even higher than with the same catalysts in MeCN. However, the products obtained in water contained a larger amount of decomposed material (according to ^{1}H NMR analyses of the crude reaction mixtures) and pure products cannot be isolated as easily as from MeCN reaction mixtures. In contrast to our previous research,[4c,d,9] this reaction cannot be carried out under solvent-free conditions, as it would not be possible to heat the reaction mixture to an adequate temperature without an excessive increase in the pressure (above 20 bar) as a consequence of the low boiling point of ethyl vinyl ether.

1,4-Diazabicyclo[2.2.2]octane and DBU were found to be the most appropriate bases. However, with DBU in certain cases the isolation presented some problems, as its use tended to lead to more decomposition products than when DABCO was applied. Therefore, as the standard procedure, we decided to apply 10 mol% of DABCO as the catalyst and MeCN as the solvent. The reactions were carried out under microwave irradiation at 120 °C, yielding the desired substituted aniline derivatives **5a–g** with good yields (64–85%, Table 2).[10]

The use of acid catalysts in the reaction between **1a** and ethyl vinyl ether (**2**) did not prove to be advantageous; moreover, with the use of PTSA the dienophile **2** is instantaneously decomposed (already at room temperature), whereas $ZrCl_4$ causes decomposition during the reaction.

Finally, we also decided to investigate the Diels–Alder reaction between ethyl vinyl ether and an electron-rich 2*H*-pyran-2-one **1h** containing a 4-methoxyphenyl substituent

Table 2 Microwave-Assisted Base-Catalyzed Transformation of 2*H*-Pyran-2-ones **1** into Aniline Derivatives **5**

Entry	Starting **1**				Time (min)[a]	Product (yield, %)[b]
	R^1	R^2	R^3			
1	Ph	CO_2Me	CH_2CO_2Me	**1a**	100	**5a** (73)
2	Ph	CO_2Et	CH_2CO_2Et	**1b**	100	**5b** (70)
3	Ph	CO_2Me	Me	**1c**	90	**5c** (68)
4	Ph	CO_2Et	Me	**1d**	90	**5d** (64)
5	Ph	Ac	Me	**1e**	60	**5e**[11] (85)
6	Ph	Bz	Me	**1f**	60	**5f** (82)
7	Me	Ac	Me	**1g**	60	**5g**[11,12] (78)
8	Ph	PMP	Me	**1h**	120	–
9	Ph	H	Me	**1i**	120	–

[a] At 120 °C in MeCN with DABCO (10 mol%).
[b] Isolated yield.

(Table 2, entry 8) or an electronically relatively unperturbed 6-methyl derivative **1i** (Table 2, entry 9). However, neither of these combinations proved to be reactive, due to the noncomplementary electronic nature of both partners and consequently no product of the type **5** was detected.

The data presented might hint at the possibility that the base facilitates the elimination steps, whereas it is not involved in the first cycloaddition step. This is further corroborated by the data obtained in the reaction between **1d** and ethyl vinyl ether (**2**), where after 90 minutes of microwave irradiation at 120 °C in MeCN a mixture of starting **1d** and product of type **3** (67% conversion) is obtained, whereas the product **5d** is not detected. However, the same reaction carried out in DMF at 160 °C yields only **5d**. Therefore, it seems that a high temperature (160 °C vs. 120 °C), more polar solvents (DMF vs. MeCN), or the use of base catalysts (like DABCO) are necessary for the reaction to proceed toward the products **5**.

In conclusion, we have presented a concise and useful way of incorporating an acetylene fragment via the Diels–Alder reaction of ethyl vinyl ether with electron-deficient 2*H*-pyran-2-ones, yielding aromatic aniline systems **5**. This relatively general reaction might also be used for other related transformations, leading to more complex products. Further work will be needed to elucidate the role of the base in this transformation and to try to prepare CO_2-containing products of type **3**.

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(10) **General Procedure**
A mixture of the starting 2*H*-pyran-2-one **1** (1 mmol), ethyl vinyl ether (**2**, 721.1 mg, 10 mmol), and DABCO (11.2 mg, 0.1 mol) in MeCN (2 mL) was irradiated in the focused microwave equipment (CEM Discover) for the time specified (Table 1). The final temperature was set to 120 °C, the power to 120 W, and the ramp time to 5 min. Thereafter, the reaction mixture was cooled, the volatile components were removed in vacuo, the remaining solid was treated with mixture of EtOH and H_2O (10:1), and cooled. The precipitated product **5** was filtered off and washed with EtOH–H_2O (10:1).
Selected Data of the Products
Methyl 5-(Benzoylamino)-2-[(methoxycarbonyl)-methyl]benzoate (5a)
Mp 169–171 °C (MeOH). IR (KBr): 3339, 1737, 1720, 1653, 1590, 1526, 1435, 1419 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 3.71 (s, 3 H, Me), 3.83 (s, 3 H, Me), 3.98 (s, 2 H, CH_2), 7.21 (d, 1 H, *J* = 8.4 Hz, 3-H), 7.52 (m, 3 H, Ph), 7.86 (m, 3 H, Ph, 4-H), 8.10 (br s, 1 H, NH), 8.18 (d, 1 H, *J* = 2.1 Hz, 6-H). ^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 39.1, 51.4, 51.9, 122.0, 123.8, 127.6, 128.4, 129.4, 130.9, 131.7, 132.8, 134.5, 138.3, 165.6, 166.7, 171.5. MS (EI): *m/z* (%) = 327 (5) [M^+], 105 (100). Anal. Calcd for $C_{18}H_{17}NO_5$: C, 66.05; H, 5.23; N, 4.28. Found: C, 66.32; H, 5.17; N, 4.26.
Ethyl 5-(Benzoylamino)-2-[(ethoxycarbonyl)-methyl]benzoate (5b)
Mp 170.5–171.5 °C (MeOH). IR (KBr): 3298, 1736, 1714, 1651, 1588, 1523, 1420 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.25 (t, 3 H, *J* = 7.1 Hz, CH_2CH_3), 1.37 (t, 3 H, *J* = 7.1

Hz, CH_2CH_3), 3.99 (s, 2 H, CH_2), 4.15 (q, 2 H, J = 7.1 Hz, CH_2CH_3), 4.32 (q, 2 H, J = 7.1 Hz, CH_2CH_3), 7.24 (d, 1 H, J = 8.9 Hz, 3-H), 7.53 (m, 3 H, Ph), 7.88 (m, 2 H, Ph), 7.95 (dd, 1 H, J_1 = 8.9 Hz, J_2 = 2.4 Hz, 4-H), 7.98 (br s, 1 H, NH), 8.10 (d, 1 H, J = 2.4 Hz, 6-H).

Methyl 5-(Benzoylamino)-2-methylbenzoate (5c)

Mp 126–127 °C (EtOH–H_2O). IR (KBr): 3270, 1732, 1720, 1649, 1582, 1528, 1498, 1428 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 2.57 (s, 3 H, Me), 3.86 (s, 3 H, Me), 7.22 (d, 1 H, J = 8.3 Hz, 3-H), 7.50 (m, 3 H, Ph), 7.81 (dd, 1 H, J_1 = 2.2 Hz, J_2 = 8.3 Hz, 4-H), 7.86 (m, 2 H, Ph), 8.02 (br s, 1 H, NH), 8.08 (d, 1 H, J = 2.2 Hz, 6-H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 21.1, 51.9, 122.3, 124.0, 127.0, 128.7, 129.8, 131.9, 132.3, 134.6, 135.7, 136.3, 165.8, 167.5. MS (EI): m/z (%) = 269 (30) [M^+], 105 (100). Anal. Calcd for $C_{16}H_{15}NO_3$: C, 71.36; H, 5.61; N, 5.20. Found: C, 71.30; H, 5.68; N, 5.22.

Ethyl 5-(Benzoylamino)-2-methylbenzoate (5d)

Mp 119–120.5 °C (EtOH–H_2O). IR (KBr): 3296, 1726, 1648, 1583, 1530, 1448, 1404 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.38 (t, 3 H, J = 7.1 Hz, CH_2CH_3), 2.57 (s, 3 H, Me), 4.35 (q, 2 H, J = 7.1 Hz, CH_2CH_3), 7.23 (d, 1 H, J = 8.1 Hz, 3-H), 7.50 (m, 3 H, Ph), 7.87 (m, 3 H, Ph, 4-H), 7.96 (br s, 1 H, NH), 8.02 (d, 1 H, J = 2.4 Hz, 6-H).

***N*-(3-Acetyl-4-methylphenyl)benzamide (5e)**[11]

Mp 131–132 °C (EtOH–H_2O); lit.[11] mp 137–138 °C (EtOH). IR (KBr): 3410, 1861, 1788, 1699, 1653, 1533, 1492 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 2.49 (s, 3 H, Me), 2.57 (s, 3 H, Me), 7.21 (d, 1 H, J = 8.4 Hz, 5-H), 7.53 (m, 4 H, Ph, 6-H), 7.87 (m, 2 H, Ph), 8.05 (br s, 1 H, NH), 8.13 (d, 1 H, J = 2.4 Hz, 2-H).

***N*-(3-Benzoyl-4-methylphenyl)benzamide (5f)**

Mp <35 °C (EtOH–H_2O). IR (neat): 1671, 1597, 1522, 1501 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 2.28 (s, 3 H, Me), 7.28 (d, 1 H, J = 8.4 Hz, 5-H), 7.52 (m, 7 H, 2 × Ph, 2-H), 7.77 (dd, 1 H, J_1 = 2.4 Hz, J_2 = 8.4 Hz, 6-H), 7.83 (m, 4 H, Ph), 7.94 (br s, 1 H, NH).

***N*-(3-Acetyl-4-methylphenyl)acetamide (5g)**[11,12]

Mp 86–88 °C (EtOH–H_2O); lit.[11] mp 94–95 °C (EtOH); lit.[12] mp 124 °C (EtOH). IR (KBr): 3331, 1686, 1668, 1585, 1536, 1497, 1453 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 2.19 (s, 3 H, Me), 2.47 (s, 3 H, Me), 2.57 (s, 3 H, Me), 7.16 (br s, 1 H, NH), 7.18 (d, 1 H, J = 8.2 Hz, 5-H), 7.40 (dd, 1 H, J_1 = 2.0 Hz, J_2 = 8.2 Hz, 6-H), 7.97 (d, 1 H, J = 2.0 Hz, 2-H).

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