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Formation of γ-Oxoacids and 1*H*-Pyrrol-2(5*H*)-ones from α,β-Unsaturated Ketones and Ethyl Nitroacetate

Maialen Aginagalde,[‡] Tamara Bello,[‡] Carme Masdeu,[†] Yosu Vara,[†] Ana Arrieta,[‡] and Fernando P. Cossío*,[‡]

[‡]*Kimika Fakultatea, Kimika Organikoa I Saila, Universidad del País Vasco-Euskal Herriko Uniberstitatea, Manuel de Lardizabal Etorbidea 3, 20018 San Sebastián-Donostia, Spain, and* [†]*IkerChem, Ltd., Tolosa Etorbidea 72, 20018 San Sebastián-Donostia, Spain*

fp.cossio@ehu.es

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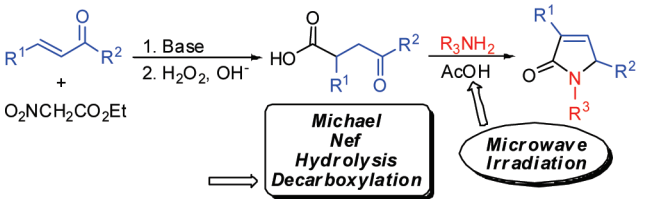

Michael addition of ethyl nitroacetate on α,β-unsaturated ketones followed by Nef oxidation under hydrolytic conditions yields γ-oxoacids instead of the corresponding α,δ-dioxoesters. A concerted decarboxylation step is proposed on the basis of computational results. Finally, conversion of the γ-ketoacids thus prepared into 1*H*-pyrrol-2(5*H*)-ones by reaction with primary amines under Paal−Knorr conditions is also reported.

Oxidative decarboxylation of α-oxoacids is an important biochemical process that requires the participation of enzymes such as the pyruvate dehydrogenase complex that in turn involves acetyl-CoA and NADH as cofactors.[1] This reaction also plays an important role in nonheme iron enzymes such as JMJ2DA histone demethylases.[2] Nonenzymatic related oxidative decarboxylations involving iodine,[2,3] hydroxyamino acids,[4] and Cu(I)/Pd(0) pairs[5] to yield amides and lactones, respectively, have been reported. Similarly, direct conversion of 2-ketoacids[6] into the corresponding carboxyacids by reaction with H_2O_2 or N_2O_3/Amberlist 15[7] has also been described.

Within our ongoing project on chemical applications of the nitro group,[8] we considered the synthetic potential of performing C−C bond forming reactions via nucleophilic addition of nitronates, followed by Nef oxidations in order to obtain α-ketoesters and their derivatives (Scheme 1). We also envisaged the possibility of performing the Nef oxidation[9] under hydrolytic and oxidizing conditions in order to obtain the corresponding carboxylic acid derivatives via oxidative decarboxylation of the in situ generated α-ketoacids.

We chose α,β-unsaturated ketones **1** as suitable electrophiles, in order to achieve an efficient addition of nitronates and enolates to Michael acceptors[10] (Scheme 2). Therefore, this approach should constitute an alternative to the conjugate hydrocyanation of α,β-unsaturated ketones followed by hydrolysis of the nitrile moiety, a methodology that can present regiochemical issues.[11]

When α,β-unsaturated ketones **1a**−**i** were treated with ethyl nitroacetate and triethylamine, a ca. 1:1 mixture of the two possible diastereomers 2-nitro-4-oxoesters was obtained in almost quantitative yield. This mixture of diastereomers was oxidized with H_2O_2/H_2O in K_2CO_3 and methanol at room temperature[12] to yield the corresponding acids **3a**−**h** with medium to good yields. The yields of purified acids **3f**−**h** having alkyl substituents were lower. In these cases, NMR analysis of the crude products revealed less clean reaction mixtures. The structure of acids **3** was verified on the basis of their spectroscopic properties and, in the case of compound **3a**, by X-ray diffraction analysis.[13] When the Nef oxidation was carried out with NaOMe/MeOH under acidic conditions, the expected α,δ-dioxoesters **2a**−**d** were obtained in acceptable yields (Scheme 2).[14] Interestingly, hydrolysis of ethyl ester **2a** (NaOH 5N, rt, overnight) yielded the

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(13) CCDC 770165 and CCDC 770164 contain the supplementary crystallographic data for compounds **3a** and **4b**, respectively. These data can be obtained free of charge via www.ccdc.ac.uk/data_requestcif, by emailing data_request@ccdc.com.ac.uk or by contacting The Cambridge Cristallography Data Centre, 12 Union Rd, Cambridge CB2 1EZ, UK; fax +44 1223 336033.
(14) For a related example see: Milne, C.; Powell, A.; Jim, J.; Al Nakeed, M.; Smith, C. P.; Micklefield, J. *J. Am. Chem. Soc.* **2006**, *128*, 11250–11259.

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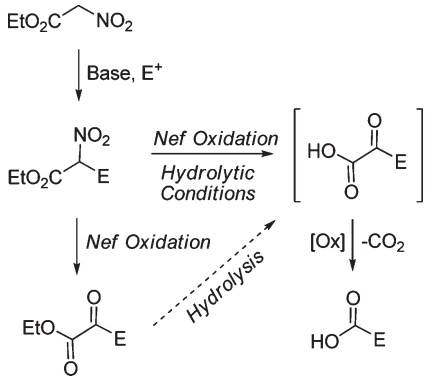
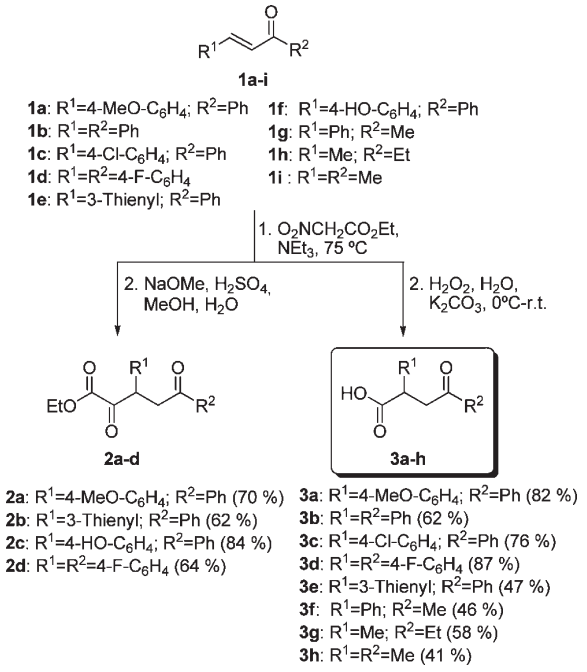
SCHEME 1. Proposed General Synthesis of Carboxylic Acids and α-Ketoesters from Ethyl Nitroacetate



SCHEME 2. Synthesis of γ-Ketoacids 3a−h and α,δ-Ketoesters 2a−d via Conjugate Addition−Nef Oxidation of Chalcones 1a−i



corresponding α,δ-dioxoacid **2a′** in almost quantitative yield (see the Supporting Information for further details). Treatment of this acid with H_2O_2−H_2O/K_2CO_3 at 0 °C−room temperature led to decarboxylated acid **3a** with a yield of 84%.

To gain a better understanding of the decarboxylation step, we performed Density Functional Theory (DFT) based calculations on the reaction between potassium pyruvate and potassium hydroperoxide to yield the corresponding acetate and bicarbonate salts.[15,16] The main stationary points associated with a reasonable reaction coordinate are gathered in

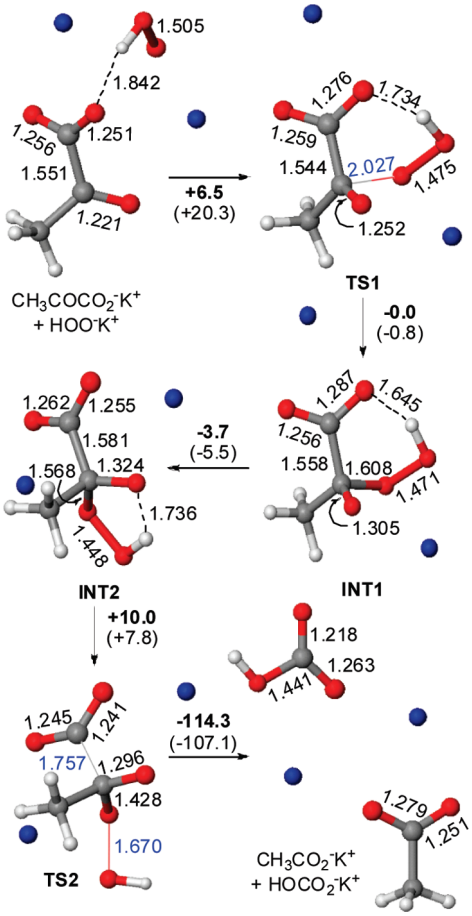


FIGURE 1. Fully optimized (B3LYP/6-311++G** level) stationary points associated with the oxidative decarboxylation of potassium pyruvate in the presence of HOO^-K^+. Carbon, oxygen, and potassium atoms are represented in gray, red, and dark blue colors, respectively. Bond distances are given in angstroms. Numbers close to the arrows are relative energies (in kcal/mol), computed at the B3LYP(PCM,MeOH)/6-311++G**//B3LYP/6-311++G** +ΔZPVE level of theory (gas phase data are given in parentheses).

Figure 1. The reaction starts by a nucleophilic addition of the hydroperoxide anion on the carbonyl group of the pyruvate. The activation barrier associated with this process is much lower in solution than in the gas phase.

The intrinsic reaction coordinate[17] (IRC) study of **TS1** led to intermediate **INT1**, which in turn evolved to the more stable intermediate **INT2**, in which there is a stronger intramolecular hydrogen bond involving 5 atoms instead of 6. Saddle point **TS2** connects **INT1** with the products via a concerted and highly synchronous cleavage of the C−C and O−O bonds. This concerted cleavage of two σ-bonds with a low energy barrier is remarkable. In contrast with the previous barrier, in the second step the computed activation energy is higher in solution than in the gas phase. After IRC analysis of **TS2** and further optimization, the final products are the acetate and bicarbonate anions. The overall reaction is highly exothermic (ΔE_{rxn} = −101.5 kcal/mol in MeOH). This fact and the low activation barriers associated with the

(15) The DFT calculations were carried out using the B3LYP hybrid functional and the 6311++G** basis set. Solvent conditions (MeOH) were considered by means of the PCM method. See: (a) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648–5652. (b) Lee, C.; Yane, W.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785–789. (c) Raghavachari, K.; Binkley, J. S.; Seeger, R.; Pople, J. A. *J. Chem. Phys.* **1980**, *72*, 650–654. (d) Tomasi, J.; Mennucci, B.; Cammi, R. *Chem. Rev.* **2005**, *105*, 2999–3093.

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formation of the O−C bond in **TS1** and with the cleavage of the C−C and O−O bonds in **TS2** are compatible with the easy oxidative decarboxylation experimentally observed.

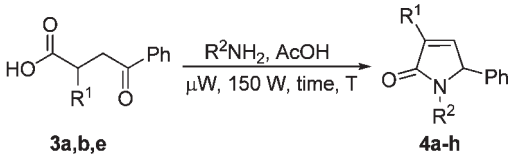
After preparing γ-ketoacids **3**, we tested the application of these compounds to the chemical synthesis of 1*H*-pyrrol-2(5*H*)-ones **4**.[18] These latter compounds are found in many biologically important natural and synthetic compounds.[19]

When a mixture of the γ-ketoacid **3** and an amine or ammonium acetate in acetic acid was irradiated with microwaves at 150 W, the corresponding α,β-unsaturated-γ-lactones **4** were obtained, in general with good yields (Table 1). Under classical heating, no formation of products **4** was observed. In the case of compound **4b** its structure was unambiguously established by X-ray diffraction analysis.[12] According to our results, formation of *N*-aryl derivatives (entries 5 and 6) requires longer reaction times and higher temperatures. *N*-Alkyl derivatives **4b**,**c** (entries 2 and 3) can also be obtained in good yields. However, when the reaction was conducted with α-amino acids or their ester derivatives (entries 8 and 9), the corresponding decarboxylated lactones **4c,h** were obtained in low yields, thus losing the stereochemical information contained in the starting homochiral amino acid moiety.

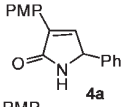
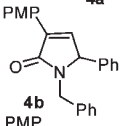
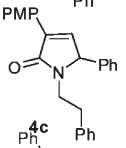
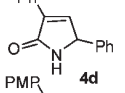
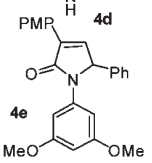
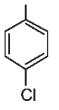
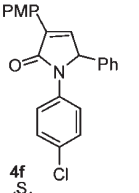
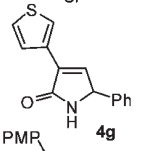
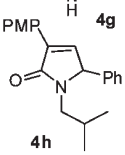
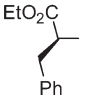
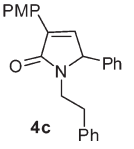
When ethyl esters **2a**−**d** were subjected to similar Paal−Knorr reaction conditions, the expected ethyl 3,5-diaryl-1*H*-pyrrole-2-carboxylates **5a**−**f** were obtained (Scheme 3).[20] For this reaction, the reaction times and temperatures required to obtain the products with good yields under microwave irradiation were similar in all cases and no significant changes in yield were observed on going from *NH* to *N*-aryl derivatives. In the case of pyrrole **5a**, this compound was obtained in a yield of 87% after 45 min of classical heating at the same temperature.

In summary, Michael addition of ethyl nitroacetate on α,β-unsaturated carbonyl compounds followed by Nef oxidation can yield either γ-ketoacids or α,δ-diketoesters depending on the hydrolytic or nonhydrolytic oxidizing reaction conditions. The computational study on a model system supports a reasonable stepwise mechanism for the oxidative decarboxylation of the intermediate α,δ-diketoacids. This proposal is compatible with the reaction conditions of the hydrolytic Nef reaction. Cyclization reaction of these γ-ketoacids in the presence of ammonium salts yields 1*H*-pyrrol-2(5*H*)-ones in good yields, thus providing a novel and convergent entry to these biologically interesting compounds.

TABLE 1. Synthesis of 1*H*-Pyrrol-2(5*H*)-ones[a] 4a−h from γ-Ketoacids 3a,b,e



3a,b,e **4a-h**

entry	3	R^2 or amine	lactam[b] 4	time (min.)	T (°C)	Yield (%)[c]
1	**3a**	NH_4OAc	 **4a**	12	90	72
2	**3a**	$PhCH_2$	 **4b**	12	90	80
3	**3a**	$Ph(CH_2)_2$	 **4c**	12	150	96
4	**3b**	NH_4OAc	 **4d**	45	90	91
5	**3a**		 **4e**	30	200	59
6	**3a**		 **4f**	30	200	89
7	**3e**	NH_4OAc	 **4g**	12	150	93
8	**3a**	L-Val	 **4h**	12	150	32
9	**3a**		 **4c**	45	170	35

[a]Conditions: **3** (0.4 mmol), amine (2 mmol), AcOH (0.1 mL), microwave irradiation. [b]PMP: *p*-methoxyphenyl group. [c]Isolated yields of pure products.

Experimental Section

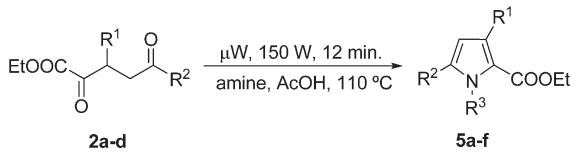
Typical Experimental Procedure for the Preparation of γ-Ketoacids 3a−h. A solution of chalcone **1** (6 mmol) and ethyl nitroacetate (6 mmol) in triethylamine (2.5 mL, 18 mmol) was stirred at 75 °C overnight. Ethyl acetate (100 mL) was added and the solution obtained was washed with 1 N HCl (4 × 50 mL), dried over Na_2SO_4, and evaporated under reduced pressure to yield an oil that was dissolved in MeOH (18 mL). A solution of

(18) For pioneering, although conceptually different methodologies for the preparation of these compounds see: (a) Moon, M. W. *J. Org. Chem.* **1977**, *42*, 2219–2223. (b) Shin, C.; Yonezawa, Y.; Watanabe, E. *Tetrahedron Lett.* **1985**, *26*, 85–88. See also ref 17.

(19) See for example: (a) Snider, B. B.; Neubert, B. J. *J. Org. Chem.* **2004**, *69*, 8952–8955. (b) Gouault, N.; Le Roch, M.; Cornée, C.; David, M.; Uriac, P. *J. Org. Chem.* **2009**, *74*, 5614–5617. (c) Rosas, N.; Sharma, P.; Arellano, I.; Ramírez, M.; Pérez, M.; Hernández, S.; Cabrera, A. *Organometallics* **2005**, *24*, 4893–4895. (d) Shiraki, R.; Sumino, A.; Tadano, K.; Ogawa, S. *Tetrahedron Lett.* **1995**, *36*, 5551–5554. (e) Grison, C.; Genève, S.; Coutrot, P. *Tetrahedron Lett.* **2001**, *42*, 3831–3834. (f) Green, M. P.; Prodger, J. C.; Hayes, C. J. *Tetrahedron Lett.* **2002**, *43*, 6609–6611. (g) Murai, M.; Miki, K.; Ohe, K. *J. Org. Chem.* **2008**, *73*, 9174–9176. (h) Shiraki, R.; Sumino, A.; Tadano, K.; Ogawa, S. *J. Org. Chem.* **1996**, *61*, 2845–2852. (i) Dittami, J. P.; Xu, F.; Qi, H.; Martin, N. W.; Bordner, J.; Decosta, D. L.; Kiplinger, J.; Reiche, J.; Ware, R. *Tetrahedron Lett.* **1995**, *36*, 4201–4204. (j) Green, M. P.; Prodger, J. C.; Hayes, C. J. *Tetrahedron Lett.* **2002**, *43*, 2649–2652.

(20) For a related reaction leading to ethyl 2,5-disubstituted-1*H*-pyrrole-3-carboxylates see: Minetto, G.; Raveglia, L. F.; Sega, A.; Taddei, M. *Eur. J. Org. Chem.* **2005**, 5277–5288.

SCHEME 3. Synthesis of Ethyl 3,5-Diaryl-1*H*-pyrrole-2-carboxylates 5a−f from α,δ-Ketoesters 2a−d under Microwave Irradiation



2a-d **5a-f**

5a: R^1=4-CH_3O-C_6H_4; R^2=Ph; R^3=H (97 %)
5b: R^1=4-CH_3O-C_6H_4; R^2=Ph; R^3=Bn (62 %)
5c: R^1=4-CH_3O-C_6H_4; R^2=Ph; R^3=3,5-$(CH_3O)_2C_6H_3$ (57 %)
5d: R^1=3-Thienyl; R^2=Ph; R^3=H (95 %)
5e: R^1=R^2=4-F-C_6H_4; R^3=H (97 %)
5f: R^1=4-HO-C_6H_4; R^2=Ph; R^3=H (81 %)

H_2O_2 (12 mL, 33% in H_2O) and K_2CO_3 (4.0 g) were added at 0 °C and the mixture was stirred at room temperature overnight. The reaction mixture was acidified with 6 N HCl and then was extracted with CH_2Cl_2 (3 × 25 mL), dried over Na_2SO_4, and evaporated under reduced pressure to yield the corresponding γ-ketoacid **3**, which was triturated with Et_2O.

2-(4-Methoxyphenyl)-4-oxo-4-phenylbutanoic acid (3a): yield 82%, white solid, mp 155−156 °C; ν_{max}/cm^{-1} (KBr) 3038−2839, 2960, 1699, 1673, 1244, 1040; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.95 (d, J = 7.2 Hz, 2H), 7.55 (d, J = 6.9 Hz, 1H), 7.45 (d, J = 7.3 Hz, 2H), 7.29 (d, J = 8.0 Hz, 2H), 6.88 (d, J = 8.1 Hz, 2H), 4.27 (d, J = 5.7 Hz, 1H), 3.87 (dd, J = 17.9, 9.9 Hz, 1H), 3.79 (s, 3H), 3.27 (d, J = 15.2 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 197.7, 178.1, 159.4, 136.6, 133.5, 130.0, 129.3, 128.8, 128.3, 114.6, 55.5, 45.5, 42.6. Anal. Calcd for $C_{17}H_{16}O_4$: C, 71.8; H, 5.7. Found: C, 71.7 ; H, 5.7.

General Procedure for the Preparation of αδ-Dioxoesters 2a−d. A solution of chalcone **1** (6 mmol) and ethyl nitroacetate (6 mmol) in triethylamine (2.5 mL, 17.94 mmol) was stirred at 75 °C overnight. Ethyl acetate (100 mL) was added and the solution obtained was washed with 1 N HCl (4 × 50 mL), dried over Na_2SO_4, and evaporated under reduced pressure, to yield a residue that was treated with a 0.5 M solution of sodium methoxide in methanol (16 mL, 8 mmol). The resulting mixture was stirred for 4 h. Then, it was poured over a mixture of H_2SO_4 (3 mL) and MeOH (16 mL) at −20 °C. The resulting mixture was stirred at 20 °C for 5 min, and then allowed to reach room temperature. H_2O (15 mL) was added, methanol was removed under reduced pressure, and the resulting aqueous solution was extracted with CH_2Cl_2 (2 × 150 mL). The combined organic layers were washed with NaCl (2 × 50 mL, saturated aqueous solution), dried over Na_2SO_4, and evaporated under reduced pressure to obtain the corresponding ethyl esters **2**.

Ethyl 2-(4-methoxyphenyl)-4-oxo-4-phenylbutanoate (2a): yield 70%, yellow oil; ν_{max}/cm^{-1} (KBr) 2979, 2915, 1726, 1679, 1254, 1182, 1035; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.94 (d, J = 7.3 Hz, 2H), 7.61−7.52 (m, 1H), 7.44 (t, J = 7.7 Hz, 2H), 7.29−7.21 (m, 2H), 6.87 (d, J = 8.7 Hz, 2H), 5.09 (dd, J = 10.3, 4.0 Hz, 1H), 4.27 (m, J = 13.1, 8.4, 4.8 Hz, 2H), 3.98 (dd, J = 18.1, 10.4 Hz, 1H), 3.78 (s, 3H), 3.38 (dd, J = 18.1, 4.0 Hz, 1H), 1.30 (t, J = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 197.7, 192.4, 160.8, 159.6, 136.3, 133.6, 130.3, 128.8, 128.4, 127.3, 114.8, 62.6, 55.5, 47.9, 43.1, 14.1. Anal. Calcd for $C_{20}H_{20}O_5$: C, 70.6; H, 5.9. Found: C, 70.5 ; H, 5.8.

General Procedure for the Preparation of 1*H*-Pyrrol-2(5*H*)-ones 4a−h. A mixture of the γ-ketoacid **3** (0.4 mmol), the corresponding amine or ammonium acetate (2 mmol), and acetic acid (0.1 mL) in a closed vessel was irradiated in a monomode microwave oven at 150 W for the time and at the temperature reported in Table 1. After finishing the irradiation, the mixture was allowed to reach room temperature and the vessel was opened. Ethyl acetate (20 mL) was added and the resulting solution was washed with $NaHCO_3$ (3 × 20 mL, saturated aqueous solution), dried over Na_2SO_4, and evaporated under reduced pressure to obtain the corresponding product **4**.

3-(4-Methoxyphenyl)-5-phenyl-1,5-dihydro-2*H*-pyrrol-2-one (4a): yield 72%, white solid, mp 188−190 °C; ν_{max}/cm^{-1} (KBr) 3193, 3054, 2932, 1678, 1261, 1035; ^{1}H NMR (500 MHz, MeOD) δ 7.84 (d, J = 8.4 Hz, 2H), 7.44−7.22 (m, 6H), 6.94 (d, J = 8.4 Hz, 2H), 5.32 (s, 1H), 3.82 (s, 3H); ^{13}C NMR (126 MHz, MeOD) δ 179.3, 169.1, 149.9, 147.0, 145.0, 142.2, 138.6, 138.1, 138.0, 137.8, 137.2, 137.0, 136.8, 133.5, 123.4, 64.7, 53.0. Anal. Calcd for $C_{17}H_{15}NO_2$: C, 77.0; H, 5.7; N, 5.3 . Found: C, 76.8; H, 5.4; N,5.6.

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Supporting Information Available: Full characterization of all novel compounds, crystallographic data of compounds **3a** and **4b**, complete ref 16, and full computational characterization of stationary points reported in Figure 1. This material is available free of charge via the Internet at http://pubs.acs.org.