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Synthesis of 1,2,4-Triazolines and Triazoles Utilizing Oxazolones

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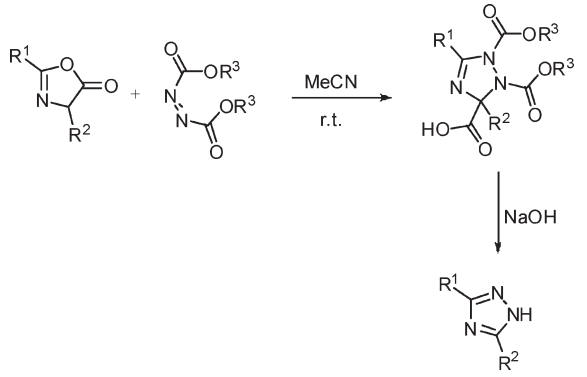

We describe herein a convenient method for the synthesis of 1,2,4-triazolines using oxazolones and azodicarboxylates. Subsequent treatment of these 1,2,4-triazolines with NaOH provides efficient access to the corresponding triazoles.

The oxazolone template has been a scaffold of interest for many research groups for the synthesis of β-lactams,[1] pyrroles,[2] pyrrolines,[3] and imidazoles.[4] Our group has also exploited the oxazolone template as a pivotal scaffold to access a wide range of heterocyclic compounds and natural products, including imidazolines, imidazolones, dihydropyrrolines, alkoxypyrrolidinones, dihydroimidazolones, and oxazoles (Figure 1).[5] Oxazolones are unique in that these templates contain multiple reactive sites capable of yielding a wide range of diverse products by just minor manipulations of the reaction conditions or reaction substrates.[6] On the basis of these previous observations, we anticipated that oxazolones would be ideal substrates to access triazoline and triazole compounds.

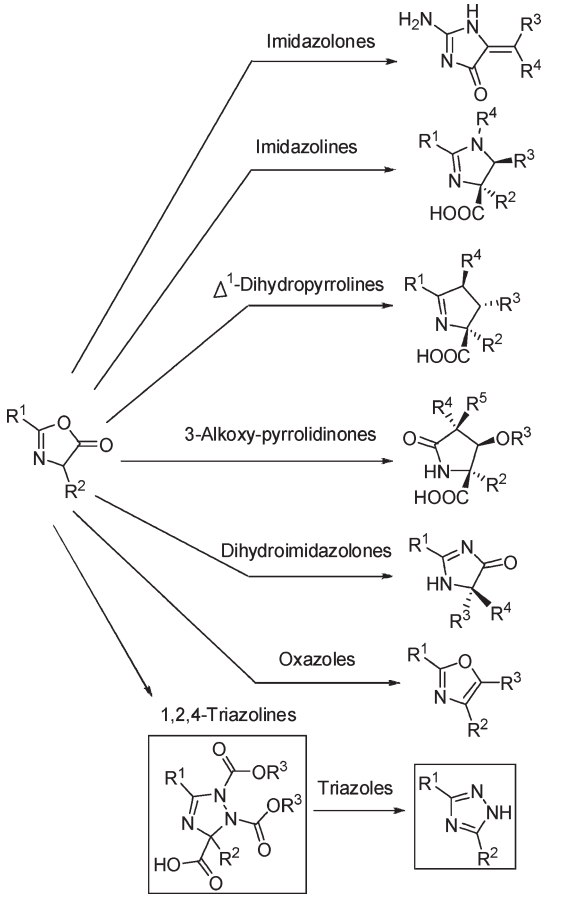

FIGURE 1. Oxazolone scaffold as template for heterocyclic reaction development.

The 1,2,4-triazoline core belongs to an underutilized class of heterocycles whose biological properties remain largely unexplored. There are only a handful of the examples of syntheses of 1,2,4-triazolines with quaternary C-3 carbon containing alkoxy carbonyl or carboxyl moieties. Kolasa and Miller[7] have reported three examples of the triazoline synthesis from α-amino acids utilizing the Mitsunobu reaction conditions. Ibata and Hassner[8] have utilized oxazoles

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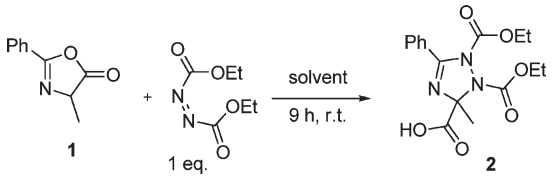
TABLE 1. Scope of the Solvent



	solvent	yield (%)
1	MeCN	94
2	DCM	75
3	C_6H_6	22
4	THF	26
5	Et_2O	15

and thiazoles for the synthesis of this triazoline motif. Anderson and Watt[9] have demonstrated the generation of a triazoline adduct along with a Michael-type addition product upon the reaction of imidazopyridine with azodicarboxylates. Similarly, Tsuge and co-workers[10] have utilized azodicarboxylate compounds with *N*-[(trimethylsilyl) methyl] iminium triflates to synthesize the imidazolines and triazolines.

Herein, we report the reaction of the oxazolones with azodicarboxylates leading to the formation of 1,2,4-triazolines in excellent yields at room temperature. Initially, 4-methyl-2-phenyloxazol-5(4*H*)-one (**1**)[5] was reacted with diethyl azodicarboxylate (DEAD) in dichloromethane at room temperature. The progress of the reaction was monitored by TLC. TLC indicated the disappearance of **1** from the reaction medium in 9 h, at which point the product was isolated and identified to be desired cycloadduct **2** in good yields (Table 1, entry 2).

The reaction was subsequently carried out in a range of solvents including acetonitrile, benzene, diethyl ether, and tetrahydrofuran for a period of 9 h at room temperature (Table 1). Acetonitrile was found to be the superior solvent for this reaction. Further examination of the reaction progress in the optimum solvent, acetonitrile, (data not shown) revealed that compound **1** was quantitatively converted into compound **2** in 11 h (Table 2). Additional monitoring of reaction for 24 h did not cause any degradation of the product or decrease in the yield.

The scope of the reaction was evaluated (Table 2) for commercially available azodicarboxylate compounds and the range of the substituents on the oxazolone. Although the diisopropyl azodicarboxylate (DIAD) is sterically more demanding than DEAD, the reaction with DIAD proceeded smoothly, leading to the excellent yield of the triazoline product **3** (Table 2, entry 2). Similarly, 4-phenyl-1,2,4-triazoline-3,5-dione (PTAD) also rendered the triazoline product **4** in excellent yield (Table 2, entry 3). It should be noted that product **4** was prepared as the TMS methyl ester for ease of purification.

Different oxazolones were prepared from *N*-acyl amino acids, using trifluoroacetic anhydride as dehydrating agent (see Supporting Information) and were subsequently evaluated for their reactivity. Different aromatic groups incorporated at the R^1 position included a phenyl, *p*-methoxy phenyl, *p*-fluoro phenyl, or *p*-nitro phenyl moiety. The reaction of the oxazolones with azodicarboxylates proceeded in very good yields for *p*-methoxy

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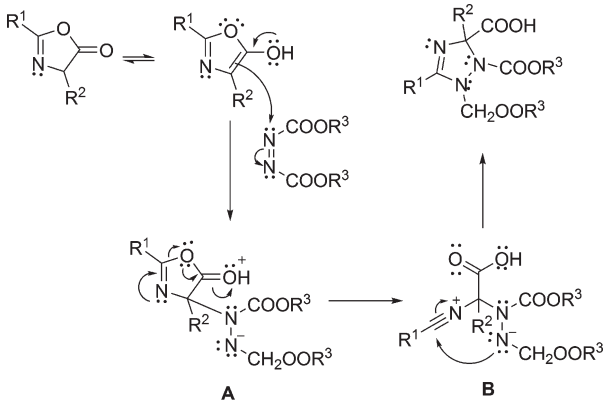
SCHEME 1. Proposed Mechanism of Triazoline Formation



phenyl and *p*-fluoro phenyl moieties (Table 2, entries 5 and 6). As anticipated, the reaction proceeded significantly more slowly when the oxazolones were substituted by the electron-withdrawing *p*-nitro phenyl group (Table 2, entry 4). Switching to a less polar solvent such as dichloromethane increased the yield in this case. The reaction was also amendable to changes at the R^2 position in most cases. The R^2 position was substituted with R^2 being a methyl, benzyl, or isopropyl (Table 2, entries 1, 7−9), which all provided the triazoline product in very good yields. However, the reaction proceeded more slowly in the presence of bulky groups such as an isopropyl group and required more time for completion (24 h).

Additional structural confirmation was established by X-ray crystallography. The crystals of compound **14** (Table 2, entry 8) were grown from dichloromethane−hexanes solution and analyzed by single crystal X-ray crystallography (as shown in Figure 2 in Supporting Information).

The reaction is believed to proceed via electrophilic attack of oxazolone to azodicarboxylate leading to the formation of dipolar intermediate **A**. This intermediate then undergoes ring opening, generating nitrilium intermediate **B**. This intermediate leads to the cycloadduct upon nucleophilic attack by the other nitrogen of azodicarboxylate via a 5-*endo*-*dig*-type ring closure (Scheme 1). Although no detailed mechanistic studies were performed, this mechanism is consistent with all products observed.

Although little is known about the biological properties of triazolines, the 1,2,4-triazole moiety constitutes the core structure of a wide range of compounds that have antiviral, anticancer, anti-inflammatory, and anticonvulsant properties.[11] In addition, this core is part of antiviral, antiasthmatic, antifungal, antibacterial, and hypotonic drugs.[12] The 1,2,4-triazolines produced in this reaction were found to be excellent precursors to prepare the triazoles.

The triazolines prepared herein were readily converted into their corresponding triazoles, after decarboxylation and

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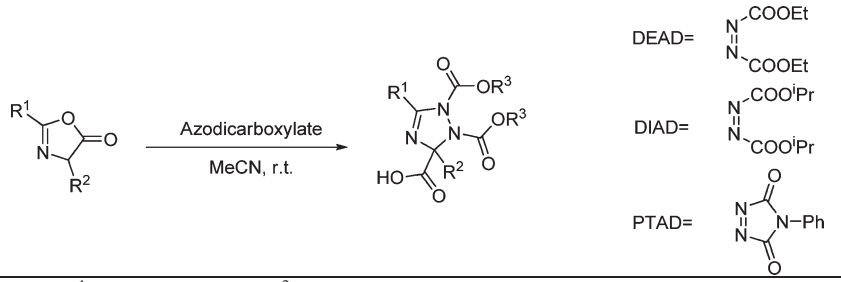
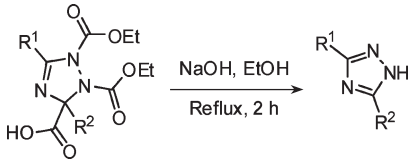
TABLE 2. Scope of the Reaction



entry	substrate	R^1	R^2	azodicarboxylate	product	reaction time (h)	yield (%)
1	**1**	Ph	Me	DEAD	**2**	11	100
2	**1**	Ph	Me	DIAD	**3**	11	99
3	**1**	Ph	Me	PTAD	**4**	4	85[a]
4	**5**	*p*-NO_2-C_6H_4	Me	DEAD	**6**	22	50[b]
5	**7**	*p*-F-C_6H_4	Me	DEAD	**8**	11	98
6	**9**	*p*-MeO-C_6H_4	Me	DEAD	**10**	11	85
7	**11**	Ph	Bn	DEAD	**12**	11	82
8	**13**	Ph	^{i}Pr	DEAD	**14**	22	95[b]
9	**15**	Ph	indolyl-3-methyl	DEAD	**16**	22	94[b]

[a]Isolated as TMS-methyl ester (**17**). [b]Yields of 89%, 84%, and 82% were obtained for entries 4, 8, and 9 respectively, when the reaction was carried out at room temperature for 9 h in dichloromethane using 2 equiv of DEAD.

TABLE 3. Conversion of Triazoline to Triazole



	R^1	R^2	product	yield (%)
1	Ph	Me	**18**	82
2	*p*-NO_2-C_6H_4	Me	**19**	74
3	*p*-F-C_6H_4	Me	**20**	84
4	Ph	indolyl-3-methyl	**21**	83

aromatization. This conversion was achieved in one step in excellent yield using alcoholic sodium hydroxide under refluxing conditions for 2 h (Table 3).

Crystals of compound **18** were grown from dichloromethane solution, and the structure of compound **18** was confirmed by single crystal X-ray crystallography as shown in Figure 3 in Supporting Information.

In conclusion, we report herein an efficient route to synthesize a range of 1,2,4-triazolines at room temperature without the assistance of any catalyst. We have also demonstrated that these heterocycles can further be transformed into triazoles by refluxing in aqueous base. Further work in this field regarding the substrate scope and decoration with various substituents to explore potential biological applications will be reported in due course.

Experimental Section

General Procedure for 1,2,4-Triazoline Formation. One equivalent of the azodicarboxylate was added to a solution of oxazolone (0.5−0.8 mmol) in 10 mL of acetonitrile in a 20 mL scintillation vial. The reaction mixture was stirred at room temperature for 4−22 h. Then the contents of the vial were transferred into a separating funnel containing aqueous sodium bicarbonate and dichloromethane. The product was extracted into the aqueous bicarbonate layer, and the dichloromethane layer was discarded. Then the aqueous sodium bicarbonate layer was acidified with HCl, and the product was extracted four times with 40 mL of dichloromethane. The dichloromethane fractions were combined and dried over sodium sulfate. Then the organic solvent was removed using a rotary evaporator giving the product, which was further dried over vacuum and analyzed.

1,2-Bis(ethoxycarbonyl)-3-methyl-5-phenyl-2,3-dihydro-1*H*-1,2,4-triazole-3-carboxylic Acid (2). ^{1}H NMR (500 MHz) ($CDCl_3$) δ: 7.77 (2H, d, J = 7 Hz), 7.44 (1H, t, J = 7 Hz) 7.36 (2H, t, J = 7 Hz), 4.18 (2H, m), 4.10 (2H, m), 1.76 (3H, s), 1.21 (3H, t, J = 7 Hz), 1.02 (3H, t, J = 7 Hz). ^{13}C NMR (125 MHz) ($CDCl_3$) δ: 171.5, 158.8, 154.3, 152.8, 131.7 (s), 129.7 (s), 128.6, 127.7 (s), 90.2, 63.9 (d), 62.8 (d), 22.6 (t), 14.1 (t), 13.7 (t). IR (film): 1759, 1700, 1631. MS (ES+) m/z: $(M + H)^+$ 350.1. HRMS (ES+): calcd for $C_{16}H_{20}N_3O_6$ $(M + H)^+$ 350.1352, found 350.1354

General Procedure for Conversion of Triazolines to Triazoles. Triazoline (0.5−1 mmol) was dissolved in 25 mL of ethanol in a 100 mL flask. Four equivalents of sodium hydroxide were added to this solution, and the solution was heated to reflux for 2 h. Subsequently, the temperature of the flask was allowed to cool down to room temperature. The excess base in the solution was neutralized with aqueous HCl. Then ethanol was removed on a rotary evaporator, and the residue was dissolved in ethyl acetate. The ethyl acetate solution was washed with brine and dried over sodium sulfate. Subsequently ethyl acetate was removed on a rotary evaporator, and silica-gel column chromatography was performed using ethyl acetate to obtain the triazole.

5-Methyl-3-phenyl-1*H*-1,2,4-triazole (18). ^{1}H NMR (500 MHz) ($CDCl_3$) δ: 7.95 (2H, d, J = 7 Hz), 7.42 (3H, m), 2.45 (3H, s). ^{13}C NMR (150 MHz, −10 °C) (CD_3OD) δ: 162.7, 155.5, 131.7, 130.6(s), 1129.8(s), 127.2 (s), 11.6 (t). IR (film): 3500 (br), 1700, 1720. MS (ES) m/z: $(M)^+$ 159.1. Mp 144−145 °C. HRMS (ES+): calcd for $C_9H_{10}N_3$ $(M + H)^+$ 160.0875, found 160.0880.

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Supporting Information Available: ^{1}H NMR, ^{13}C NMR, and X-ray data including CIF files. This material is available free of charge via the Internet at http://pubs.acs.org.