A Simple Synthesis of 2,3-Diketo Amides from 3-Keto Amides

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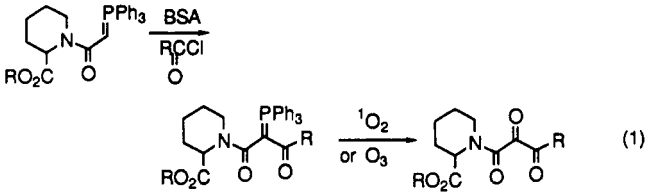
The conversion of 3-keto amides to 2-(nosyloxy)-3-keto amides **4a–g** followed by DBU-promoted, reductive elimination of *p*-nitrobenzenesulfinic acid provides a short, simple method for the preparation of 2,3-dioxo amides (tricarbonyl amides) **5a–f** in high yields.

Introduction

Interest in the chemistry of 1,2,3-tricarbonyl compounds has increased markedly in the last several years because this functional grouping has been found to occur in the powerful imunosuppressant FK-506[1] and related antibiotics[2] and because Wasserman has shown that this functionality is extremely useful for the synthesis of a wide variety of heterocyclic compounds.[3]

While introduction of the tricarbonyl group can be accomplished by a variety of methods,[4-6] most of these have been applied to the production of 1,2,3-triketones and 2,3-diketo esters. Methods for the preparation of 2,3-diketo amides are much less numerous, which is particularly surprising since this functional grouping plays a key, albeit not completely understood, role in the immunosuppressive activity of FK-506.[7] Recently, Wasserman reported that 2,3-diketo amides could be prepared by the oxidative cleavage of phosphoranes obtained by the acylation of amido phosphoranes (eq 1).[4] Danishefsky has also reported a new general route to tricarbonyl amides that uses the Dess–Martin oxidation of 2-(phenylthio)-3-hydroxy amides (eq 2).[8] This 2-fold oxidative approach parallels the strategy used to install the tricarbonyl group in the total synthesis of FK-506.[9]



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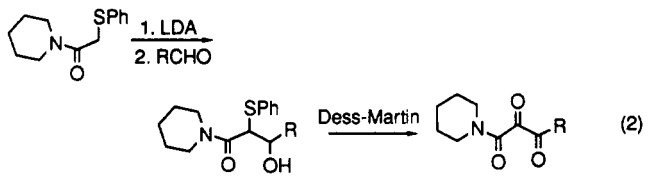
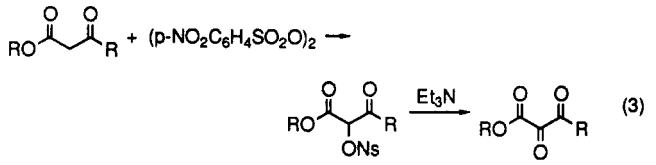


(2)

We have shown previously that 2,3-dioxo esters can be easily prepared from β-keto esters by conversion to 2-(nosyloxy)-3-keto esters with *p*-nitrobenzenesulfonyl peroxide (pNBSP)[10] followed by reductive elimination (eq 3).[11]

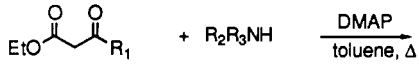


(3)

The extension of similar chemistry to 3-keto amides would provide a short route to 2,3-dioxoamides, which could be applied to the synthesis of a variety of FK-506 analogues with potential immunosuppressive activity. Such has been found to be the case, and this report describes a new route to tricarbonylamides utilizing this approach.

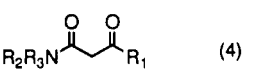
Results and Discussion

The preparation of β-keto amide starting materials **3** was achieved by refluxing a toluene solution of commercially available β-keto esters **1a–e** and an amine **2a–c** in the presence of DMAP according to the procedure of Cossy (eq 4).[12] In our hands, yields of the keto amide products



1a, R_1 = Ph
1b, R_1 = Me
1c, R_1 = i-Pr
1d, R_1 = n-Pr
1e, R_1 = benzyl

2a, R_1=R_2 = Et
2b, R_1=R_2 = $(CH_2)_2O$
2c, R_1=R_2 = $(CH_2)_5$



(4)

3aa(43%), **3ba**(14%), **3ca**(28%), **3da**(27%), **3ab**(46%), **3bc**(18%)

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Table I. Formation of 2-(Nosyloxy)-3-keto Amides from the Reaction of β-Keto Amides with pNBSP and $ZnCl_2$ in Ethyl Acetate at −78 °C

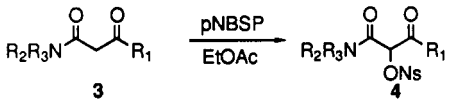
entry	β-keto amide	product	% yield[a]
1	**3aa**, R_1 = Ph, R_2, R_3 = Et	**4a**	77 (55)
2	**3ba**, R_1 = Me, R_2, R_3 = Et	**4b**	83 (66)
3	**3ca**, R_1 = *i*-Pr, R_2, R_3 = Et	**4c**	91 (60)
4	**3da**, R_1 = *n*-Pr, R_2, R_3 = Et	**4d**	93 (47)
5	**3ab**, R_1 = Ph, R_2, R_3 = $(CH_2)_2O$	**4e**	90 (64)
6	**3bc**, R_1 = Me, R_2, R_3 = $(CH_2)_5$	**4f**	92 (62)
7	**3ea**, R_1 = $PhCH_2$, R_2, R_3 = Et	**4g**	100

[a] Yields are isolated yields. Yields in parentheses are recrystallized yields of analytically pure products.

(14–46%) were generally lower than those reported,[12] and some limitations of the method became apparent. The structure of the amine is most important to the success of the reaction. Thus, diethylamine, **2a**, and morpholine, **2b**, gave generally moderate yields of products. However, reaction of piperidine, **2c**, with **1b** gave only a low (18%) yield of keto amide **3bc** even after 7 days of reflux. Pyrrolidine failed to undergo reaction with **1b** after 7 days of reflux. Other reactions were not occurring since only unreacted starting materials were recovered. Presumably, the greater basicity of piperidine and pyrrolidine results in sufficient deprotonation of the keto ester to preclude nucleophilic attack. Primary amines also failed to yield keto amide products, but instead gave only 3-enamino esters as has been reported.[12] While the above procedure afforded usable quantities of β-keto amide starting materials, recent improvements[13] should permit the synthesis of both secondary and tertiary β-keto amides in much better yields.

β-Keto amide **3ea** was prepared by condensation of the anion of *N,N*-diethylacetamide with methyl phenylacetate (72%). This type of condensation provides a versatile alternative route to tertiary β-keto amides as seen in this example and literature reports.[14,15] All of the β-keto amides were found to contain significant amounts (15–53%) of the enol tautomer in chloroform-*d* solution. The extent of enolization was determined by integration of the signals for the methylene group of the keto tautomer (δ 3.5–4.2) and the vinyl hydrogen of the enol tautomer (δ 5.1–5.8).

Reaction of β-keto amides **3aa**, **3ba**, **3ca**, **3da**, **3ab**, **3bc**, and **3ea** with pNBSP in the presence of zinc chloride at −78 °C led to smooth disappearance of the peroxide and consequent formation of 2-(nosyloxy)-3-keto amides **4a–g** in high yields (64–100%) (eq 5). Due to the high enol



3 4 (5)

contents of the starting β-keto amides, reactions were usually complete in about 1 h at −78 °C, and it was determined that comparable results could also be obtained using reaction temperatures up to 0 °C. The crude products were of good purity by ^1H NMR, and recrystallization gave products of analytical purity. The results are shown in Table I.

Nosyloxy keto amides **4a–g** are crystalline solids that are stable to normal workup conditions and storage at room temperature. Exposure to silica gel caused slight decomposition, which rendered recrystallization difficult.

Table II. Conversion of 2-(Nosyloxy)-3-keto Amides to Quinoxalines via Tricarbonyl Amides

entry	2-(nosyloxy)-3-keto amide	quinoxaline	% yield[a]	% yield[b]
1	**4a**	**6a**	89 (78)	79
2	**4b**	**6b**	91 (70)	86
3	**4c**	**6c**	96 (92)	
4	**4d**	**6d**	69 (59)	
5	**4e**	**6e**	77 (68)	
6	**4f**	**6f**	93 (87)	
7	**4g**	**6g**	0	

[a] Yields are isolated yields, and yields in parentheses are yields of recrystallized pure products. [b] Yields are for purified products prepared from 3-keto amide **3** without isolation of intermediates.

None of the isolated 2-((*p*-nitrobenzenesulfonyl)oxy)-3-oxoalkanamides **4a–g** contained any detectable enol content as determined by ^1H NMR analysis in chloroform-*d* solution. This effect has been noted earlier for 2-(nosyloxy)-3-keto esters that contain a much lower enol content than the starting 3-keto esters.[16] The decrease in enol content upon nosyloxy substitution at C-2 has been attributed to resonance electron donation by the nosyloxy group.[16,17]

Several base–solvent systems were surveyed for the reductive elimination of *p*-nitrobenzenesulfinate from **4c**. Triethylamine, which was used effectively for the preparation of tricarbonyl esters,[11] failed to react with **4c**, as did diisopropylamine. Ultimately, it was found that treatment of **4c** with DBU in toluene at −78 °C followed by warming to room temperature gave the tricarbonyl amide in high yield.[18]

Since triethylamine (pK_a = 10.5) and diisopropylamine (pK_a = 11) in toluene failed to promote the desired elimination while DBU (pK_a = 11.6)[19] did, the pK_a of the 2-position in 2-(nosyloxy)-3-keto amides is probably ≥11.6. It is consequently less acidic by about 2 pK_a units than the corresponding hydrogen in 2-(nosyloxy)-3-oxoalkanoate esters. It is also possible that factors other than pK_a's significantly influence the progress of these reductive elimination reactions, since DBU, which promotes elimination effectively, and diisopropylamine, which does not promote elimination, differ in pK_a by only 0.6 pK_a units. One possible explanation for the much greater efficacy of DBU is that elimination occurs by a concerted, dipolar mechanism in which DBU can simultaneously function as a base and provide ionic stabilization of the sulfinate leaving group. A similar mechanism has been proposed to explain the facile dehydrohalogenation of alkyl halides by DBU.[20]

The series of 2-(nosyloxy)-3-keto amides **4a–g** was treated with DBU and converted to tricarbonyl compounds **5a–g**. While the tricarbonylamides can be isolated from the reaction mixture by silica gel chromatography,[8] we found it more convenient to trap them as their quinoxaline derivatives **6a–g** by heating the crude products with *o*-phenylenediamine (eq 6). The results presented in Table II indicate that the quinoxalines, and hence the tricarbonyl compounds, are produced in good to excellent yields. With

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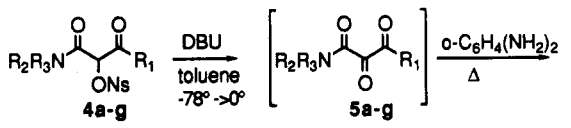
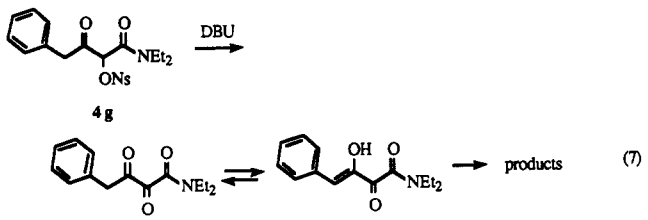


(6)

6a-g

the exception of **4g**, which gave a mixture of products, the reactions were very clean and produced a single product as determined by TLC analysis of the reaction mixture. The failure of **4g** to give quinoxaline may be related to increased enolization in the tricarbonyl product **5g** facilitated by the phenyl substituent, which could lead to aldol-like condensations and complex products (eq 7). Other conjugating substituents at C-4 might likewise give poor results.



4g 5g (7)

It was also demonstrated that 3-keto amides **3aa** and **3ba** could be converted to quinoxalines **6a** and **6b**, respectively, without isolation of any intermediates in 79% and 86% overall yields of purified products. This sequential process represents a very efficient conversion of 3-keto amides to the corresponding tricarbonylamides.

In summary, we have developed a synthesis of tricarbonylamides by a simple and efficient method that may prove very useful for the preparation of compounds that influence the immune response.

Experimental Section

Melting points were obtained on a Mel-Temp apparatus and are uncorrected. Infrared spectra were taken on a Perkin-Elmer Model 283 FTIR spectrometer. ^{1}H NMR spectra were obtained at 200 MHz on a Varian XL-200 instrument, and ^{13}C NMR spectra were obtained on a Varian Unity-400 instrument. Chemical shifts are reported for chloroform-*d* solutions in ppm relative to internal Me_4Si. Thin-layer chromatography was performed on silica gel 60 F_{254} plates from EM Reagents and visualized by UV irradiation and/or iodine. Radial chromatography was performed on a Chromatatron Model 7924T from Harrison Research using a 2-mm layer of silica gel 60 PF_{254} containing gypsum. Elemental analyses were performed by M-H-W Laboratories, Phoenix, AZ. *p*-Nitrobenzenesulfonyl peroxide was prepared by the literature method.[21]

***N,N*-Diethyl-3-oxo-3-phenylpropanamide, 3aa**, was prepared from ethyl benozylacetate (10 g, 70 mmol), diethylamine (14.5 mL, 140 mmol), and DMAP (2.56 g, 21 mmol) in toluene (100 mL)[12] as a colorless oil (13.2 g, 43%) after purification by bulb to bulb distillation with the collecting bulb at room temperature: ^{1}H NMR δ 8.01 (m, 1 H), 7.80 (m, 1 H), 7.43 (m, 3 H), 5.74 (s, 0.53 H, HOC=C*H* enol), 4.06 (s, 1.47 H, O=CH_2C=O keto), 3.39 (m, 4 H, NCH_2), 1.18 (m, 6 H, NCH$_2$CH_3); ^{13}C NMR δ 194.26, 171.38, 171.31, 166.08, 136.36, 135.22, 133.53, 130.49, 128.71, 128.66, 128.59, 128.47, 128.40, 125.88, 84.92, 60.37, 45.73, 42.75, 42.28, 40.49, 40.38, 40.20, 14.32, 14.21, 13.35, 12.87; IR (neat) 3062, 2976, 2934, 2873, 1736, 1691, 1627, 1598, 1577, 1489, 1444 cm^{-1}. Anal. Calcd for $C_{13}H_{17}NO_2$: C, 71.19; H, 7.83; N, 6.39. Found: C, 71.32; H, 7.84; N, 6.12.

***N,N*-Diethyl-3-oxobutanamide, 3ba**, was prepared from ethyl acetoacetate (130.2 g, 200 mmol), diethylamine (41.4 mL, 400 mmol), and DMAP (7.33 g, 60 mmol) in toluene (300 mL)[12] as a colorless oil (4.5 g, 14%) after purification by radial chromatography (ethyl acetate/hexane (2:1)): ^{1}H NMR δ 5.08 (s, 0.28 H, HOC=C*H* enol), 3.51 (s, 1.72 H, O=CCH_2C=O keto), 3.40 (q, J = 7.30 Hz, 2 H, NCH_2), 3.29 (q, J = 7.12 Hz, 2 H, NCH_2), 2.29 (s, 2.16 H, O=CCH_3), 1.95 (s, 0.84 H, HOCCH_3), 1.16 (m, 6 H, NCH$_2$CH_3); ^{13}C NMR δ 202.89, 174.60, 171.18, 165.78, 87.06, 49.99, 42.68, 42.00, 40.24, 30.20, 22.01, 14.21, 13.32, 12.91; IR (neat) 2976, 2935, 2876, 1721, 1639, 1591, 1491, 1436 cm^{-1}. Anal. Calcd for $C_8H_{15}NO_2$: C, 61.10; H, 9.63; N, 8.91. Found: C, 60.91; H, 9.84; N, 8.71.

***N,N*-Diethyl-4-methyl-3-oxopentanamide, 3ca**, was prepared from ethyl isobutyrylacetate (10.9 g, 70 mmol), diethylamine (14.5 mL, 140 mmol), and DMAP (2.56 g, 21 mmol) in toluene (100 mL)[12] as a colorless oil (3.63 g, 28%) after purification by radial chromatography (ethyl acetate/hexane (2:1): ^{1}H NMR δ 5.07 (s, 0.33 H, OHC=C*H* enol), 3.57 (s, 1.67 H, O=CCH_2CC=O keto), 3.34 (m, 4 H, NCH_2), 2.83 (m, 0.33 H, C*H*(CH$_3$)$_2$ enol), 2.39 (m, 0.67 H, C*H*(CH$_3$)$_2$ keto), 1.17 (m, 12 H, CH(CH_3)$_2$, NCH$_2$CH_3); ^{13}C NMR δ 208.70, 182.65, 171.58, 166.12, 83.98, 46.97, 42.69, 42.09, 40.87, 40.29, 40.14, 34.50, 19.98, 18.07, 14.19, 13.34, 12.90; IR (neat) 2972, 2934, 2874, 1716, 1631, 1590, 1494, 1464 cm^{-1}. Anal. Calcd for $C_{10}H_{19}NO_2$: C, 64.81; H, 10.36; N, 7.56. Found: C, 64.57; H, 10.19; N, 7.53.

***N,N*-Diethyl-3-oxohexanamide, 3da**, was prepared from ethyl butyrylacetate (11.1 mL, 70 mmol), diethylamine (14.5 mL, 140 mmol) and DMAP (2.56 g, 21 mmol) in toluene (100 mL)[12] as a colorless oil (3.50 g, 27%) after purification by radial chromatography (ethyl acetate/hexane (1:1)): ^{1}H NMR δ 5.06 (s, 0.3 H, HOC=C*H* enol), 3.49 (s, 1.7 H, O=CCH_2C=O keto), 3.35 (m, 4 H, NCH_2), 2.57 (t, J = 7.20 Hz, 2 H, O=CCH_2), 1.63 (m, 2 H, CH$_2$CH_2CH$_3$), 1.17 (t, J = 6.80 Hz, 3 H, NCH$_2$CH_3), 1.14 (t, J = 7.23 Hz, 3 H, NCH$_2$CH_3), 0.92 (t, J = 7.40 Hz, 3 H, CH$_2$CH$_2$CH_3); ^{13}C NMR δ 204.97, 177.81, 171.31, 165.92, 86.50, 60.38, 49.20, 44.81, 42.63, 42.05, 40.19, 37.94, 19.95, 16.96, 14.20, 13.69, 13.59, 13.34, 12.90; IR (neat) 2967, 2935, 2875, 1718, 1636, 1591, 1492, 1459 cm^{-1}. Anal. Calcd for $C_{10}H_{19}NO_2$: C, 64.81; H, 10.36; N, 7.56. Found: C, 64.63; H, 10.49; N, 7.37.

***N*-(3-Phenyl-1,3-dioxopropyl)morpholine, 3ab**, was prepared from ethyl benzoylacetate (12.11 g, 63.2 mmol), morpholine (11 g, 126 mmol), and DMAP (4.62 g, 19 mmol) in toluene (100 mL) by refluxing for 2 days.[12] A colorless oil (6.8 g, 46%) was obtained after purification by radial chromatography (ethyl acetate/hexane (1:1)): ^{1}H NMR δ 8.04 (m, 1 H), 7.76 (m, 1 H), 7.49 (m, 3 H), 5.79 (s, 0.4 H, HOC=C*H* enol), 4.12 (s, 1.6 H, O=CCH_2C=O, keto), 3.68 (m, 6 H, NCH_2CH_2O), 3.50 (t, J = 4.37 Hz, 2 H, NCH_2CH$_2$O); ^{13}C NMR δ 193.71, 172.02, 171.05, 165.38, 135.98, 133.86, 130.80, 128.79, 128.70, 128.47, 125.93, 83.92, 66.73, 66.61, 47.00, 45.68, 42.33; IR (neat) 3062, 2965, 2920, 2857, 1686, 1639, 1598, 1576, 1481, 1447 cm^{-1}. Anal. Calcd for $C_{13}H_{15}NO_3$: C, 66.93; H, 6.49; N, 6.01. Found: C, 66.70; H, 6.22; N, 5.94.

***N*-(1,3-Dioxobutyl)piperidine, 3bc**, was prepared from ethyl acetoacetate (13 g, 100 mmol), piperidine (17 g, 200 mmol), and DMAP (3.67 g 30 mmol) in toluene (100 mL). The reaction was refluxed for 7 days.[12] A yield of 3.0 g (18%) was obtained after purification by radial chromatography (ethyl acetate/hexane (1:1)): ^{1}H NMR δ 5.16 (s, 0.15 H, HOC=C*H* enol), 3.57 (m, 2 H, NCH_2), 3.55 (s, 1.85 H, O=CCH_2C=O keto), 3.35 (m, 2 H, NCH_2), 2.28 (s, 2.55 H, O=CCH_3 keto), 1.95 (s, 0.45 H, HOCCH_3 enol), 1.59 (m, 6 H, NCH$_2$CH_2CH_2CH_2); ^{13}C NMR δ 202.58, 164.72, 86.41, 50.21, 47.49, 42.85, 30.10, 26.30, 25.00, 25.47, 24.53, 24.34, 22.04; IR (neat) 3001, 2936, 2856, 1721, 1637, 1585, 1487, 1444 cm^{-1}. Anal. Calcd for $C_9H_{15}NO_2/0.1H_2O$: C, 63.19; H, 8.86; N, 8.19. Found: C, 63.17; H, 8.64; N, 8.15.

***N,N*-Diethyl-3-oxo-4-phenylbutanamide, 3ea**, was prepared using *n*-butyllithium (48.2 mmol), diisopropyl amine (6.76 mL, 48.2 mmol), *N,N*-diethylacetamide (6 mL, 48.2 mmol), and methyl phenylacetate (3.5 mL, 24.1 mmol).[14,15] A yield of 4.01 g (72%) was obtained after purification by radial chromatography (ethyl acetate/hexane (1:1)): ^{1}H NMR δ 7.30 (m, 5 H), 5.01 (s, 0.21 H, HOC=C*H* enol), 3.89 (s, 1.79 H, O=CCH_2C=O keto), 3.49 (s, 2 H, PhCH_2), 3.38 (q, J = 7.01 Hz, 2 H, NCH_2), 3.16 (q, J = 7.16

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Hz, 2 H, NCH_2), 1.13 (t, J = 7.13 Hz, 3 H, NCH_2CH_3), 1.07 (t, J = 7.19 Hz, 3 H, NCH_2CH_3); ^{13}C NMR δ 202.48, 176.23, 171.09, 165.78, 136.50, 129.65, 129.15, 128.74, 128.45, 127.16, 126.76, 87.53, 49.80, 47.84, 42.58, 42.27, 42.06, 40.25, 14.07, 13.28, 12.91; IR (neat) 3065, 3031, 2980, 2935, 2875, 1721, 1618, 1493, 1437 cm^{-1}. Anal. Calcd for $C_{14}H_{19}NO_2$: C, 72.16; H, 8.22; N, 6.00. Found: C, 71.90; H, 8.04; N, 6.14.

Preparation of *N,N*-Dialkyl-2-((*p*-nitrobenzenesulfonyl)oxy)-3-oxoalkanamides 4a–g. General Procedure. Ethyl acetate (400 mL), $ZnCl_2$(1.36 g, 10 mmol), and pNBSP[21] (4.04 g, 10 mmol) were placed in a round-bottom flask equipped with a magnetic stirring bar. The solids were dissolved with the aid of sonication, the flask was sealed with a septum and vented with a drying tube, and the mixture was cooled to −78 °C. The appropriate *N,N*-dialkyl-3-oxoalkanamide (10 mmol) was added to the cold solution via syringe. The solution was stirred for 3 hours at −78 °C, after which the reaction allowed to warm to room temperature. The reaction was extracted with saturated $NaHCO_3$ (3 × 50 mL), 1 N HCl (3 × 50 mL), and saturated NaCl (50 mL). The organic layer was dried ($MgSO_4$), and the solvent was removed by rotary evaporation, followed by high vacuum. The crude product was dissolved in a minimum of warm ethyl acetate, hexane was added until the solution turned cloudy, and the mixture was slowly (2 h) cooled to room temperature and then kept at 0 °C overnight. The solution, which had some crystal growth, was stored at −20 °C for 24 h. Finally, the solution was placed in a −78 °C bath for 2 h, after which the crystals were collected using vacuum filtration and rinsed with hexane. Exposure to silica gel must be avoided in the purification, since it causes slight decomposition of the product and increased difficulty of crystallization.

***N,N*-Diethyl-3-phenyl-2-((*p*-nitrobenzenesulfonyl)oxy)-3-oxopropanamide, 4a**, was prepared from *N,N*-diethyl-3-oxo-3-phenylpropanamide, **3aa** (2.19 g, 10 mmol), pNBSP (4.25 g, 10 mmol), and zinc chloride (1.36 g, 10 mmol). The crude product (oil, 4.20 g, 77%) was recrystallized to yield **4a** as a white, crystalline solid (2.66 g, 55%), mp 144–145 °C: ^1H NMR δ 8.33 (m, 2 H), 8.10 (m, 2 H), 8.00 (m, 2 H), 7.61 (m, 1 H), 7.41 (m, 2 H), 6.32 (s, 1 H, O=CC*H*C=O), 3.46 (m, 2 H, NCH_2), 3.33 (m, 2 H, NCH_2), 1.21 (t, J = 7.16 Hz, 3 H, NCH_2CH_3), 1.04 (t, J = 7.20 Hz, 3 H, NCH_2CH_3); ^{13}C NMR δ 189.63, 161.73, 150.87, 141.61, 134.40, 133.42, 129.56, 129.41, 128.74, 124.22, 81.06, 42.09, 41.20, 13.93, 12.37; IR ($CHCl_3$) 3106, 2980, 2939, 2875, 1701, 1656, 1598, 1536, 1463, 1449 cm^{-1}. Anal. Calcd for $C_{19}H_{20}N_2O_7S$: C, 54.27; H, 4.80; N, 6.67. Found: C, 54.14; H, 4.73; N, 6.54.

***N,N*-Diethyl-2-((*p*-nitrobenzenesulfonyl)oxy)-3-oxobutanamide, 4b**, was prepared from *N,N*-diethyl-3-oxobutanamide, **3ba** (1.14 g, 8.76 mmol), pNBSP (3.73 g, 8.76 mmol, 95%), and zinc chloride (1.19 g, 8.76 mmol). The crude product (oil, 2.98 g, 83%) was recrystallized to yield **4b** as a white, crystalline solid (2.25 g, 66%), mp 93–94 °C: ^1H NMR δ 8.42 (m, 2 H), 8.20 (m, 2 H), 5.67 (s, 1 H, O=CC*H*C=O), 3.47 (m, 2 H, NCH_2), 3.34 (m, 2 H, NCH_2), 2.30 (s, 3 H, O=CCH_3), 1.23 (t, J = 7.16 Hz, 3 H, NCH_2CH_3), 1.05 (t, J = 7.09 Hz, 3 H, NCH_2CH_3); ^{13}C NMR δ 198.91, 161.54, 150.97, 141.64, 129.57, 124.36, 80.68, 42.27, 26.56, 13.99; IR ($CHCl_3$) 3106, 2981, 2939, 2876, 1732, 1656, 1608, 153, 1464 cm^{-1}. Anal. Calcd for $C_{14}H_{18}N_2O_7S$: C, 46.91; H, 5.07; N, 7.82. Found: C, 46.93; H, 5.09; N, 7.58.

***N,N*-Diethyl-4-methyl-2-((*p*-nitrobenzenesulfonyl)oxy)-3-oxopentanamide, 4c**, was prepared from *N,N*-diethyl-4-methyl-3-oxopentanamide, **3ca** (1.85 g, 10 mmol), pNBSP (4.04 g, 10 mmol), and zinc chloride (1.36 g, 10 mmol). The crude product (oil, 3.52 g, 91%) was recrystallized to yield **4c** as a white crystaline solid (2.30 g, 60%), mp 124.5–125 °C: ^1H NMR δ 8.42 (m, 2 H), 8.19 (m, 2 H), 5.83 (s, 1 H, O=CC*H*C=O), 3.31 (m, 4 H, NCH_2), 3.04 (sept, 6.95 H, $CH(CH_3)_2$), 1.24 (t, J = 7.30 Hz, 3 H, NCH_2CH_3), 1.12 (d, J = 6.9 Hz, 6 H, $CH(CH_3)_2$), 1.09 (t, J = 6.4 Hz, 3 H, NCH_2CH_3); ^{13}C NMR δ 204.57, 161.75, 150.91, 141.780, 129.54, 124.26, 80.14, 42.25, 41.09, 36.98, 18.31, 17.79, 13.95, 12.42; IR ($CHCl_3$) 3106, 3057, 3048, 2979, 2938, 2876, 1724, 1656, 1608, 1536, 1463 cm^{-1}. Anal. Calcd for $C_{16}H_{22}N_2O_7S$: C, 49.72; H, 5.75; N, 7.25. Found: C, 49.48; H, 5.71; N, 7.07.

***N,N*-Diethyl-2-((*p*-nitrobenzenesulfonyl)oxy)-3-oxohexanamide, 4d**, was prepared from *N,N*-diethyl-3-oxohexanamide, **3da** (1.85 g, 10 mmol), pNBSP (4.04 g, 10 mmol), and zinc chloride (1.36 g, 10 mmol). The crude product (oil, 3.60 g, 93%) was recrystallized to yield **4d** as a white, crystalline solid (1.69 g, 47%), mp 75.5–77 °C: ^1H NMR δ 8.44 (m, 2 H), 8.39 (m, 2 H), 5.69 (s, 1 H, O=CC*H*C=O), 3.47 (m, 2 H, NCH_2), 3.30 (m, 2 H, NCH_2), 2.61 (t, J = 6.92 Hz, 2 H, $CH_2CH_2CH_3$), 1.59 (m, 2 H, $CH_2CH_2CH_3$), 1.23 (t, J = 7.19 Hz, 3 H, NCH_2CH_3), 1.04 (t, 7.23 H, NCH_2CH_3), 0.89 (t, J = 7.58 Hz, 3 H, $CH_2CH_2CH_3$); ^{13}C NMR δ 201.06, 161.66, 150.94, 141.75, 129.56, 124.31, 80.71, 42.23, 41.18, 40.58, 16.26, 13.97, 13.38, 12.46; IR ($CHCl_3$) 3106, 2974, 2937, 2877, 1727, 1659, 1608, 1537, 1464 cm^{-1}. Anal. Calcd for $C_{16}H_{22}N_2O_7S$: C, 49.72; H, 5.75; N, 7.25. Found: C, 49.67; H, 5.77; N, 7.17.

***N*-(2-((*p*-Nitrobenzenesulfonyl)oxy)-3-phenyl-1,3-dioxo-1-propyl)morpholine, 4e**, was prepared from *N*-(3-phenyl-1,3-dioxopropyl)morpholine, **3ab** (4 g, 17.1 mmol), pNBSP (6.91 g, 17.1 mmol), and zinc chloride (2.33 g, 17.1 mmol). The crude product (oil, 6.21 g, 90%) was recrystallized to yield **4e** as a white crystalline solid (4.37 g, 64%), mp 154–155 °C: ^1H NMR δ 8.38 (m, 2 H), 8.14 (m, 2 H), 7.97 (m, 2 H), 7.64 (m, 1 H), 7.51 (m, 2 H), 6.39 (s, 1 H, O=CC*H*C=O), 3.62 (m, 8 H, NCH_2CH_2O); ^{13}C NMR δ 189.15, 161.10, 150.98, 141.31, 134.79, 133.09, 129.55, 129.45, 129.35, 128.91, 124.36, 81.07, 66.46, 66.34, 46.40, 43.29; IR ($CHCl_3$) 3106, 3044, 2974, 2927, 2863, 1693, 1658, 1598, 1538, 14489, 1406 cm^{-1}. Anal. Calcd for $C_{19}H_{18}N_2O_8S$: C, 52.52; H, 4.18; N, 6.45. Found: C, 52.58; H, 4.25; N, 6.47.

***N*-(2-((*p*-Nitrobenzenesulfonyl)oxy)-1,3-dioxo-1-butyl)-piperidine, 4f**, was prepared from *N*-(1,3-dioxo-1-butyl)piperidine, **3bc** (1.82 g, 10.73 mmol), pNBSP (4.34 g, 10.73 mmol), and zinc chloride (1.46 g, 10.73 mmol). The crude product (oil, 3.65 g, 92%) was recrystallized to yield **4f** as a white crystalline solid (2.45 g, 62%), mp 94–95 °C: ^1H NMR δ 8.40 (m, 2 H), 8.21 (m, 2 H), 5.73 (s, O=CC*H*C=O), 3.44 (m, 4 H, NCH_2), 2.29 (s, 3 H, O=CCH_3), 1.61 (m, 6 H, NCH2C$H_2H_2CH_2$); ^{13}C NMR δ 198.23, 160.41, 150.98, 141.54, 129.59, 124.36, 81.23, 47.17, 44.01, 26.46, 26.04, 25.37, 24.14; IR ($CHCl_3$) 3068, 3030, 2946, 2863, 1732.4, 1656, 1608, 1536, 1446, 1405 cm^{-1}. Anal. Calcd for $C_{15}H_{18}N_2O_7S$: C, 48.64; H, 4.91; N, 7.56. Found: C, 48.49; H, 5.09; N, 7.55.

***N,N*-Diethyl-2-((*p*-nitrobenzenesulfonyl)oxy)-3-oxo-4-phenylbutanamide, 4g**, was prepared from *N,N*-diethyl-3-oxo-4-phenylbutanamide, **3ea** (2.33 g, 10 mmol), pNBSP (4.04 g, 10 mmol), and zinc chloride (1.36 g, 10 mmol). The crude product (oil, 4.34 g, 100%) was recrystallized to yield **4g** as a white, crystalline solid (2.56 g, 59%), mp 102–103 °C: ^1H NMR δ 8.34 (m, 2 H), 8.14 (m, 2 H), 7.30 (m, 3 H), 7.18 (m, 2 H), 5.77 (s, 1 H, O=CC*H*=O), 3.92 (s, 2 H, PhCH_2), 3.30 (m, 4 H, NCH_2), 1.16 (t, J = 7.12 Hz, 3 H, NCH_2CH_3), 1.05 (t, J = 7.15 Hz, 3 H, NCH_2CH_3); ^{13}C NMR δ 198.14, 161.48, 150.91, 141.45, 131.90, 129.70, 129.55, 128.81, 127.54, 124.28, 80.27, 45.62, 42.22, 41.24, 13.88, 12.46; IR ($CHCl_3$) 3106, 2980, 2938, 2876, 1734, 1653, 1608, 1537, 1496, 1454 cm^{-1}. Anal. Calcd for $C_{20}H_{22}N_2O_7S$: C, 55.28; H, 5.11; N, 6.45. Found: C, 55.05; H, 5.11; N, 6.32.

Preparation and Trapping of 2,3-Dioxoalkanamides as *N,N*-Dialkyl-2-quinoxalinecarboxamides. General Procedure. To a round-bottom flask equipped with a Dean–Stark trap, a condenser, a magnetic stirring bar and a septum with drying tube was added toluene (100 mL) and the appropriate *N,N*-dialkyl-2-((*p*-nitrobenzenesulfonyl)oxy)-3-oxoalkanamide (2 mmol). The solution was cooled to −78 °C, and DBU (2.2 mmol, 1.1 equiv) was added to the stirred solution via syringe. After 30 min the mixture was allowed to warm to room temperature. *o*-Phenylenediamine (4 mmol, 2 equiv) and *p*-toluenesulfonic acid (TsOH) (50 mg) was added to the reaction mixture, and the solution was slowly heated until 20 mL of solvent had collected in the Dean–Stark trap. The solution was then cooled to room temperature, and 100 mL of ethyl acetate was added. The reaction was washed with 1 N HCl (3 × 100 mL), saturated $NaHCO_3$, (3 × 100 mL), and saturated NaCl (50 mL). The organic layer was dried ($MgSO_4$), and the solvent was removed by rotary evaporation. The residual solvent removed by high vacuum. The crude product was recrystallized from hexane/ethyl acetate or methanol/water or isolated via bulb to bulb distillation. In cases where the crude product did not crystallize spontaneously due to impurities, radial chromatography was used to isolate the product using hexane/ethyl acetate (1:1).

***N,N*-Diethyl-3-phenyl-2-quinoxalinecarboxamide, 6a**, was prepared using *N,N*-diethyl-3-phenyl-2-((*p*-nitrobenzenesulfonyl)oxy)-3-oxopropanamide, **4a** (0.42 g, 1 mmol), DBU (0.157 mL, 1.05 mmol, 1.05 equiv), *o*-phenylenediamine (0.22 g, 2 mmol,

2 equiv), and TsOH (50 mg) in toluene (60 mL). The crude product (0.27 g, 89%) was recrystallized from methanol/water to give **6a** (0.24 g, 78%) as a white solid, mp 131–133 °C: ^{1}H NMR δ 8.17 (m, 2 H), 7.92 (m, 2 H), 7.82 (m, 2 H), 7.50 (m, 3 H), 3.54 (q, J = 7.23 Hz, 2 H, NCH_2), 2.97 (q, J = 6.84 Hz, 2 H, NCH_2), 1.13 (t, J = 7.20 Hz, 3 H, NCH$_2$CH_3), 0.92 (t, J = 7.05 Hz, 3 H, NCH$_2$CH_3); ^{13}C NMR δ 167.37, 151.02, 149.67, 141.95, 140.26, 136.98, 130.79, 130.36, 129.85, 129.38, 129.23, 129.08, 128.66, 42.68, 39.12, 13.33, 12.06; IR ($CHCl_3$) 3066, 2981, 2937, 2876, 1634, 1545, 1481, 1445 cm^{-1}. Anal. Calcd for $C_{19}H_{19}N_3O$: C, 74.72; H, 6.28; N, 13.76. Found: C, 74.50; H, 6.18; N, 13.51.

Quinoxaline **6a** could also be prepared directly from *N,N*-diethyl-3-oxo-3-phenylpropanamide, **3aa**, without isolation of the intermediate nosylate **4a**. pNBSP (3.06 g, 7.57 mmol) and zinc chloride (1.03 g, 7.57 mmol) were dissolved in ethyl acetate (300 mL). The mixture was cooled to 0 °C, and **3aa** (1.66 g, 7.57 mmol) was added via syringe. The reaction was worked up after 2 h in the usual manner and the solvent removed in vacuo. Toluene (150 mL) was added to the crude product, the flask was fitted with a rubber septum and drying tube, and the solution was cooled to −78 °C. DBU (1.25 mL, 8.33 mmol, 1.1 equiv) was added via syringe. After being stirred for 30 min, the deep orange solution was allowed to warm to room temperature, after which *o*-phenylenediamine (1.64 g, 15.14 mmol, 2 equiv) and TsOH (200 mg) were added. The reaction flask was fitted with a Dean–Stark trap and heated as usual. Workup in the usual manner gave a clear oil (1.82 g, 79%) that was crystallized from ethyl acetate/hexane.

***N,N*-Diethyl-3-methyl-2-quinoxalinecarboxamide, 6b**, was prepared from *N,N*-diethyl-2-((*p*-nitrobenzenesulfonyl)oxy)-3-oxobutanamide, **4b** (0.33 g, 1 mmol), DBU (0.18 mL, 1.2 mmol), *o*-phenylenediamine (0.22 g, 2 mmol, 2 equiv), and TsOH (50 mg) in toluene (60 mL). The crude product (220 mg, 91%) gave 170 mg (70%) of a clear oil by bulb to bulb distillation. The oil was recrystallized from ethyl acetate/hexane to give **6b** as a white crystalline solid, mp 49–51 °C: ^{1}H NMR δ 8.06 (m, 2 H), 7.753 (m, 2 H), 3.67 (q, J = 7.27 Hz, 2 H, NCH_2), 3.21 (q, J = 7.23 Hz, 2 H, NCH_2), 2.77 (s, 3 H, N=CCH_3), 1.35 (t, J = 7.06 Hz, 3 H, NCH$_2$CH_3), 1.15 (t, J = 7.05 Hz, 3 H, NCH$_2$CH_3); ^{13}C NMR δ 167.60, 151.26, 150.06, 141.76, 139.72, 130.44, 130.37, 129.50, 129.16, 128.54, 42.93, 39.61, 21.96, 14.05, 12.86; IR ($CHCl_3$) 2976, 2936, 1635, 1565, 1486, 1444 cm^{-1}. Anal. Calcd for $C_{14}H_{17}N_3O$: C, 69.10; H, 7.06; N, 17.27. Found: C, 68.94; H, 6.94; N, 17.12.

Quinoxaline **6b** was also prepared directly from *N,N*-diethyl-3-oxopropanecarboxamide, **3ba**, without isolation of the intermediate nosylate **4b** by dissolving pNBSP (0.81 g, 2 mmol) and zinc chloride (0.27 g, 2 mmol) in ethyl acetate (100 mL). The solution was cooled to 0 °C, and **3ba** (0.31 g, 2 mmol) was added via syringe. The reaction was worked up after 2 h in the usual manner and the solvent removed in vacuo. Toluene (60 mL) was then added to the residue in a flask fitted with a rubber septum and drying tube, the mixture was cooled to −78 °C, and DBU (0.33 mL, 2.2 mmol, 1.1 equiv) was added via syringe. After 30 min the deep orange solution was allowed to warm to room temperature, after which *o*-phenylenediamine (0.43 g, 4 mmol, 2 equiv) and TsOH (40 mg) were added. The reaction flask was fitted with a Dean–Stark trap and heated as usual. Workup in the usual manner gave **6b** as a clear oil (0.42 g, 86%).

***N,N*-Diethyl-3-isopropyl-2-quinoxalinecarboxamide, 6c**, was prepared from *N,N*-diethyl-4-methyl-2-((*p*-nitrobenzenesulfonyl)oxy)-3-oxopentanamide, **4c** (0.39 g, 1 mmol), DBU (0.18 mL, 1.2 mmol), *o*-phenylenediamine (0.22 g, 2 mmol, 2 equiv), and TsOH (50 mg) in toluene (60 mL). The crude product (0.27 g, 96%) was a cloudy oil that was purified by bulb to bulb distillation to give **6c** as a clear oil (0.25 g, 92%): ^{1}H NMR δ 8.07 (m, 2 H), 7.74 (m, 2 H), 3.67 (q, J = 7.19 Hz, 2 H, NCH_2), 3.37 (sept, J = 6.80 Hz, 1 H, CH(CH$_3$)$_2$), 3.19 (q, J = 7.13 Hz, 2 H, NCH_2), 1.41 (d, J = 6.80 Hz, 6 H, CH(CH_3)$_2$), 1.35 (t, J = 7.16 Hz, 3 H, NCH$_2$CH_3), 1.16 (t, J = 7.09 Hz, 3 H, NCH$_2$CH_3); ^{13}C NMR δ 167.41, 159.36, 149.59, 142.12, 139.74, 130.11, 129.37, 129.08, 128.91, 71.67, 43.03, 39.46, 32.58, 22.05, 13.85, 12.74; IR (neat) 3063, 2973, 2934, 2873, 1740, 1640, 1611, 1563, 1524, 1483, 1444 cm^{-1}. Anal. Calcd for $C_{16}H_{21}N_3O$: C, 70.80; H, 7.82; N, 15.49. Found: C, 71.04; H, 7.89; N, 15.27.

***N,N*-Diethyl-3-propyl-1-quinoxalinecarboxamide, 6d**, was prepared from *N,N*-diethyl-2-((*p*-nitrobenzenesulfonyl)oxy)-3-oxohexanamide, **4d** (0.35 g, 1 mmol), DBU (0.18 mL, 1.2 mmol), *o*-phenylenediamine (0.22 g, 2 mmol, 2 equiv), and TsOH (50 mg) in toluene (60 mL). The crude product was a light yellow oil (0.19 g, 69%) that gave **9d** as a clear oil (0.16 g, 59%) after bulb to bulb distillation: ^{1}H NMR δ 8.07 (m, 2 H), 7.75 (m, 2 H), 3.67 (q, J = 7.23 Hz, 2 H, NCH_2), 3.18 (q, J = 6.98 Hz, 2 H, NCH_2), 3.00 (t, J = 7.69 Hz, 2 H, CH_2CH$_2$CH$_3$), 1.902 (m, 2 H, CH$_2$CH_2CH$_3$), 1.35 (t, J = 6.98 Hz, 3 H, NCH$_2$CH_3), 1.17 (t, J = 7.05 Hz, 3 H, NCH$_2$CH_3), 1.05 (t, J = 7.47 Hz, 3 H, CH$_2$CH$_2$CH_3); ^{13}C NMR δ 167.22, 154.87, 150.03, 141.88, 139.68, 130.30, 129.44, 129.16, 128.72, 43.03, 39.48, 37.16, 22.11, 14.22, 13.92, 12.71; IR (neat) 3066, 2969, 2936, 2874, 1718, 1630, 1563, 1526, 1484, 1464, 1446 cm^{-1}. Anal. Calcd for $C_{16}H_{21}N_3O$: C, 70.80; H, 7.82; N, 15.49. Found: C, 70.64; H, 7.51; N, 15.27.

***N*-((2-Benzyl-3-quinoxalinyl)carbonyl)morpholine, 6e**, was prepared from *N*-(2-((*p*-nitrobenzenesulfonyl)oxy)-3-phenyl-1,3-dioxo-1-propyl)morpholine, **4e**, (1.69 g, 5 mmol), DBU (0.90 mL, 6 mmol, 1.2 equiv), *o*-phenylenediamine (1.08 g, 10 mmol) and TsOH (250 mg) in toluene (200 mL). The light brown crude solid (1.11 g, 77%) was recrystallized from ethyl acetate/hexane to give **6e** as a white crystalline solid (0.99 g, 68%), mp 106–107 °C: ^{1}H NMR δ 8.18 (m, 2 H), 7.91 (m, 2 H), 7.84 (m, 2 H), 7.57 (m, 3 H), 3.75 (m, 2 H, NCH_2), 3.61 (m, 2 H, NCH_2), 3.10 (m, 2 H, OCH_2), 3.01 (m, 2 H, OCH_2); ^{13}C NMR δ 166.34, 150.87, 148.49, 142.12, 140.45, 136.77, 131.18, 130.54, 130.18, 129.43, 129.26, 129.06, 128.91, 66.12, 65.87, 46.62, 41.90; IR ($CHCl_3$) 3061, 3017, 2925, 2862, 1640, 1545, 1480, 1442 cm^{-1}. Anal. Calcd for $C_{19}H_{17}N_3O_2$: C, 71.45; H, 5.38; N, 13.16. Found: C, 71.33; H, 5.54; N, 13.19.

***N*-((2-Methyl-3-quinoxalinyl)carbonyl)piperidine, 6f**, was prepared from *N*-(2-((*p*-nitrobenzenesulfonyl)oxy)-1,3-dioxo-1-butyl)piperidine, **4f** (1.48 g, 4 mmol), DBU (0.72 mL, 4.8 mmol, 1.2 equiv), *o*-phenylenediamine (0.86 g, 8 mmol, 2 equiv), and TsOH (200 mg) in toluene (175 mL). The crude product (0.95 g, 93%) was a pale yellow oil that was purified by bulb to bulb distillation to give **6f** as a clear oil (0.89 g, 87%): ^{1}H NMR δ 8.05 (m, 2 H), 7.76 (m, 2 H), 3.84 (t, J = 4.44 Hz, 2 H, NCH_2), 3.25 (t, J = 5.68 Hz, 2 H, NCH_2), 2.78 (s, 3 H, N=CCH_3), 1.74 (m, 4 H, NCH$_2$CH_2), 1.57 (m, 2 H, NCH$_2$CH$_2$CH_2); ^{13}C NMR δ 165.93, 151.25, 150.00, 141.72, 139.38, 130.49, 129.54, 129.13, 128.53, 47.81, 42.71, 26.42, 25.53, 24.50, 22.04; IR (neat) 3051, 3003, 2944, 2860, 1719, 1632, 1485, 1448 cm^{-1}. Anal. Calcd for $C_{15}H_{17}N_3O/0.2H_2O$: C, 69.57; H, 6.63; N, 16.23. Found: C, 69.34; H, 6.51; N, 15.99.

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