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Magnesium Iodide Promoted Reactions of Nitrones with Cyclopropanes: A Synthesis of Tetrahydro-1,2-oxazines

Michael D. Ganton and Michael A. Kerr*

Department of Chemistry, The University of Western Ontario, London, Ontario, Canada, N6A 5B7

makerr@uwo.ca

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Abstract: Anhydrous magnesium iodide (MgI_2) is shown to be an effective promoter of the "homo 3+2" dipolar cycloaddition of nitrones with 1,1-cyclopropane diesters. In almost all cases the products tetrahydro-1,2-oxazines are formed in excellent yields. The reactions are highly diastereoselective for a cis relationship between the substitutents at the 3- and 6-positions on the tetrahydrooxazine ring. As an alternative to using a preformed nitrone, the reaction may be performed in a 3-component sense by combining an aldehyde, an hydroxylamine, and the cyclopropane in the presence of catalytic MgI_2.

Heterocyclic compounds hold a special place in organic chemistry. Their role as lead candidates in drug design cannot be overstated and the appearance of heterocyclic motifs in natural products is astronomically frequent. Many heterocycles (e.g. indoles, quinolines, pyridines, pyrroles, etc) have received an enormous amount of attention from synthetic chemists from the standpoint of both their preparation and their reactivity. Other heterocycles are much rarer and have received very little attention. One such class is the tetrahydro-1,2-ozazine (Figure 1). It is not an abundant motif in nature, appearing in only a few naturally occurring compounds, most notably FR900482 and related molecules.[1] This fact along with a paucity of methods for its construction[2] have resulted in it being overlooked by the synthetic organic chemist. Its utility, however, is clear when one considers that upon cleavage of the N−O bond a synthetically important 1,4-amino alcohol results, which in turn can be converted to a variety of useful compounds. In addition the heterocycle itself may be a useful scaffold for the development of lead drug candidates. An efficient method for its construction in a stereodefined manner would be an important contribution.

Recently we described the $Yb(OTf)_3$- catalyzed reactions of nitrones with 1,1-cyclopropanediesters in a cycloadditive sense to form the product tetrahydro-1,2-oxazines in good to excellent yields.[3] We then reported a three-component coupling modification in which the nitrone could be formed in situ by combination of a hydroxylamine with an aldehyde under the Lewis acid conditions required for the cycloaddition.[4] At that time we screened a number of other Lewis acids in the hopes of expanding the scope of the reaction but none surpassed $Yb(OTf)_3$ in efficiency. We were of course aware of the contributions from the groups of Carriera,[5] Lautens,[6] and Olsson[7] in which they each activated the ring opening of cyclopropanes using MgI_2.[8] We then turned to our system and applied anhydrous MgI_2 as a catalyst in our "homo 3+2" dopolar cycloaddition of nitrones with 1,1-cyclopropanediesters. Carriera postulates a discrete magnesioenolate/alkyl iodide intermediate upon treatment of his spirocyclopropyl oxindole with magnesium iodide. In the ytterbium triflate-catalyzed reactions, it is possible that the reactions are proceeding via a concerted (or near concerted) mechanism and we had hopes that with magnesium iodide the reaction would be stepwise and might result in a differing stereoselection as well as a better mechanistic understanding of the reaction. Herein we report the results of this research which describe MgI_2 as an effective and useful catalyst for this reaction.

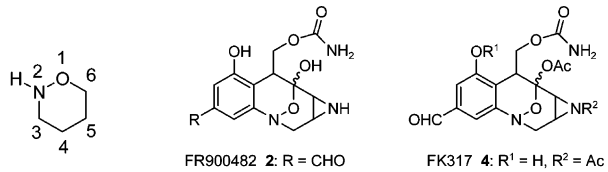

FIGURE 1. Tetrahydro-1,2-oxazine-containing compounds and the parent heterocycle.

Table 1 shows the reaction of a variety of nitrones[9] with 1,1-cyclopropanediesters[10] under the influence of MgI_2 catalysis. In a typical experiment the nitrone (1.5 equiv), the cyclopropane (1 equiv), and anhydrous MgI_2 (10 mol %) were combined in dry THF and stirred for between 16 and 24 h. The reaction rates for MgI_2 are somewhat shorter than those observed when $Yb(OTf)_3$ was used as the catalyst. In many cases the yields are superior to those obtained by us using $Yb(OTf)_3$ as a catalyst and in other cases the yields are lower. In this sense the catalysts are complementary. Most notable about the

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TABLE 1. The MgI_2-Catalyzed Reactions of Nitrones with Cyclopropane Diesters

Entry	Nitrone	Cyclopropane	Product (cis shown)	Yield (cis:trans)
1	**6a**	**7a**	**8a**	98% (15:1)
2	**6a**	**7b**	**8b**	99% (12:1)
3	**6a**	**7c**	**8c**	27% (6:1)
4	**6a**	**7d**	**8d**	76% (7:1)
5	**6a**	**7e**	**8e**	86% (5:1)
6	**6a**	**7f**	**8f**	91% (10:1)
7	**6b**	**7b**	**8g**	89% (6:1)
8	**6b**	**7a**	**8h**	98% (7:1)
9	**6c**	**7b**	**8i**	82% (5:1)
10	**6d**	**7f**	**8j**	78% (NA)
11	**6e**	**7e**	**8k**	88% (7:1)
12	**6e**	**7d**	**8l**	88% (4:1)
13	**6f**	**7b**	**8m**	87% (4:1)
14	**6f**	**7f**	**8n**	70% (5:1)
15	**6g**	**7g**	**8o**	45%[a] (N/A)

[a] The reaction was performed in refluxing acetonitrile.

results reported here is the fact that while $Yb(OTf)_3$ results in the formation of almost a single diastereomer, reactions promoted by MgI_2 result in the formation of

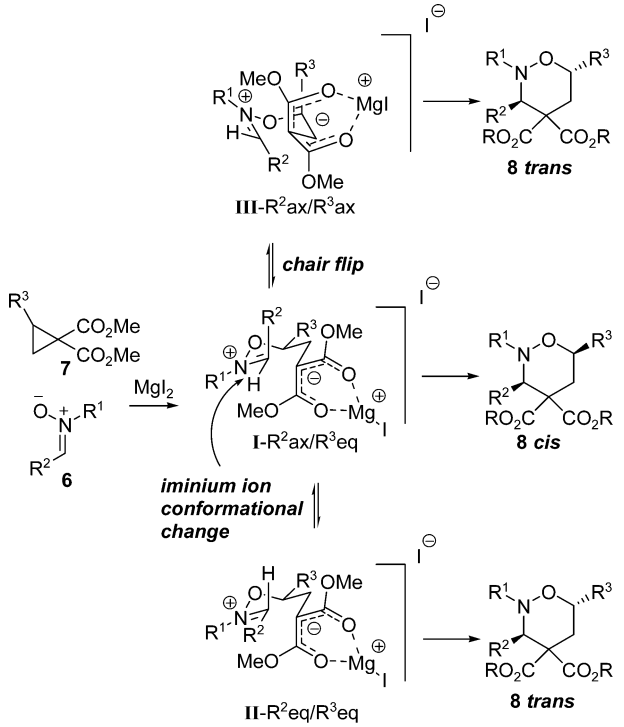

FIGURE 2. Explanation for the formation of the trans isomer.

noticeable amounts of adducts bearing a trans relationship between the substituents at the 3- and 6-positions. In all cases the selectivity for the cis isomer is good to excellent and the cis isomer can be isolated as the sole compound after a single recrystallization. Also of note is that the nitrone derived from formaldehyde behaves well under these conditions (affording compound **8j**), something we have not shown to be true using $Yb(OTf)_3$. This is important because it leaves this position on the oxazine ring unsubstituted, which is crucial if this method is to be used for the total synthesis of FR900482 and related compounds.

With regards to the diastereoselectivity observed here, a possible explanation is shown in Figure 2. If one envisions the ring opening of the cyclopropane **7** by the nitrone **6** to proceed via an intermediate of type **I**, the imminium moiety may exist in a *Z* (R^2 axial) and *E* (R^2 equatorial) conformation. Closure of the magnesiomalonate onto the iminium species would give the observed major product **8**-*cis*. A loss of stereochemical integrity at the iminium CN bond could yield **II** in which both R_2 and R_3 are equatorial. This intermediate would close to give the minor **8**-*trans* isomer. Alternatively, **I** may undergo a chair flip to give **III** in which both R_2 and R_3 are axial. This intermediate would also produce **8**-*trans*. The observance of the trans isomer in the case of the MgI_2-promoted reactions and not in the $Yb(OTf)_3$-promoted reactions may be explained by the fact that the magesiomalonate is probably more kinetically stable than its lanthanide counterpart. Although ytterbium is known for its oxophilicity and, as a result, a thermodynamically stable Yb−O bond, it is kinetically labile and undergoes rapid dissociation from its oxygen ligands.[11] Such a

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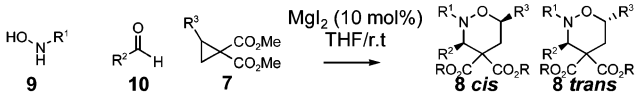
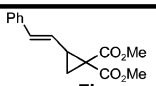
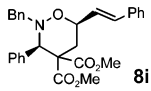
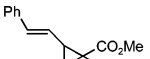
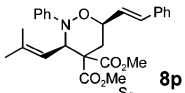
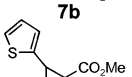
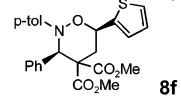
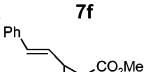
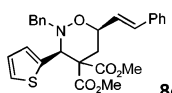
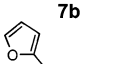
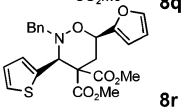
TABLE 2. The MgI_2-Catalyzed Three-Component Coupling of Aldehydes, Hydroxylamines, and Cyclopropane Diesters



Entry	RNHOH 9	RCHO 10	Cyclopropane 7	Product (cis shown)	Yield (cis:trans)
1	 9a	 10a	 7b	 8i	89% (8:1)
2	 9b	 10b	 7b	 8p	98% (6:1)
3	 9c	 10a	 7f	 8f	89% (5:1)
4	 9a	 10c	 7b	 8q	83% (5:1)
5	 9a	 10c	 7e	 8r	97% (3:1)

dissociative process in the case of a putative intermediate like **I** would leave a more naked malonate anion to undergo ring closure. The net result would be a faster ring closure, thereby maintaining a cis relationship. A magnesiomalonate, on the other hand, would result in a longer lived acyclic intermediate, allowing for increased probability of stereochemical leakage to the trans isomer. It must be noted that the involvement of an intermediate in which an iodide nucleophilically opens the cyclopropane prior to nitrone addition[5] cannot be ruled out. Attempts to modulate the diastereoselectivity through variation of the temperature and solvent met with no success.

In many cases it is desirable to generate the nitrone in situ, particularly when the nitrone is unstable. To this end we demonstrated that the MgI_2 catalyst protocol is amenable to a three-component coupling procedure. Table 2 shows a short series of five adducts generated by this method. In general the yields are comparable to the method in which a preformed nitrone is used. It is worthy of note that like our previous 3-component couplings[4] using $Yb(OTf)_3$, it is required to premix the hydroxylamine and aldehyde for a short period of time prior to addition of the cyclopropane to avoid ring opening of the cyclopropane by the nucleophilic hydroxylamine.

In conclusion, we have presented herein an alternative catalyst system for a relatively new type of dipolar cycloaddition reaction. The yields of the cycloadducts obtained with catalytic MgI_2 were, in many cases, superior to those obtained with $Yb(OTf)_3$ as the catalyst. In addition we have now been able to employ the less stable formaldehyde nitrone in the cycloaddition. This will make the reaction more applicable to molecules such as FR900482. This new protocol, then, represents a complimentary approach for use in organic synthesis. Most importantly, however, we now have observed significant quantities of the trans cycloadduct in some instances. This is exciting because it allows for the formulation of a model that explains this effect and provides some insight into the mechanistic aspects which could in turn result in the development of a catalyst that is selective for the trans isomer.

Experimental Section

Typical Experimental Procedure for the Cycloaddition of Nitrones with 1,1-Cyclopropane Diesters (Two-Component Coupling): Synthesis of Tetrahydro-1,2-oxazine 8a. Cyclopropane **7a** (0.100 g) and 1.5 equiv of nitrone **6a** were added to a sealed tube with 2 mL of dry THF, the mixture was thoroughly degassed with argon for 2 min, and the screw cap was replaced. MgI_2 (10 mol %) was added and the mixture was stirred for approximately 20 h. After this time the contents were preabsorbed on 500 mg of SiO_2 and subjected to flash column chromatography (elution with a 0−10% gradient of ethyl acetate to hexanes) to yield pure cycloadduct **8a** as a 15:1 mixture of cis and trans diastereomers. Recrystallization of this compound was effected in 1 mL of dichloromethane and 4 mL of hexanes in a small vial with a septum over top for 2 days. The recrystallized product was found to be the pure cis isomer. The yield after chromatography was 0.186 g (98% yield). The major diastereomer was purified by crystallization as colorless needles. Mp 154−155 °C; ^{1}H NMR (400 MHz, $CDCl_3$) major diastereomer, δ 7.62 (dd, J = 1.5, 8.4, 2H), 7.59 (d, J = 7.5, 2H), 7.48 (dd, J = 7.5, 7.5, 2H), 7.43−7.40 (m, 1H), 7.24−7.20 (m, 3 H), 7.03 (d, J = 8.7, 2H), 6.97 (d, J = 8.7, 2H), 5.78 (s, 1H), 5.07 (dd, J = 12.0, 3.0, 1H), 3.95, (s, 3H), 3.49 (s, 3H), 2.91−2.80 (m, 2H), 2.20 (s, 3H), and representative peaks for the minor diastereomer (note: some aromatic peaks for the minor diastereomer are indistinguishable from those of the major diastereomer) δ 7.44 (d, J = 8.7, 2H), 7.38 (dd, J = 7.5, 7.5, 2H), 7.18 (d, J = 8.7, 2H), 7.07 (d, J = 8.7, 2H), 6.69 (dd, J = 12.0, 3.0, 1H), 5.58 (s, 1H), 3.47 (s, 3H), 3.45 (s, 3H), 3.18 (dd, J = 18.0, 8.0, 1H), 2.72 (dd, J = 18.0, 6.0, 1H), 2.28 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) major diastereomer, δ 170.1, 168.3, 146.2, 139.5, 135.1, 130.9, 130.5, 129.0, 128.6, 128.2, 128.0, 127.9, 126.4, 116.0, 78.7, 66.0, 59.5, 53.4, 52.5, 31.6, 20.5. These data match the data previously reported by us for this compound (ref 3).

Typical Experimental Procedure for the Three-Component Coupling of Aldehydes, Hydroxylamines, and Cyclopropanes: Synthesis of Tetrahydro-1,2-oxazine 8i. MgI_2 (12 mg, 10 mol %) was added to a solution of the hydroxylamine **9a** (0.070 g, 0.567 mmol, 1.3 equiv) and aldehyde **10a** (0.065 g, 0.436 mmol, 1.4 equiv) in THF (2 mL) containing activated 4 Å molecular sieves. The solution was stirred under an argon atmosphere for 30 min at room temperature, after which the cyclopropane (0.100 g, 0.436 mmol) was added. Solid cyclopropanes were added directly to the solution, while oils were added as a solution in toluene (2 × 1 mL). After the reaction was complete as determined by TLC, the contents were preabsorbed on 500 mg of SiO_2 and subjected to flash column chromatography (elution with a 0−10% gradient of ethyl acetate to hexanes) to yield pure cycloadduct **8i** as an 8:1 mixture of cis and trans diastereomers. Samples could be recrystallized from CH_2Cl_2/hexanes as above to yield the pure cis diastereomer. Yield after flash chromatography was 0.166 g, 89%. The major diastereomer was purified by crystallization as small colorless prisms. Mp 127−130 °C; ^{1}H NMR (400 MHz, DMSO) major diastereomer, δ 7.52 (d, J = 3.6, 2H), 7.49−7.42 (m, 2H), 7.36−7.33 (m, 3H), 7.30 (d, J = 4.4, 2H), 7.25 (d, J = 4.4, 2H), 7.24−7.19 (m, 2H), 7.15 (d, J = 6.8, 2H), 6.62 (d, J = 15.6, 1H), 6.44−6.38 (dd, J = 15.6, 6.0, 1H), 4.75 (s, 1H), 4.43−4.39 (m, 1H), 3.77 (s, 3H), 3.68 (d, J = 14.0, 1H), 3.58 (J = 14.0, 1H), 3.27 (s, 3H), 2.42 (d, J = 11.6, 1H), 2.37−2.32 (dd, J = 11.6, 3.2, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.4, 168.8, 137.0, 136.8, 132.1, 131.5, 129.2, 128.8 (2C), 128.5, 128.3 (3C), 128.1, 127.4, 126.8 (2C), 76.5, 59.6, 59.3, 53.3, 52.6, 30.6; IR (thin film) ν_{max} 3061, 3030, 2953, 2894, 1743, 1495, 1453, 1436, 1259, 1198, 1179, 1077, 967, 922, 746, 699; HRMS calcd for $C_{29}H_{29}NO_5$ 471.2046, found 471.2041.

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Supporting Information Available: Complete experimental procedures as well as ^{1}H NMR and ^{13}C NMR data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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