1,3-Dipolar Cycloadditions

A Homo [3+2] Dipolar Cycloaddition: The Reaction of Nitrones with Cyclopropanes**

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Cycloadditions are among the most trusted of chemical transformations available to the synthetic chemist. The predictability of the transition state based on steric and electronic considerations allows for the strategic construction of complex molecular assemblies. While the Diels–Alder reaction has received the most attention, 1,3-dipolar cycloadditions have also maintained a place of prominence in the toolbox of the synthetic chemist.[1]

During recent studies of the synthetic reactions of cyclopropanediesters,[2] we were struck by the fact that simple 1,1-cyclopropane diesters behaved very much like α,β-unsaturated carbonyl compounds in their ability to react with nucleophiles in what could be considered a homo-Michael addition (an observation not unnoticed by others).[3,4] The strained bonds in the cyclopropane ring have long been considered to have a significant π character[5] and in 1,1-cyclopropane diesters this bond can be polarized and further weakened by coordination of a Lewis acid to one or both of the ester moieties. This reactivity suggests that such compounds are one-carbon homologues of electron-deficient olefins, and led us to investigate their reactions with nitrones in what is naively a dipolar homo [3+2] cycloaddition[6] (Scheme 1) resulting in the formation of tetrahydro-1,2-oxazines.[7] In this communication we disclose the first reaction of a nitrone with a cyclopropane to produce a

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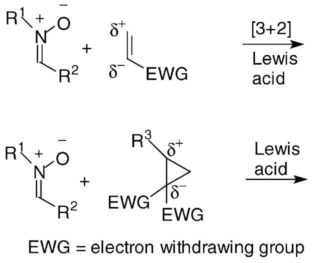


Scheme 1. The homo [3 + 2] cycloaddition of nitrones with cyclopropanes.

tetrahydro-1,2-oxazine and the application of this "cycloaddition" to the synthesis of the [3.3.1] bicyclic core of FR-900482 and related compounds.[8]

In the initial experiment we combined the *N-p*-tolyl nitrone (**1a**) with dimethyl-2-phenyl-1,1-cyclopropanedicarboxylate (**2b**) in the presence of 5 mol% Yb(OTf)$_3$ in dichloromethane. The mixture was stirred overnight, and yielded the expected cycloadduct in 94% yield (see Table 1). To probe the generality of this reaction, a number of nitrones[9] **1a**–**d** were treated with several readily prepared cyclopropanes **2a**–**d**.[10] The results are shown in Table 1. A brief survey of a series of common Lewis acids (BF$_3$·OEt$_2$, Cu(OTf)$_2$, Sc(OTf)$_3$, TiCl$_4$, SnCl$_4$, and AlCl$_3$) failed to identify a catalyst superior to Yb(OTf)$_3$.[11] The nitrones bearing a *p*-tolyl group on the nitrogen atom were significantly more reactive than those bearing a methyl group and proceeded to give the products in generally better yields. The presence of a phenyl, styryl, or vinyl substituent vicinal to the diester moiety on the cyclopropane unit greatly reduced the reaction times and for the phenyl and styryl cases, resulted in excellent yields. The modest yields observed with the vinyl cyclopropane may be due to some polymerization under the Lewis acid conditions. In all cases the sole regioisomer isolated had the oxygen atom of the nitrone distal to the geminal diester moiety. This regioselectivity, as well as the increased reaction rates with a π system vicinal to the diester moiety, is explained by considering that the cyclopropane likely undergoes a significant degree of charge separation in the presence of a Lewis acid such as Yb(OTf)$_3$ (Figure 1). Such a charge separation would be enhanced by the presence of a carbocation-stabilizing group on the cyclopropane unit (R^1 or R^2 = phenyl or vinyl). In every case examined the reactions produced, as a single diastereomer, the product in which the substituents at C3 and C6 bore a *cis* relationship. This was confirmed by analysis of the coupling constants in the ^{1}H NMR spectra and by single-crystal X-ray analysis in the case of compounds **3b**, **c**, and **f** (entries 2, 3, and 6).

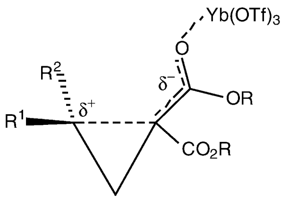


Figure 1. Lewis acid induced polarization of 1,1-cyclopropanediesters.

While it is convenient to label this reaction as a cycloaddition based on the formation of a ring structure and by analogy to the reaction of a nitrone with an alkene, the transformation may proceed in a number of ways. Figure 2 shows three models for the reaction course: 1) A stepwise annulation mechanism involving an initial attack of the nitrone oxygen atom onto the cyclopropane followed by the attack of the resulting malonate onto the imminium species **I** via a chair conformation, 2) a concerted reaction in which the transition state has the cyclopropane largely ring-opened to a 1,3-dipolar species and reacting with the 1,3-dipolar nitrone **II**, and 3) a fully concerted [3 + 2] cycloaddition in which the transition state has the nitrone reacting with the strained σ bond in a half-chair conformation (**III**). In each case the most favorable conformation would result in the observed *cis* relationship between the substituents at C3 and C6 on the newly formed tetrahydro-1,2-oxazine. The fact that the reactions are entirely stereoselective and yield what is most likely to be the kinetic product (an axial/equatorial relationship between the C3 and C6 substituents) implies a concerted process although a stepwise process (via species **I**), in which there is no bond rotation before ring closure cannot be ruled out. It is conceivable that in cases where the substituent on the cyclopropane unit can stabilize a developing carbocation, the process may resemble a transition state such as **II** (substantial charge separation in the cyclopropane) whereas in the case of the unsubstituted cyclopropane **2a** there would be much less charge separation prior to reaction with the nitrone and transition state **III** may be a more accurate description. Efforts are in progress to perform computer-modeling experiments at a high level of theory to gain insight into a possible course of reaction.

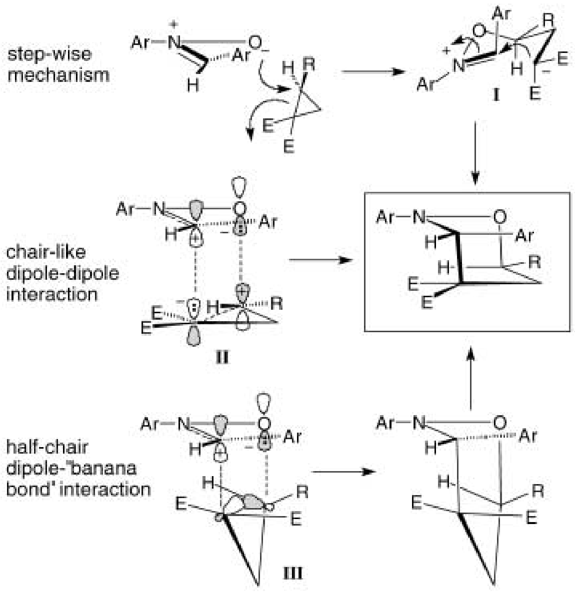
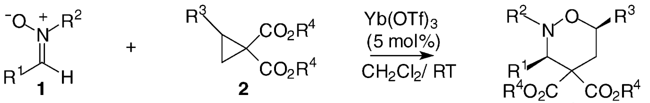


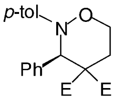
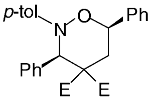
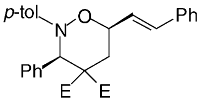
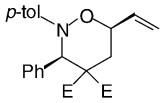
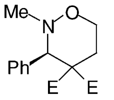
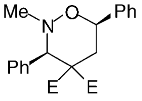
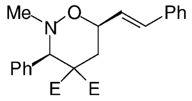
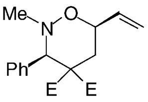
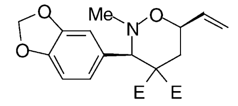
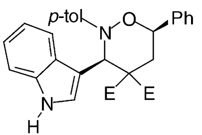
Figure 2. Possible reaction modes for nitrones with cyclopropane diesters.

Table 1: The reaction of nitrones with 1,1-cyclopropanediesters.



1a R^1 = Ph, R^2 = *p*-tolyl
1b R^1 = Ph, R^2 = Me
1c R^1 = 3,4-methylenedioxyphenyl, R^2 = Me
1d R^1 = 3-indolyl, R^2 = *p*-tolyl

2a R^3 = H, R^4 = Et
2b R^3 = Ph, R^4 = Me
2c R^3 = styryl, R^4 = Me
2d R^3 = vinyl, R^4 = Et

Entry	Nitrone	Cyclopropane	*t* [h]	Product (**3**)[c]	Yield
1	**1a**	**2a**	18[a]	 **3a**	77%
2	**1a**	**2b**	18	 **3b**	94%
3	**1a**	**2c**	5	 **3c**	95%
4	**1a**	**2d**	42	 **3d**	73%
5	**1b**	**2a**	18[b]	 **3e**	76%
6	**1b**	**2b**	42	 **3f**	84%
7	**1b**	**2c**	36	 **3g**	74%
8	**1b**	**2d**	18[b]	 **3h**	52%
9	**1c**	**2c**	42	 **3i**	50%
10	**1d**	**2b**	3[d]	 **3j**	96%

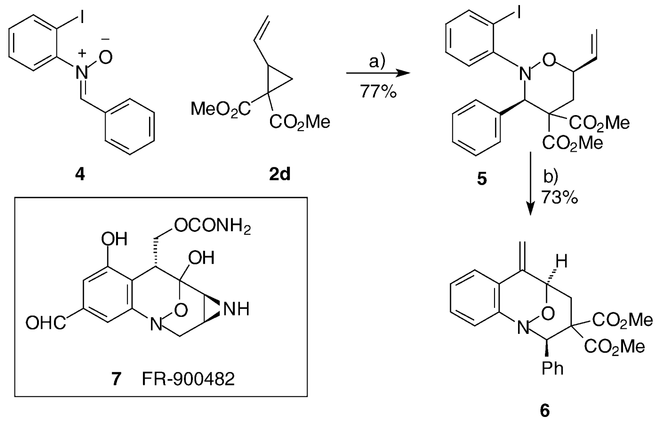
[a] $Yb(OTf)_3$ (20 mol%) was used. [b] The reaction was performed in refluxing 1,2-dichloroethane. [c] E = methyl or ethyl ester. [d] CH_3CN was used as solvent.

Recently there have been several total syntheses of the antitumor antibiotic FR-900482 (**7**, Scheme 2), a compound that bears the tetrahydro-1,2-oxazine ring as a key structural element.[12] A significant portion of the synthetic efforts were aimed at the preparation of the [3.3.1] bicyclic core, a task that is well suited to the reactions described above. The synthesis of the tricyclic ring system present in FR-900482 commences with the treatment of nitrone **4** with cyclopropane **2d** under the influence of catalytic $Yb(OTf)_3$, which yields 1,2-oxazine **5** in 77% yield. Heck cyclization (in the style of Danishefsky[12b]), produced the desired target compound **6** in 73% yield, and 56% over the two steps.

In conclusion, we have presented a new mode of chemical reactivity for cyclopropanediesters and nitrones, which has resulted in a valuable, high-yielding, and stereoselective synthetic protocol. This reaction represents the first example of a dipolar homo [3+2] cycloaddition. The utility of the reaction was demonstrated in a two-step preparation of the tricyclic skeleton of FR-900482 with its unusual tetrahydro-1,2-oxazine core. Our future and ongoing efforts in this regard include the investigation of a Kobayashi-type chiral ytterbium catalyst[13] to generate adducts as a single antipode, an investigation of the mechanistic nature of the reaction, the application of this transformation to the chemical synthesis of FR-900482, and the chemical transformations of the adducts to yield useful intermediates for chemical synthesis.

Experimental Section

3: $Yb(OTf)_3{\cdot}xH_2O$ (5 mol%) was added to a solution of cyclopropane **2** (0.5 mmol) and nitrone **1** (0.6 mmol) in CH_2Cl_2 (4 mL) or 1,2-dichloroethane. Reactions in CH_2Cl_2 were performed at room temperature, while reactions in 1,2-dichloroethane were refluxed for the time indicated in Table 1. The reaction mixture was then preadsorbed onto silica gel and the pure product was obtained after flash column chromatog-



Scheme 2. Synthesis of the FR-900482 skeleton. a) Yb(OTf)$_3$, CH$_2$Cl$_2$, 25 °C, 18 h; b) [Pd(PPh$_3$)$_4$] (20 mol%), Et$_3$N, 80 °C, 18 h.

raphy on silica gel (elution with 2% ethyl acetate in hexanes). Samples could be recrystallized from CH$_2$Cl$_2$/hexanes if desired.

Physical properties for **3c**: m.p. 141–142 °C, colorless needles. $R_f = 0.36$ (20% ethyl acetate in hexanes); ^{1}H NMR (400 MHz, CDCl$_3$): $\delta = 7.58$–7.55 (m, 2H), 7.51–7.49 (m, 2H), 7.40–7.36 (m, 2H), 7.33–7.28 (m, 1H), 7.22–7.19 (m, 3H), 7.02–6.95 (m, 4H), 6.83 (d, $^3J = 16.4$ Hz, 1H), 6.43 (dd, $^3J = 16.4$, 6.4 Hz, 1H), 5.68 (s, 1H), 4.71–4.66 (m, 1H), 3.92 (s, 3H), 3.48 (s, 3H), 2.74–2.65 (m, 2H), 2.19 ppm (s, 3H). ^{13}C NMR (100 MHz, CDCl$_3$) $\delta = 170.0$, 168.3, 146.2, 136.6, 135.0, 132.5, 131.0, 130.5, 129.0, 128.6, 128.0, 128.0, 127.9, 127.0, 126.6, 116.1, 77.1, 59.1, 53.4, 52.6, 30.6, 20.5 ppm.; IR (thin film): $\tilde{\nu} =$ 3057, 3026, 2951, 2928, 1741, 1612, 1508, 1438, 1239, 1200, 1075, 965, 816, 747, 698 cm^{-1}.; HRMS (70 eV) calcd for C$_{29}$H$_{29}$O$_5$N = 471.2047, found 471.2034.

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