Intramolecular Diels–Alder Reaction of the Diene Unit of Furan in 2.0 M $CaCl_2$

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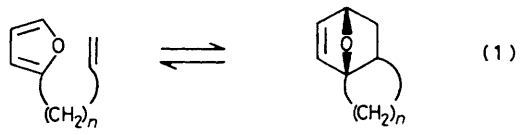
The intramolecular Diels–Alder reaction of substituted 6-(2-furyl)hex-1-en-3-ones (**1**)—(**6**) in 2.0 M calcium chloride provides 11-oxatricyclo[6.2.1.$0^{1,6}$]undec-9-en-5-ones (**7**)—(**12**) in moderate to good yield.

The intramolecular Diels–Alder (IMDA) reaction is a versatile synthetic operation often employed for the simultaneous formation of two rings with stereo- and regio-control.[1] The use of a furan as the diene has been studied extensively in the cases where the side chain connecting the dienophile to the furan contains three atoms (equation 1; $n = 3$); however, there are 13 examples in which the side chain contains four atoms (equation 1; $n = 4$)[1] and of these three involve the use of a side chain containing only carbon atoms.[2,3] In an effort to understand why so few examples have been reported for $n = 4$ carbon atoms, we prepared six IMDA furan precursors (**1**)—(**6**) and herein report the conditions necessary to effect a successful IMDA reaction.

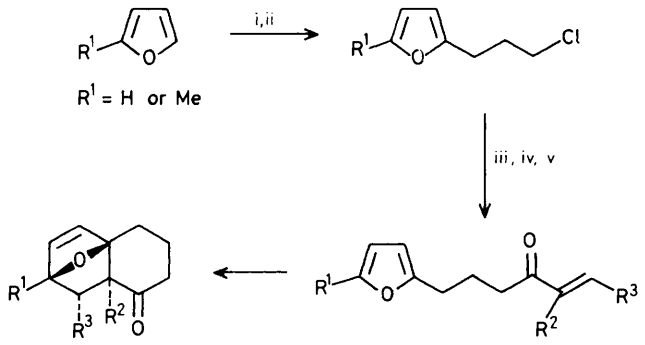
Compounds (**1**)—(**6**) were prepared in overall yields varying from 30 to 35%† (Scheme 1). Furan (**1**) has been reported[2] to undergo the IMDA reaction in a methylene chloride–fluorosil mixture after 6 days stirring at room temperature to produce a 93:7 equilibrium mixture of compounds (**7**) and (**1**). Both compounds (**1**) and (**2**) undergo the IMDA reaction under these conditions (Table 1) with compound (**2**) requiring 14 days to produce a 7:1 ratio of compounds (**8**) and (**2**). Surprisingly, precursors (**3**)—(**6**) gave exclusively starting material; changing the solvent (benzene, toluene, or ethanol) and/or temperature was to no avail. Presumably, the addition of a methyl substituent on the

† All new compounds provided analytical and/or spectroscopic data consistent with their structures.



(1)

n = 3 (a CH_2 may be substituted by an S, O, or N atom)
n = 4 (a CH_2 may be substituted by an O, or N atom)



(7)	$R^1 = R^2 = R^3 = H$	(1)
(8)	$R^2 = R^3 = H$, R^1 = Me	(2)
(9)	$R^1 = R^3 = H$, R^2 = Me	(3)
(10)	$R^3 = H$, $R^1 = R^2$ = Me	(4)
(11)	$R^1 = R^2 = H$, R^3 = Me	(5)
(12)	$R^2 = H$, $R^1 = R^3$ = Me	(6)

Scheme 1. *Reagents and conditions:* i, Bu^nLi, −20 °C, tetrahydrofuran (THF), 4 h; ii, 1-bromo-3-chloropropane; iii, Mg, Et_2O; iv, acrolein, methacrolein, or crotonaldehyde; v, pyridinium dichromate (PDC), CH_2Cl_2.

dienophile or 5-position of the furan is interfering with the catalytic effect of the fluorosil.[2] We therefore concentrated our efforts on maximizing the formation of adduct (**10**) from (**4**).

Lithium chloride has been found to enhance the hydrophobic effect and so accelerate Diels–Alder reactions,[4] but we found that concentrations of lithium chloride varying from 2 to 4.86 M gave poorer ratios than the use of water alone (Table 2). A solution of 2.0 M calcium chloride is reported to have the same 'salting out' properties as 4.86 M lithium chloride.[5] We found that a 2.0 M calcium chloride solution gave a 2 : 1 ratio of adduct (**10**) to starting material (**4**); increasing or decreasing the concentration of calcium chloride resulted in a drop in the ratio (Table 2). Increasing the pressure (~2000 p.s.i.) did not noticeably change the ratio and increasing the temperature resulted in only starting material. Interestingly, β-cyclodextrin, a catalyst reported to accelerate the IMDA reaction of some furans,[6] gave no sign of adduct (**10**); in addition, the recovery of starting material was low (~20%).

Compounds (**1**)—(**6**) were each subjected to a 2.0 M calcium chloride solution and water alone (Table 1). In all cases, the former treatment gave a higher ratio of adduct : starting material; this is attributable to the hydrophobic effect exerted by salts in aqueous solutions.[4] The low ratio obtained for compounds (**1**) and (**2**) in comparison to those for compounds (**3**)—(**6**) was unexpected; on steric arguments alone we thought the unsubstituted dienophiles would result in a higher ratio of adduct to starting material than dienophiles with substituents. However, adducts (**7**) and (**8**) are water soluble while compounds (**9**)—(**12**) are not, so the ratios resulting from compounds (**1**) and (**2**) cannot be compared with those

Table 1. IMDA reaction of furans (**1**)—(**6**).

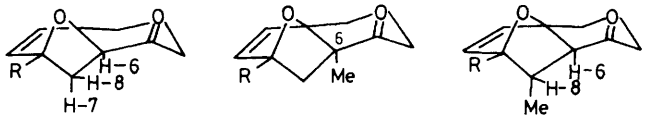
	Adduct: starting material (% yield)[b,c]					
Conditions[a]	(**7**) : (**1**)	(**8**) : (**2**)	(**9**) : (**3**)	(**10**) : (**4**)	(**11**) : (**5**)	(**12**) : (**6**)
CH_2Cl_2, fluorosil	9 : 1[d](71)	7 : 1[e](65)	N.R.[e]	N.R.[e]	N.R.[e]	N.R.[e]
H_2O[f]	1 : 1(69)	1 : 3(72)	2 : 1(70)	1 : 1(71)	2 : 1(70)	1 : 10(−)
2.0 M $CaCl_2$[f]	1 : 1(66)	1 : 2(68)	4 : 1(73)	2 : 1(78)	2 : 1(69)	1 : 2(61)

[a] All reactions at atmospheric pressure. [b] Yield based on recovered starting material. [c] Ratio obtained by ^{1}H n.m.r. [d] Stirred 6 days, room temp. [e] Stirred 14 days, room temp. [f] Stirred 4 days, room temp.

Table 2. Various IMDA reaction conditions for furan (**4**).

Conditions	Adduct: starting material[b]
H_2O[a]	1 : 1
2 M LiCl[a]	1 : 1
3 M LiCl[a]	2 : 3
4.86 M LiCl[a]	1 : 2
1.0 M $CaCl_2$[a]	1 : 1
2.0 M $CaCl_2$[a]	2 : 1
4.0 M $CaCl_2$[a]	1 : 1
2.0 M $CaCl_2$ (2000 p.s.i.)	2 : 1
2.0 M $CaCl_2$ (90 °C)	N.R.
β-Cyclodextrin	N.R.

[a] Stirred 4 days, room temp., atmospheric pressure. [b] Ratio obtained by ^{1}H n.m.r.



(**7**); R = H (**9**); R = H (**11**); R = H-9
(**8**); R = Me (**10**); R = Me (**12**); R = Me

obtained from precursors (**3**)—(**6**) since different equilibria are operating. With compounds (**1**) and (**2**) there are two equilibria to consider: one in which the starting material and adduct are insoluble and another in which both are soluble. In the case of compounds (**3**)—(**6**) only the former equilibrium exists.

In all cases, the adducts could be isolated in pure form by ether extraction followed by the use of a fast flash silica gel column (<2 min). The tendency of the isolated adducts (**7**)—(**12**) to revert to starting material (at room temp.) was minimized by storing them at 0 °C.

Adducts (**7**)—(**12**) all possess the stereochemistry resulting from an *exo*-mode of cyclization, H-7 in both compounds (**7**) and (**8**) showing only one vicinal coupling of 8.3 and 8.5 Hz, respectively.[2] The $J_{8,9}$ coupling of 4.2 Hz in compound (**11**) indicates that H-8 is *exo* while the $J_{8,6}$ coupling of 4.3 Hz shows that H-6 is *endo* (*vide supra*). Thus the methyl group in compound (**11**) is *endo*; this is further supported by its unusually high upfield shift (δ 0.91) due to shielding from the double bond. The characteristic upfield shift of the *endo* methyl group was also seen in compound (**12**) (δ 0.92); the $J_{6,8}$ coupling of 4.0 Hz indicates that the side-chain in (**12**) is *exo*. The 6-Me resonances in adducts (**9**) and (**10**) appear at δ 1.1 and 1.09, respectively, indicative of *endo*-oriented methyl groups[7] with the side-chain being *exo*.

The stereochemistry of adducts (**9**)—(**12**) indicates that cyclization followed by epimerization at position 6 is not occurring. Adducts (**9**) and (**10**) have quaternary carbon atoms at position 6 and thus cannot epimerize. The ^{1}H n.m.r.

spectra of compounds (**5**) and (**6**) clearly indicate that the geometry about the double bond in both compounds is *E*.‡ *endo*-Cyclization of the side-chain would place the methyl group at position 7 in an *exo*-orientation in compounds (**11**) and (**12**). If epimerization then occurred at position 6, both the methyl group and side-chain would be *exo*; this stereochemistry is not observed (*vide supra*).

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‡ The vinyl coupling constants for (**5**) and (**6**) were 15.8 and 16.1 Hz respectively.

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