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Self-Catalyzed Mannich-Type Reaction of Enolizable Cyclic 1,3-Dicarbonyls to Acyclic Nitrones: An Entry to Functionalized β-Enamino Diones

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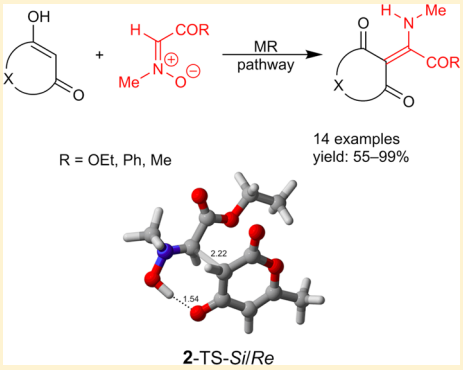
ABSTRACT: A new method for the preparation of highly functionalized β-enamino diones has been developed. The protocol involves an initial self-catalyzed Mannich-type reaction of enolizable cyclic 1,3-dicarbonyls to nitrones, followed by a spontaneous intramolecular reorganization of the resulting nonisolated hydroxylamine to enamino derivatives. These compounds retain the features of unnatural α-amino acids. The ease of preparation makes them attractive intermediates for the synthesis of peptidomimetics, polyheterocycles, and other multifunctional compounds. All experimental results have been efficiently rationalized by in silico studies at the M06-2X level of theory, and a valid mechanistic pathway has been proposed.



INTRODUCTION

Nitrones are powerful tools in organic synthesis. They easily undergo 1,3-dipolar cycloaddition reactions with a large variety of olefinic dipolarophiles. The resulting isoxazolidines are key intermediates for the synthesis of more complex molecular architectures, such as isoxazolidinyl nucleoside analogues.[1−4] In addition to their classical reactivity as 1,3-dipoles, nitrones are able to reacting as electrophiles in nucleophilic addition reactions.[5−7] Representative examples are the organometallic[8,9] and Mannich-type[10] additions.

Over the past years, the reactions between enolizable carbonyl derivatives and a variety of C═N systems, such as imines, iminium ions, hydrazones, and nitrones, have been used for preparing enantiomerically pure amino acids, nucleoside analogues, carbohydrates, and alkaloids.[11]

In particular, the reaction employing preformed imines has received considerable attention as a powerful method for constructing a variety of β-amino carbonyl derivatives.[12−14] Less attention has been paid to other C═N-functionalized substrates, such as nitrones, oximes, and hydrazones, which can also act as electrophiles in this process to generate products containing nitrogen functionality in an intermediate oxidation state, such as hydroxylamino and hydrazine derivatives.[10]

In the framework of our studies dealing with the design of new polifunctionalized *N*,*O*-heterocycles,[15−25] we have found a new route for the construction of unnatural amino acids, in very good yield, starting from a variety of nitrones and selected enolizable cyclic 1,3-dicarbonyls.

Interestingly, the nucleophilic addition of the carbonyls to nitrones is the pathway effectively pursued, and we have observed the formation, under mild conditions, of highly substituted and functionalized β-enaminodione derivatives, retaining the features of unnatural aminoacids.

The synthesis of unnatural amino acids has attracted special attention in recent years.[26] Because of their structural diversity and functional versatility, they are widely used as chiral building blocks in the design and synthesis of combinatorial libraries of pharmacologically relevant molecules, peptidomimetics, and enzyme inhibitors.[27−29]

RESULTS AND DISCUSSION

Chemistry. Initially, we performed preliminary experiments using *C*-ethoxycarbonyl-*N*-methyl-nitrone. Our strategy is outlined in Scheme 1. Enolizable cyclic 1,3-dicarbonyls **1a−h** reacted with nitrone **2** in 1,4-dioxane under reflux conditions, affording the β-ethoxycarbonyl-β-enaminodiones **3a−h**. After work up, the final compounds, having the structure of dehydroamino acids, were isolated in good to excellent yields (Scheme 1).

All products **3a−h** were characterized by spectroscopic methods and were exclusively observed as the β-enamino dione tautomer (Scheme 2, form **A**) under the studied conditions, according to the literature.[30,31]

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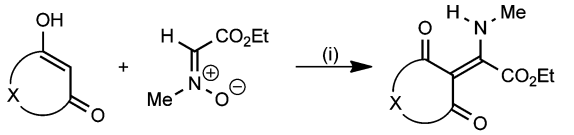
Scheme 1. Synthesis of Compounds 3a–h and Yields[a]



1a–h 2 3a–h

	X	Yield %		X	Yield %		X	Yield %
a		88	d		65	g		86
b		99	e		76	h		55
c		80	f		85			

[a]Key: (i) 1,4-dioxane, reflux, 1 h; yields referred to pure isolated compounds.

Scheme 2. Tautomers of Compounds 3a–h: Enaminone Form A and Ketoenol Form B

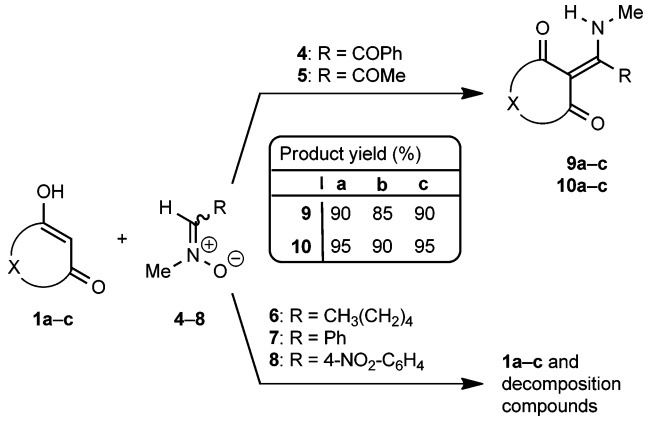
A B

Moreover, for asymmetric compounds **3b**, **3f**, and **3g**, both *E*/*Z* diastereomers were observed (*E*/*Z* ratio 2.5–2.8:1); the assignment of stereochemistry was made on the basis of the chemical shift observed for the NH proton of symmetric compounds **3a,c,d,e**, and for compounds **3b**, further confirmed by selective heteronuclear 1D NOE (s-1DHOESY) experiments and DFT calculations. In particular, for compounds **3a,d,e** the NH proton, hydrogen bonded with the carbonyl moiety, resonates at 12.1–12.3 ppm, whereas in compound **3c**, in which the hydrogen bond is established with a carbamoyl moiety, it resonates highfield, at 11.3 ppm. So, in the ^{1}H NMR spectra of *E*/*Z* mixtures of compounds **3b,f,g** the observed resonances at 12.9–13.4 ppm are reasonably due to (*E*)-isomer, whereas the ones at 10.8–12.0 ppm belong to the (*Z*)-isomer. Moreover, for compounds **3b** the s-1DHOESY on proton at 12.9 ppm gives rise to an enhancement of the carbonyl resonance at 185.0 ppm whereas the same experiment conducted on the signal at 10.8 ppm shows an enhancement of the resonance at 164.6 ppm, according with the ^{1}H NMR observations.

Thus, we turned our attention to testing the reactivity of nitrones **4–8** toward seleted enolizable cyclic 1,3-dicarbonyls **1a–c** (Scheme 3). Under similar reaction conditions, the expected *β*-enaminodione derivatives **9a–c** and **10a–c** were isolated only with nitrones **4** and **5**, bearing a carbonyl group on the carbon atom. Conversely, the proposed reaction carried out using nitrones **6–8**, without a carbonyl group, did not proceed and upon further 2, 4, 8, 16 h of reflux we isolated only reduced quantities of the initial 1,3-dicarbonyl and an ever more complex mixture of decomposition compounds.

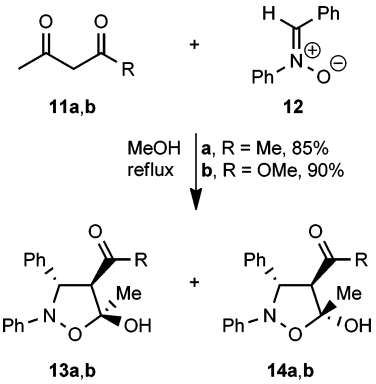
Considerations on Reaction Mechanism. To date, only one paper reports the formal 1,3-dipolar cycloaddition (1,3-DC) between a nitrone and some 1,3-dicarbonyl compounds.[32] In Scheme 4, we report the reaction of *C*,*N*-diphenyl nitrone **12**

Scheme 3. Synthesis of Compounds 9a–c and 10a–c and Yields



Product yield (%)			
	a	b	c
9	90	85	90
10	95	90	95

Scheme 4. Reaction of *C*,*N*-Diphenyl Nitrone 12 with Dicarbonyls 11[32]



11a,b 12 13a,b 14a,b

with dicarbonyls **11a,b** that resemble the cyclic ones, **1a,b**, used by us. In both cases, only the two anomeric hemiacetals **13** and **14** have been isolated, with an overall yield of 85–90%.

Compounds containing a 5-hydroxyisoxazolidinyl core have been isolated as stable products both from 1,3-DC of nitrones to enolic substrates[33−38] and Mannich-type reaction (MR) of *N*-alkylhydroxylamines to *α*,*β*-insaturated carbonyl compounds;[39−42] in two of these cases, it was demonstrated that there exists a hemiketal equilibrium of 5-hydroxyisoxazolidines that involves a ring-opening and subsequent recyclization of the corresponding hydroxylamine acyclic isomers[33,37] and in one of these cases the hydroxylamine intermediate was isolated as stable compound.[33] Moreover, the dehydration of 5-hydroxyisoxazolidine core to the corresponding Δ^4-isoxazoline one was never observed if not intentionally induced by a quantitative Lewis acid treatment at reflux temperature in toluene.[43]

On the basis of aforementioned experimental results, the formation of compounds **3** can occur, theoretically, by an initial five-membered concerted [3 + 2] 1,3-DC or by an initial seven-membered concerted Mannich-type reaction (MR) of the enolic compounds **1** to the electron-poor nitrone **2**, followed by a dehydration of the enolic form **III** of the hydroxylamine intermediate **II** (Scheme 5). The reaction via 1,3-DC leads to the nonisolated 5-hydroxyisoxazolidine derivative **I** that

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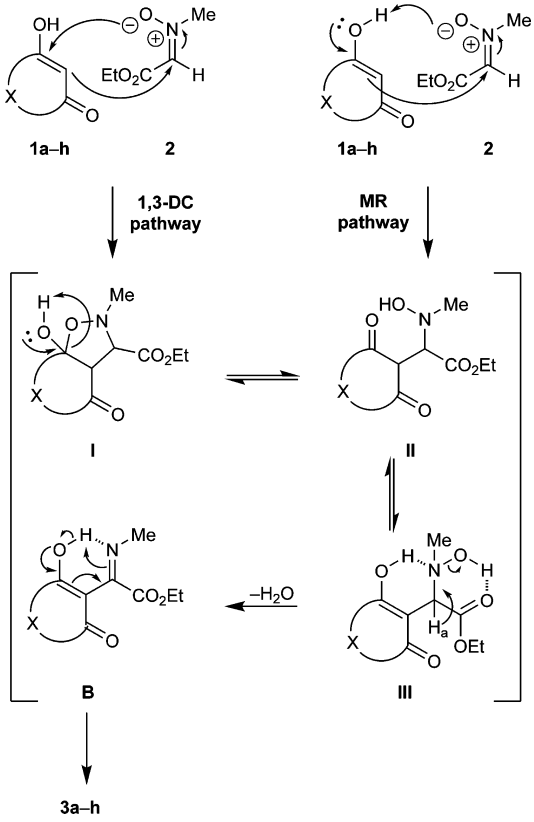
Scheme 5. Proposed Mechanisms for the Obtainment of Compounds 3a–h



equilibrates with **II**, whereas in the MR the hydroxylamine intermediate **II** is directly generated; finally, the intermediate **II** enolizes to **III** (due to the formation of two intramolecular cyclic six-membered hydrogen bonds), which dehydrates to the corresponding imine **B** that tautomerizes to the more stable compound **3**.

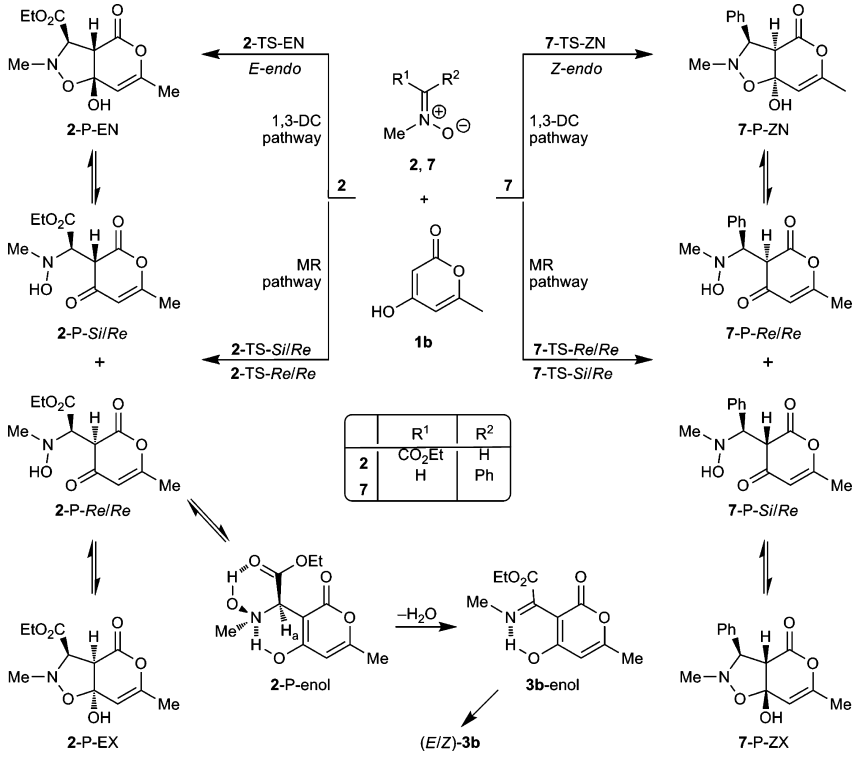
Computational Studies. To solve which of the two proposed pathways, 1,3-DC or MR, is effectively pursued, to get more insight into the reaction mechanisms, and to understand the failure of the reaction with *C*-aryl and *C*-alkyl nitrones **6**–**8**, we have conducted a DFT computational study at the M06-2X level of theory[44,45] and the Dunning's correlation-consistent polarized valence triple-ζ (cc-pVTZ)[46] basis set in dioxane with the polarizable continuum model (PCM) developed by Tomasi and co-workers,[47] choosing the asymmetric enol **1b** and nitrones **2** and **7** as representative model compounds.

For all carbonyls at hand, it is already documented that they exist in equilibrium between enolic and dicarbonyl tautomers, whose distribution depends by solvent and temperature; however, we computationally verified that, in dioxane at 25 °C, the enolic form of compound **1b** is more stable than the ketonic one by 2.09 kcal/mol, so we utilize only it for computation purposes.

Considering that nitrone **2** exists as a mixture of *E*/*Z*-isomers (3.5:1) with the *E*-one being more reactive,[48] and in the *cisoid* conformation,[49] and nitrone **7** exists only as *Z*-isomer,[50] and that both undergo 1,3-DC to enols with the exclusive formation of 5-regioisomers,[48] we have studied, at first approach and only for comparative energy evaluation respect to MR pathway, the transition states originating from a 5-*E*-*endo* and 5-*Z*-*endo* approach to nitrones **2** and **7**, respectively (Scheme 6).[48] In both cases, the *endo* approach was referred to the enolic hydroxyl.

The MR pathway was studied considering the approach of both *Re* and *Si* faces of enol **1b** to the *Re* face of nitrones **2** and

Scheme 6. Nomenclature Used for Defining Transition States and Stationary Points of 1,3-DC and MR Pathways



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7 in *E*- and *Z*-configuration, respectively. The nomenclature used for defining stationary and transition-state points for the 1,3-DC and MR is given in Scheme 6, whereas Table 1 reports all enthalpies and free energies for transition states, intermediates, and products involved in the two proposed pathways.

Table 1. M06-2X Relative Enthalpies (ΔH) (kcal/mol) and Relative Free Energies (ΔG) (kcal/mol) for the Reactions of Enol 1b with Nitrones 2 and 7

entry	transition states and stationary points[a]	ΔH[b]	ΔG[b]
1	**2**-TS-EN	18.73	31.97
2	**2**-TS-*Re*/*Re*	3.01	17.14
3	**2**-TS-*Si*/*Re*	4.05	17.86
4	**2**-P-*Re*/*Re*	−16.59	−2.68
5	**2**-P-*Si*/*Re*	−16.66	−1.94
6	**2**-P-EX	−14.55	−0.04
7	**2**-P-EN	−16.59	−1.81
8	**2**-P-enol	−25.33	−11.57
9	**3b**-enol	−52.85	−51.24
10	(*E*)-**3b**	−56.37	−54.74
11	(*Z*)-**3b**	−55.71	−54.12
12	**2**-pre-TS-*Re*/*Re*	−9.88	−0.95
13	**2**-pre-TS-*Si*/*Re*	−10.09	0.22
14	**7**-TS-ZN	18.99	34.07
15	**7**-TS-*Re*/*Re*	3.41	17.52
16	**7**-TS-*Si*/*Re*	7.05	20.36
17	**7**-P-*Re*/*Re*	−8.92	3.84
18	**7**-P-*Si*/*Re*	−10.10	3.49
19	**7**-P-ZN	−10.20	5.26
20	**7**-P-ZX	−10.97	4.34

[a]For nomenclature, see Scheme 6. [b]Relative to reagents, **1b** + **2** or **1b** + **7**; for TS read as activation enthalpy and activation free energy.

From inspection of Table 1, it is evident that the 1,3-DC of dicarbonyl **1b** with both nitrones **2** and **7** possess a higher activation energy with respect to the MR (up to 14−16 kcal/mol, entries 1 and 14 vs 2 and 15, respectively), so only this last pathway effectively operates. In the case of MR of **1b** with **2**, both *Si* and *Re* channels are populated (entries 2 and 3) leading to intermediate products **2**-P-*Re*/*Re* and **2**-P-*Si*/*Re* (entries 4 and 5) that rapidly tautomerize to give, in both cases, the more stable **2**-P-enol (entry 8). In the most stable conformation of **2**-P-enol the relatively acid proton H_a and the hydroxylaminic hydroxyl are reciprocally diaxial and antiperiplanar so that the dehydration, by an E2 elimination, is deeply favored (Figure 1) and the afforded **3b**-enol rearranges in the *E*/*Z* mixture of the final most stable compound **3b**, with the *E*-isomer that predominates according to its higher stability (entries 10 vs 11). Moreover, the intrinsic reaction path (IRC) from **2**-TS-*Si*/*Re* and **2**-TS-*Re*/*Re* to reactants gives a molecular complex, pre-**2**-TS-*Si*/*Re* and pre-**2**-TS-*Re*/*Re*, respectively, in which the enolic hydrogen atom of **1b** establishe a hydrogen bond with the oxygen atom of nitrones **2** and **7**. Finally, the two intermediate compounds **2**-P-*Si*/*Re* and **2**-P-*Re*/*Re* are in equilibrium with their closed isoxazolidine isomers **2**-P-EN and **2**-P-EX, formally corresponding to the products of the direct 1,3-DC channel, but the dehydration step shifts the equilibrium to compound **3b**.

In the case of the MR of **1b** with **7** the two intermediates **7**-P-*Re*/*Re* and **7**-P-*Si*/*Re* are both higher in energy with respect to the reactants (entries 17 and 18) so the endoergonicity of the reaction precludes the obtainment of the hydroxylamine and the prolonged reaction times give rise only to a moderate recovery of the starting dicarbonyl, whereas the nitrone is degraded.

Presumably, nitrones **4** and **5** operate as nitrone **2**; in these cases, the more electron-withdrawing carbonyl group improves both the hydrogen bond of the hydroxylamine intermediate and the acidity of H_a, making the dehydration easier.

For the asymmetric products **3b**, **3f**, and **3g**, dealing with a tautomerization process, the *E*/*Z* configuration ratio respects the thermodynamic stabilities.

Interestingly, the concerted MR at hand, engaging eight electrons in a pericyclic process, should be forbidden according to Woodward−Hoffmann (WH) rules. A more detailed study inside the IRC path showed that the process takes a roundabout route to avoid the direct approach of the two molecules and the violation of the WH rules. In Table 2 are resumed the opportunely selected bond lengths, Wiberg bond indexes[52] (WIs) (utilized to obtain a more deepen analysis of the extent of bond formation or bond breaking along a reaction pathway), and NPA charges for the key stages involved in the MR of ketoenol **1b** to nitrone **2**, computed by using the NBO population analysis as implemented in Gaussian 09. From the comparison of the WIs between the reactants and the **2**-pre-TS-*Si*/*Re* intermediate it is evident the formation of the hydrogen bond, already highlighted by the high negative enthalpy of reaction (−10.09 kcal/mol, Table 1), accomplished by a change in the charges of the two carbon atoms directly involved in the MR; the C_{enol} becomes slightly more negative (−0.47 to −0.49 au), whereas the $C_{nitrone}$ becomes almost neutral and the entire nitrone fragment takes a slight positive charge (0.06 au). This picture can be interpreted as an internal H-bonding additive that acts like Lewis acid catalysts;[53,54] i.e., the reaction is triggered by acid self-catalysis.

Successively, at the TS (**2**-TS-*Si*/*Re*) the enolic hydrogen results almost completely transferred to the nitronic oxygen and the WI of 0.59 is very close to that of 0.73 calculated for both reactant **1b** and product **2**-P-*Si*/*Re*, whereas the incoming bond between C_{enol}−$C_{nitrone}$ atoms has a WI of only 0.31 with respect to the 0.94 value observed in the product. Moreover, considering that the enolic hydrogen now belongs to the nitrone moiety, the NPA charge on nitrone fragment is 0.71 au and the same charge with opposite sign is on the quasi enolate **1b**, which is the reaction pass to charge control. Then the MR is characterized by a concerted but very asynchronous self-catalyzed process that permits bypassing the violation of WH rules.

Finally, from the results of the second-order perturbation theory (SOPT) analysis of the Fock matrix in NBO basis, according to the definition of delocalization energy given by Weinhold,[55,56] it emerges that the TS is stabilized by a series of delocalizations of which the main are the n→π^* (136.08 kcal/mol) of the C_{enol} *p*-orbital (the quasi-anion sp^2 hybridized carbon atom, i.e., the nucleophilic center) with the antibonding orbital of the $C_{nitrone}$=$N_{nitrone}$ double bond and the n→σ^* (42.05 kcal/mol), due to the O_{enol} long pair with the antibonding orbital of the $O_{nitrone}$−H_{enol} single bond (Figure 2); a series of minor secondary orbitals interactions between the lactone and ester moieties further contributing to the stabilization. This is in accord with an almost complete transfer, at the TS, of the enolic proton to the nitrone oxygen atom, and now, the quasi-enolate anion acts as nucleophile on the quasi-protonate nitrone (see the animated IRC.gif).

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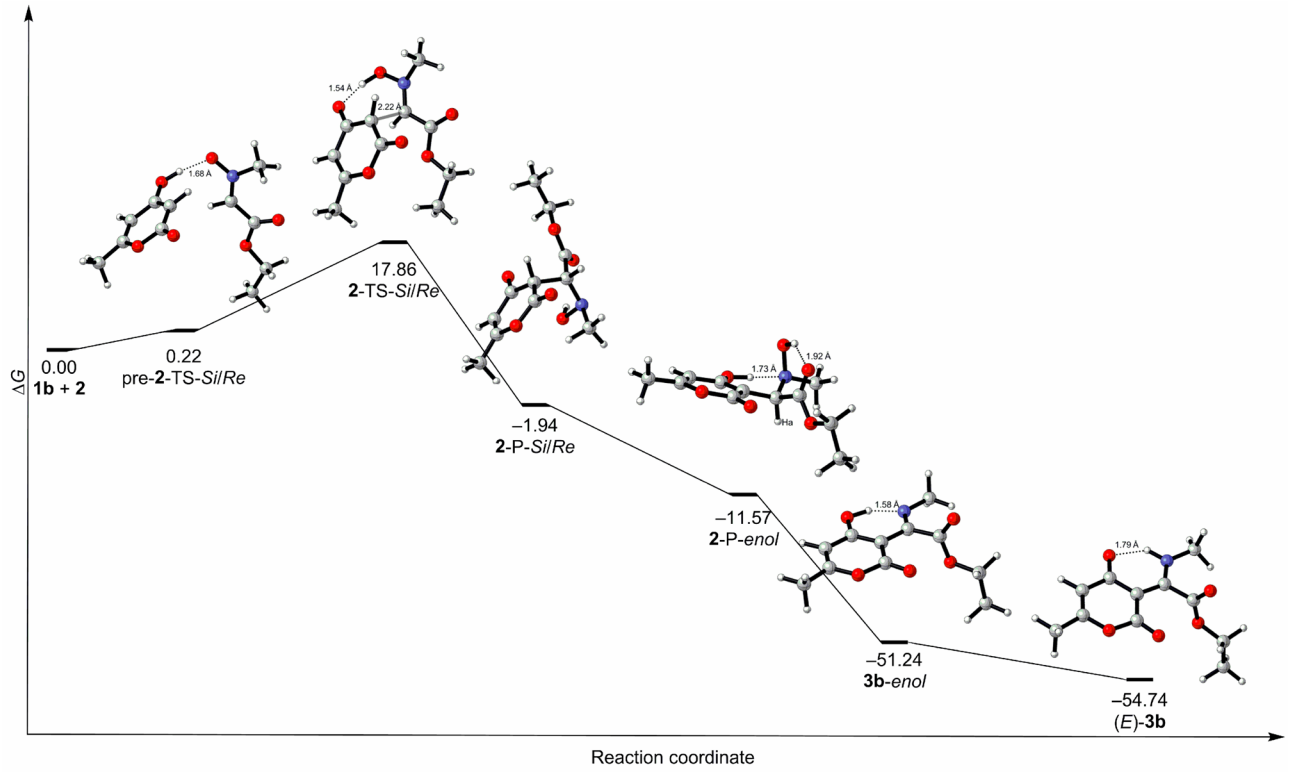

Figure 1. Transition states, intermediates, and product for the MR reaction of **1b** with **2** according to *Si*/*Re* channel. Carried out with CYLview.[51]

Table 2. Bond Lengths (Å), Bond Orders (Wiberg Indexes), and NPA Charges (au) for the Key Stages of the MR of Enol 1b to Nitrone 2

	Bond lengths/Wiberg indexes			NPA charges		
transition states and stationary points[a]	O−H enol	O−H nitrone	C_{enol}−$C_{nitrone}$	C_{enol}	$C_{nitrone}$	nitrone fragment
1b	0.96/0.73			−0.47		
2					−0.15	
2-pre-TS-*Si*/*Re*	0.99/0.63	1.67/0.08	3.43/0.00	−0.49	−0.09	0.06
2-TS-*Si*/*Re*	1.54/0.13	1.02/0.59	2.22/0.31	−0.53	0.06	0.71[b]
2-P-*Si*/*Re*		0.96/0.73	1.56/0.94	−0.46	−0.11	

[a]For nomenclature, see Scheme 6. [b]With enolic hydrogen.

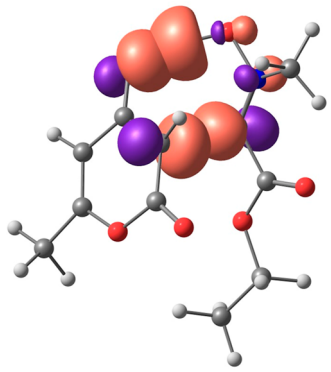

Figure 2. Principal orbital interactions for **2**-TS-*Si*/*Re* as derived by the SOPT analysis.

CONCLUSION

In conclusion, an efficient approach for the synthesis of highly substituted and functionalized *β*-enamino diones has been achieved. Their formation was computationally rationalized in terms of an initial self-catalyzed MR of the enolic form of dicarbonyls to nitrones leading to an hydroxylamine intermediate; the latter, upon dehydration, furnishes the desired product.

The procedure offers several advantages, including mild conditions, high product yield, and simple workup, and provides straightforward access to important synthetic intermediates.

The observed results and the reaction mechanism have been rationalized on the basis of an in silico study at the quantum mechanical DFT level of calculation in dioxane that has evidenced the importance of the *C*-substituent in the nitrone. A fine-tuning of this substituent could expand the possibilities of this reaction and future developments of the discussed approach are expected to contribute to the synthesis of more complex molecular architectures and novel biologically interesting compounds.

EXPERIMENTAL SECTION

General Remarks. Melting points were determined on a melting point apparatus and are uncorrected. IR spectra were recorded in Nujol. ^{1}H and ^{13}C NMR spectra were obtained on a 500 MHz

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spectrometer at 300 K. The chemical shifts (δ) and coupling constants (J) are expressed in ppm and hertz, respectively. Microanalyses are reported. Mass spectrometry analyses were carried out on a mass spectrometer. All solvents and reagents were obtained from commercial sources and purified before use if necessary. TLC separations were performed on silica gel GF_{254} plates; silica gel 60 (0.063−0.100 mm) was used for column chromatography. Nitrones were prepared according to literature procedures.[57,58]

Typical Experimental Procedure for the Preparation of Compounds 3a−h, 9a−c, and 10a−c. 1,3-Dicarbonyl **1a−h** (500 mg; 1 equiv) and nitrone **2**, **4**, **5** (1 equiv) were dissolved in 1,4-dioxane. The reaction mixture was stirred and heated at reflux for 1 h. The solvent was removed by vacuum evaporation, and the residue was purified by flash column chromatography on silica gel (eluent CH_2Cl_2/EtOAc 95:5) or recrystallization from CH_2Cl_2/Et_2O to afford **3a−h**, **9a−c**, and **10a−c**. Compounds **3b**, **3f**, **3g**, **9b**, and **10b** were isolated by column chromatography as an inseparable mixture of E/Z isomers; the E/Z ratio was determined on the crude reaction mixture in perdeuterated 1,4-dioxane, and the reported percent yields are referred to these measurements.

Ethyl 2-(2,6-dioxocyclohexylidene)-2-(methylamino)acetate (3a): yellowish solid; yield 900 mg; 88%; mp 108−110 °C; IR (Nujol, ν, cm^{-1}) 1742, 1653, 1582; ^1H NMR (500 MHz, $CDCl_3$) δ = 12.3 (bs, 1H), 4.47 (q, J = 7.1 Hz, 2H), 3.07 (d, J = 5.3 Hz, 3H), 2.52 (t, J = 6.0 Hz, 2H), 2.46 (t, J = 6.0 Hz, 2H), 1.97 (quin, J = 6.0 Hz, 2H), 1.42 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 200.7, 195.0, 162.7, 162.4, 106.0, 62.6, 37.9, 37.2, 31.2, 19.4, 13.8; MS (ESI) m/z 226 $[M + H]^+$. Anal. Calcd for $C_{11}H_{15}NO_4$: C, 58.66; H, 6.71; N, 6.22. Found: C, 58.76; H, 6.73; N, 6.19.

(*E*,*Z*)-Ethyl 2-(6-methyl-2,4-dioxo-2*H*-pyran-3(4*H*)-ylidene)-2-(methylamino)acetate (3b): inseparable 2.5:1 mixture of E/Z isomers; mp 182−183 °C; white solid; yield 950 mg; 99%; IR (Nujol, ν, cm^{-1}) 1746, 1713, 1652, 1592; (E)-isomer (70.7%) ^1H NMR (500 MHz, $CDCl_3$) δ = 12.9 (bs, 1H), 5.69 (s, 1H), 4.51 (q, J = 7.2 Hz, 2H), 3.14 (d, J = 5.4 Hz, 3H), 2.12 (s, 3H), 1.40 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 185.0, 165.2, 164.6, 161.0, 107.3, 93.9, 63.3, 32.2, 20.1, 13.79; (Z)-isomer (28.3%) ^1H NMR (500 MHz, $CDCl_3$) δ = 10.8 (bs, 1H; NH), 5.68 (s, 1H, CH), 4.51 (q, J = 7.2 Hz, 2H, CH_2), 3.17 (d, J = 5.4 Hz, 3H, CH_3), 2.13 (s, 3H, CH_3), 1.42 (t, J = 7.1 Hz, 3H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 185.0, 165.2, 164.6, 161.0, 108.2, 93.9, 63.2, 31.9, 19.9, 13.84; MS (ESI) m/z 240 $[M + H]^+$. Anal. Calcd for $C_{11}H_{13}NO_5$: C, 55.23; H, 5.48; N, 5.86. Found: C, 55.12; H, 5.46; N, 5.88.

Ethyl 2-(1,3-dimethyl-2,4,6-trioxotetrahydropyrimidin-5(6*H*)-ylidene)-2-(methylamino)acetate (3c): purple solid; yield 700 mg; 80%; mp 113−115 °C; IR (Nujol, ν, cm^{-1}) 1738, 1713, 1645, 1592; ^1H NMR (500 MHz, $CDCl_3$) δ = 11.3 (bs, 1H), 4.60−4.44 (m, 2H), 3.32 (s, 3H), 3.29 (s, 3H), 3.13 (d, J = 5.3 Hz, 3H), 1.43 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 165.5, 163.3, 161.9, 161.6, 151.5, 88.6, 63.0, 31.7, 27.8, 27.4, 13.9; MS (ESI) m/z 270 $[M + H]^+$. Anal. Calcd for $C_{11}H_{15}N_3O_5$: C, 49.07; H, 5.62; N, 15.61. Found: C, 49.18; H, 5.63; N, 15.57.

Ethyl 2-(3,5-dioxo-2*H*-thiopyran-4(3*H*,5*H*,6*H*)-ylidene)-2-(methylamino)acetate (3d): yellow solid; yield: 600 mg; 65%; mp 135−136 °C; IR (Nujol, ν, cm^{-1}) 1747, 1670, 1576; ^1H NMR (500 MHz, $CDCl_3$) δ = 12.1 (bs, 1H), 4.44 (q, J = 7.1 Hz, 2H), 3.36 (s, 2H), 3.31 (s, 2H), 3.09 (d, J = 4.5 Hz, 3H), 1.39 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 195.1, 189.5, 164.4, 162.0, 105.2, 62.7, 36.3, 35.9, 31.6, 13.8; MS (ESI) m/z 244 $[M + H]^+$. Anal. Calcd for $C_{10}H_{13}NO_4S$: C, 49.37; H, 5.39; N, 5.76, S 13.18. Found: C: 49.26; H, 5.38; N, 5.77, S 13.22.

Ethyl 2-(4,4-dimethyl-2,6-dioxocyclohexylidene)-2-(methylamino)acetate (3e): yellowish solid; yield: 700 mg; 76%; mp 95−96 °C; IR (Nujol, ν, cm^{-1}) 1747, 1670, 1576; ^1H NMR (500 MHz, $CDCl_3$) δ = 12.1 (bs, 1H), 4.50 (q, J = 7.1 Hz, 2H), 3.00 (d, J = 5.5 Hz, 3H), 2.32 (s, 2H), 2.26 (s, 2H), 1.34 (t, J = 7.1 Hz, 3H), 0.99 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 200.0, 194.6, 162.5, 162.2, 104.8, 67.0, 62.5, 51.6, 50.9, 31.3, 30.9, 28.1, 13.8; MS (ESI) m/z 254 $[M + H]^+$. Anal. Calcd for $C_{13}H_{19}NO_4$: C, 61.64; H, 7.56; N, 5.53. Found: C, 61.72; H, 7.58; N, 5.51.

Ethyl (*E*,*Z*)-2-(2,4-dioxo-1,2-dihydroquinolin-3(4*H*)-ylidene)-2-(methylamino)acetate (3f): inseparable 2.8:1 mixture of E/Z isomers; mp 209−210 °C; yellowish solid; yield 720 mg; 85%; IR (Nujol, ν, cm^{-1}) 3248, 1748, 1662, 1578; (E)-isomer (62.6%) ^1H NMR (500 MHz, $CDCl_3$) δ = 13.4 (bs, 1H), 10.3 (s, 1H), 8.09−7.00 (m, 4H), 4.65−4.58 (m, 2H), 3.21 (d, J = 5.3 Hz, 3H), 1.44 (t, J = 7.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 183.1, 164.5, 164.1, 140.1, 133.7 133.6, 125.9, 122.5, 120.4, 115.8, 98.9, 62.9, 31.8, 14.1; (Z)-isomer (22.4%) ^1H NMR (500 MHz, $CDCl_3$) δ = 12.0 (bs, 1H), 9.4 (s, 1H), 8.09−7.00 (m, 4H), 4.56−4.45 (m, 2H), 3.23 (d, J = 5.3 Hz, 3H), 1.46 (t, J = 7.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 183.0, 164.6, 162.0, 140.1, 133.4, 133.3, 126.2, 122.1, 120.4, 115.8, 98.9, 62.7, 31.8, 14.1; MS (ESI) m/z 275 $[M + H]^+$. Anal. Calcd for $C_{14}H_{14}N_2O_4$: C, 61.31; H, 5.14; N, 10.21. Found: C, 61.42; H, 5.15; N, 10.18.

(*E*,*Z*)- Ethyl 2-(2,4-dioxochroman-3-ylidene)-2-(methylamino)acetate (3g): inseparable 2.7:1 mixture of E/Z isomers; mp 133−135 °C; white solid; yield 750 mg; 86%; IR (Nujol, ν, cm^{-1}): 1737, 1709, 1641, 1596; (E)-isomer (62.7%) ^1H NMR (500 MHz, $CDCl_3$) δ = 13.1 (bs, 1H), 8.03−7.20 (m, 4H), 4.53 (q, J = 6.9 Hz, 2H), 3.22 (d, J = 5.3 Hz, 3H), 1.43 (t, J = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 182.1, 165.6, 161.9, 161.0, 154.3, 134.5, 126.4, 125.7, 123.9, 120.0, 117.0, 94.4, 63.3, 32.4, 13.8; (Z)-isomer (23.3%) ^1H NMR (500 MHz, $CDCl_3$) δ = 11.1 (bs, 1H), 8.03−7.20 (m, 4H), 4.59 (q, J = 6.9 Hz, 2H), 3.23 (d, J = 5.3 Hz, 3H), 1.45 (t, J = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 177.1, 164.3, 161.9, 161.0, 154.3, 134.5, 126.2, 125.6, 124.3, 120.4, 116.9, 94.8, 63.2, 32.0, 13.8; MS (ESI) m/z 276 $[M + H]^+$. Anal. Calcd for $C_{14}H_{13}NO_5$: C, 61.09; H, 4.76; N, 5.09. Found: C, 61.22; H, 4.78; N, 5.07.

Ethyl 2-(1,3-dioxo-1*H*-inden-2(3*H*)-ylidene)-2-(methylamino)acetate (3h): light orange solid; yield 450 mg; 55%; mp 201−203 °C; IR (Nujol, ν, cm^{-1}) 1742, 1651, 1585; ^1H NMR (500 MHz, $CDCl_3$) δ = 12.3 (bs, 1H), 7.74−7.71 (m, 2H), 7.63−7.60 (m, 2H), 4.57 (q, J = 7.1 Hz, 2H), 3.12 (d, J = 5.5 Hz, 3H), 1.47 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 195.1, 189.5, 164.4, 162.0, 147.8, 145.0, 123.6, 123.5, 118.4, 118.0, 105.2, 62.7, 31.8, 13.8; MS (ESI) m/z 260 $[M + H]^+$. Anal. Calcd for $C_{14}H_{13}NO_4$: C, 64.86; H, 5.05; N, 5.40. Found: C, 64.92; H, 5.06; N, 5.39.

2-(1-(Methylamino)-2-oxo-2-phenylethylidene)cyclohexane-1,3-dione (9a): yellowish solid; yield 1.05 g; 90%; mp 190−191 °C; IR (Nujol, ν, cm^{-1}) 1679, 1642, 1599, 1571; ^1H NMR (500 MHz, $CDCl_3$) δ = 12.4 (bs, 1H), 7.87 (d, J = 7.5 Hz, 2H), 7.59 (t, J = 7.5 Hz, 1H), 7.49 (t, J = 7.5 Hz, 2H), 2.93 (d, J = 5.8 Hz, 3H), 2.57 (t, J = 6.6 Hz, 2H), 2.40−2.30 (m, 2H), 1.99−1.95 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 200.1, 195.6, 189.3, 169.6, 134.7, 133.8, 129.1, 127.6, 108.2, 37.9, 37.0, 31.3, 19.7; MS (ESI) m/z 258 $[M + H]^+$. Anal. Calcd for $C_{15}H_{15}NO_3$: C, 70.02; H, 5.88; N, 5.44. Found: C, 70.10; H, 5.88; N, 5.45.

(*E*,*Z*)-6-Methyl-3-(1-(methylamino)-2-oxo-2-phenylethylidene)-2*H*-pyran-2,4(3*H*)-dione (9b): inseparable 2.6:1 mixture of E/Z isomers; mp 168−170 °C; white solid; yield 1.05 g; 85%; IR (Nujol, ν, cm^{-1}) 1692, 1651, 1581; (E)-isomer (61.4%) ^1H NMR (500 MHz, $CDCl_3$) δ = 13.1 (bs, 1H), 7.90−7.49 (m, 5H), 5.75 (q, J = 1.1 Hz, 1H), 2.98 (d, J = 5.4 Hz, 3H), 2.09 (d, J = 1.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 188.5, 184.9, 171.3, 164.7, 134.7, 129.3, 128.3, 127.7, 107.5, 95.6, 32.0, 20.1; (Z)-isomer (23.6%) ^1H NMR (500 MHz, $CDCl_3$) δ = 10.9 (bs, 1H), 7.90−7.49 (m, 5H), 5.58 (q, J = 1.1 Hz, 1H), 3.00 (d, J = 5.4 Hz, 3H), 2.12 (d, J = 1.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 188.7, 186.5, 170.9, 162.9, 134.3, 129.3, 128.3, 127.7, 108.1, 96.4, 31.9, 19.9; MS (ESI) m/z 272 $[M + H]^+$. Anal. Calcd for $C_{15}H_{13}NO_4$: C, 66.41; H, 4.83; N, 5.16. Found: C, 66.50; H, 4.84; N, 5.14.

1,3-Dimethyl-5-(1-(methylamino)-2-oxo-2-phenylethylidene)pyrimidine-2,4,6(1*H*,3*H*,5*H*)trione (9c): brownish solid; yield 1.23 g; 90%; mp 168−171 °C; IR (Nujol, ν, cm^{-1}) 1711, 1685, 1646, 1582; ^1H NMR (500 MHz, $CDCl_3$) δ = 11.5 (bs, 1H), 7.93 (d, J = 7.5 Hz, 2H), 7.62 (t, J = 7.5 Hz, 1H), 7.52 (t, J = 7.5 Hz, 2H), 3.34 (s, 3H), 3.15 (s, 3H), 2.96 (d, J = 5.7 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 189.2, 169.4, 165.4, 161.9, 151.6, 134.5, 134.3, 129.4, 128.0, 90.3, 31.6, 27.8, 27.5; MS (ESI) m/z 302 $[M + H]^+$. Anal.

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Calcd for $C_{15}H_{15}N_3O_4$: C, 59.79; H, 5.02; N, 13.95. Found: C, 59.86; H, 5.00; N, 13.99.

2-(1-(Methylamino)-2-oxopropylidene)cyclohexane-1,3-dione (10a): yellowish solid; yield 840 mg; 95%; mp 164−166 °C; IR (Nujol, ν, cm^{-1}) 1708, 1641, 1572; ^1H NMR (500 MHz, $CDCl_3$) δ = 12.2 (bs, 1H), 3.03 (d, J = 5.4 Hz, 3H), 2.52 (t, J = 6.4 Hz, 2H), 2.45 (t, J = 6.4 Hz, 2H), 2.43 (s, 3H), 1.96 (quin, J = 6.4 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 200.8, 195.9, 195.8, 170.3, 106.5, 37.8, 37.0, 30.9, 29.4, 19.7; MS (ESI) m/z 196 $[M + H]^+$. Anal. Calcd for $C_{10}H_{13}NO_3$: C, 61.53; H, 6.71; N, 7.18. Found: C, 61.60; H, 6.70; N, 7.16.

(*E*,*Z*)-6-Methyl-3-(1-(methylamino)-2-oxopropylidene)-2*H*-pyran-2,4(3*H*)-dione (10b): inseparable 2.6:1 mixture of *E*/*Z* isomers; mp 123−125 °C; white solid; yield 850 mg; 90%; IR (Nujol, ν, cm^{-1}) 1700, 1650, 1586; (*E*)-isomer (65%) ^1H NMR (500 MHz, $CDCl_3$) δ = 12.8 (bs, 1H), 5.69 (q, J = 0.9 Hz, 1H), 3.08 (d, J = 5.8 Hz, 3H), 2.48 (d, J = 0.9 Hz, 3H), 2.12 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 195.7, 180.3, 171.8, 164.6, 164.2, 107.5, 93.8, 31.6, 29.3, 19.9; (*Z*)-isomer (25%) ^1H NMR (500 MHz, $CDCl_3$) δ = 10.7 (bs, 1H), 5.66 (q, J = 0.9 Hz, 1H), 3.11 (d, J = 5.8 Hz, 3H), 2.46 (d, J = 0.9 Hz, 3H), 2.13 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 195.8, 185.1, 174.4, 166.4, 164.6, 107.9, 95.3, 31.4, 29.4, 19.6; MS (ESI) m/z 210 $[M + H]^+$. Anal. Calcd for $C_{10}H_{11}NO_4$: C, 57.41; H, 5.30; N, 6.70. Found: C 57.34; H, 5.29; N, 6.72.

1,3-Dimethyl-5-(1-(methylamino)-2-oxopropylidene)-pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (10c): brownish solid; yield 1.02 g; 95%; mp 146−147 °C; IR (Nujol, ν, cm^{-1}): 1725, 1709, 1652, 1579; ^1H NMR (500 MHz, $CDCl_3$) δ = 11.2 (bs, 1H), 3.29 (s, 3H), 3.25 (s, 3H), 3.06 (d, J = 5.3 Hz, 3H), 2.49 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 196.2, 170.2, 165.4, 162.3, 151.5, 88.5, 31.2, 29.7, 27.7, 27.4; MS (ESI) m/z 240 $[M + H]^+$. Anal. Calcd for $C_{10}H_{13}N_3O_4$: C, 50.21; H, 5.48; N, 17.56. Found: C, 50.32; H, 5.52; N, 17.60.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^1H and ^{13}C NMR spectra of all new compounds. Additional details on computations, including Cartesian coordinates and energies for computed structures. The animated IRC calculation for the MR of **1b** to **2**. This material is available free of charge via the Internet at http://pubs.acs.org.

Ⓦ Web-Enhanced Feature

An animated molecule is available in the HTML version of the paper.

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Notes

The authors declare no competing financial interest.

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