2-(Alkylamino)-4-cyclopentene-1,3-diones via Addition of Imidoyl Lithiates to Cyclobutenediones

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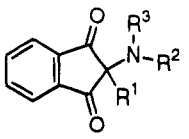
Introduction

A number of studies of the 2-aminoindan-1,3-dione ring system[1-3] **1** have been carried out. In addition to its relevance to the "ninhydrin reaction"[4] it is claimed that the 2-aminoindan-1,3-dione system possesses antibacterial and analgesic activity,[5-7] and it has been used in the synthesis of various peptidic frameworks.[8,9] Relatively little is known about the analogous 2-amino-4-cyclopentene-1,3-dione ring system **2**, an example of which was recently reported.[10]



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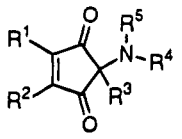


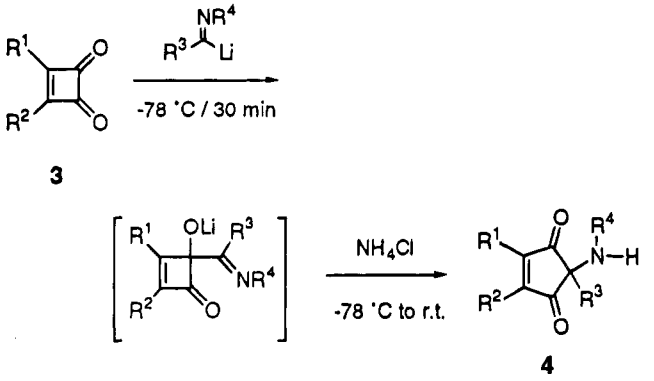
2

In a continuing effort to explore the synthetic utility of cyclobutenediones **3**,[11-17] it was found that 2-(alkylamino)-4-cyclopentene-1,3-diones **4** could be prepared in good yield in most cases by the addition of imidoyl lithiates to cyclobutenediones (Table 1). The results of that brief study are reported herein.

Results and Discussion

Imidoyl lithiates were generated according to the method of Walborsky.[18,19] Best results were obtained when the lithiates were generated in diethyl ether solution at −15 to −10 °C for 30 min; prolonged reaction time (2 h) or using THF as solvent sometimes resulted in lower yields of the ultimate products **4**. The solutions of imidoyl lithiates were transferred to a THF solution of the cyclobutenedione **3** held at −78 °C; optimum yields were obtained with a slight excess of the imidoyl lithiate (1.11–1.15 equiv). Attempts to trap the initially formed 1,2-adducts with Ac_2O, Me_3SiCl, or *t*-$BuMe_2SiCl$ failed. In all cases the only isolable products were the ring expansion products **4** which, in most cases, were obtained in good to excellent yields after a low temperature (−78 °C) aqueous NH_4Cl quench and workup.

Table 1. The Synthesis of 2-(Alkylamino)-4-cyclopentene-1,3-diones (4)



products	R^1	R^2	R^3	R^4 [a]	yield (%)
4a	^{i}PrO	^{i}PrO	^{n}Bu	TMB[b]	77
4b	^{i}PrO	^{i}PrO	^{t}Bu	TMB	91
4c	^{i}PrO	^{i}PrO	^{t}Bu	^{t}Bu	80
4d	^{i}PrO	^{i}PrO	^{n}Bu	^{t}Bu	87
4e	^{i}PrO	Ph	^{n}Bu	TMB	66
4f	^{i}PrO	Ph	^{n}Bu	^{t}Bu	76
4g	^{i}PrO	^{n}Bu	^{n}Bu	TMB	44
4h	^{n}Bu	^{n}Bu	^{n}Bu	TMB	52
4i	^{n}Bu	Me	^{n}Bu	TMB	44
4j	Me	Me	^{n}Bu	TMB	12

[a] Because primary and secondary isocyanides are easily deprotonated by alkyllithium reagents,[20] this reaction is limited to isocyanides bearing tertiary alkyl groups. [b] TMB = 1,1,3,3-tetramethylbutyl.

As seen in Table 1, substituents on the cyclobutenedione **3** affect the outcome of the reaction. The electron-releasing isopropoxy substituent results in the highest yields of the ring expansion products **4a–d**. Replacing one isopropoxy group with a phenyl substituent gave good yields (**4e**, **f**), but replacing one or both isopropoxy groups with an alkyl substituent larger than methyl gave only moderate yields (**4g–i**). Dimethylcyclobutenedione (**3**, R^1, R^2 = Me) gave the ring expansion product **4j** in poor yield. Both *n*-butyl- and *tert*-butyllithium add efficiently to isocyanides to form imidoyl lithiates which gave the products shown in Table 1. Treatment of RN=C (R = *t*-Bu or 1,1,3,3-tetramethylbutyl) with either methyllithium or phenyllithium followed by addition of a cyclobutenedione did not lead to isolable 2-(alkylamino)-4-cyclopentene-1,3-diones, a problem attributed to inherent difficulties in the formation of imidoyllithiates from isocyanides and both methyllithium and phenyllithium.[19]

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Conclusions

In conclusion, 2-(alkylamino)-4-cyclopentene-1,3-diones are easily accessed from cyclobutenediones which are versatile starting materials for the synthesis of a wide variety of synthetically useful compounds.[11,12,21-30]

Experimental Section

Materials and Methods. ^1H and ^{13}C NMR spectra were recorded on a General Electric QE-300 (^1H at 300 MHz; ^{13}C at 75.5 MHz) spectrometer in deuteriochloroform ($CDCl_3$) with chloroform (7.26 ppm ^1H, 77.00 ppm ^{13}C) as an internal reference unless otherwise stated. Data are reported in the following order: chemical shifts are given (δ, ppm); multiplicity is indicated (br (broadened), s (singlet), d (doublet), t (triplet), q (quartet), hex (hextet), sept (septet), m (multiplet), exch (exchangeable)); coupling constants, J, are reported in Hz, and integration is provided. Infrared spectra were recorded on a Nicolet 510 FT-IR spectrometer. Peaks are reported (cm^{-1}) with the following relative intensities: s (strong, 67–100%), m (medium 40–67%), and w (weak 20–40%). High-resolution mass spectra were recorded on a GS-70 mass spectrometer.

Analytical thin-layer chromatography (TLC) was performed on Merck silica gel plates with F-354 indicator. Visualization was accomplished by UV light. Solvents for extraction and chromatography were reagent grade and used as received. Flash column chromatography was performed with 32–63 μm silica gel (Woelm). Solvents used as reaction media were distilled immediately before use: Et_2O and THF were distilled from Na/benzophenone ketyl. Reagents purchased from commercial sources were used directly without further purification. All reactions were performed under a dry argon atmosphere in flame-dried glassware. "Brine" refers to a saturated aqueous solution of NaCl. Unless otherwise specified, solutions of NH_4Cl and $NaHCO_3$ refer to saturated aqueous solutions.

tert-Butyl isocyanide and 1,1,3,3-tetramethylbutyl isocyanide were purchased from Aldrich Chemical Co. and were used as received. Cyclobutenediones were prepared by literature procedures: diisopropyl squarate, 3-*n*-butyl-4-isopropyl-3-cyclobutene-1,2-dione, 3-*n*-butyl-4-isopropyl-3-cyclobutene-1,2-dione, 3-isopropyl-4-phenyl-3-cyclobutene-1,2-dione, 3-*n*-butyl-4-methyl-3-cyclobutene-1,2-dione, and 3,4-dimethyl-3-cyclobutene-1,2-dione,[31] 3,4-di-*n*-butyl-3-cyclobutene-1,2-dione.[14]

2-*n*-Butyl-4,5-diisopropoxy-2-[(1,1,3,3-tetramethylbutyl)amino]-4-cyclopentene-1,3-dione (4a). A solution of 1,1,3,3-tetramethylbutyl isocyanide (175 μL, 1.00 mmol, 1.11 equiv) in ether (5.0 mL) was treated with *n*-butyllithium (2.20 M in hexanes, 0.50 mL, 1.10 mmol, 1.22 equiv) at −15 °C. The reaction mixture was stirred at −15 to −10 °C for 30 min and was then cannulated slowly into a THF solution (5.0 mL) of diisopropyl squarate (178 mg, 0.90 mmol, 1.00 equiv) at −78 °C. After 30 min, the reaction was quenched with saturated NH_4Cl (0.5 mL). After being warmed to room temperature, the mixture was partitioned between ether (30 mL) and brine (20 mL). The aqueous layer was extracted with ether (20 mL), the combined organic layers were dried over Na_2SO_4, and the solvent was removed by rotary evaporator and vacuum pump. The product was purified by flash silica gel chromatography (0.5 in. × 4 in., 10% ethyl acetate in hexanes) to give 272 mg (0.69 mmol, 77%) of 2-*n*-butyl-4,5-diisopropoxy-2-[(1,1,3,3-tetramethylbutyl)amino]-4-cyclopentene-1,3-dione (**4a**) as a viscous yellow oil, TLC (silica gel, 20% ethyl acetate in hexanes, $R_f = 0.55$). IR (CH_2Cl_2, NaCl, cm^{-1}): 2957 (s), 2873 (s), 1685 (s), 1607 (m), 1466 (s), 1384 (s), 1372 (m), 1304 (m), 1096 (m). ^1H NMR ($CDCl_3$, 300 MHz): δ 5.45 (pent, $J = 6.0$ Hz, 2 H), 1.56 (m, 2 H), 1.43 (br s, 1 H), 1.31 (d, $J = 6.0$ Hz, 12 H), 1.30 (s, 2 H), 1.16 (m, 4 H), 0.97 (s, 6 H), 0.95 (s, 9 H), 0.75 (t, $J = 7.2$ Hz, 3 H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 200.0, 149.5, 74.2, 64.5, 57.4, 56.2, 38.7, 31.8, 31.0, 25.6, 23.0, 22.9, 22.8, 13.6. Anal. Calcd for $C_{23}H_{41}NO_4$: C, 69.83; H, 10.45; N, 3.54; O, 16.18. Found: C, 69.70; H, 10.41; N, 3.50.

2-*tert*-Butyl-4,5-diisopropoxy-2-[(1,1,3,3-tetramethylbutyl)amino]-4-cyclopentene-1,3-dione (4b). A solution of 1,1,3,3-tetramethylbutyl isocyanide (200 μL, 1.14 mmol, 1.14 equiv) in ether (5.0 mL) was treated with *tert*-butyllithium (1.5 M in pentane, 0.80 mL, 1.20 mmol, 1.20 equiv) at −15 °C. As for **4a**, above, cannulation into a THF (5.0 mL) solution of diisopropyl squarate (198 mg, 1.00 mmol, 1.00 equiv) at −78 °C, quench after 30 min (0.5 mL saturated NH_4Cl), partition between ether (30 mL) and brine (20 mL), workup, and flash silica gel chromatography (0.5 in. × 4 in., 10% ethyl acetate in hexanes) gave 359 mg (0.91 mmol, 91%) of 2-*tert*-butyl-4,5-diisopropoxy-2-[(1,1,3,3-tetramethylbutyl)amino]-4-cyclopentene-1,3-dione (**4b**) as a yellow oil. TLC (silica gel, 10% ethyl acetate in hexanes, $R_f = 0.32$). IR (CH_2Cl_2, NaCl, cm^{-1}): 2981 (s), 1680 (s), 1616 (m), 1382 (s), 1368 (m), 1300 (m), 1095 (m). ^1H NMR ($CDCl_3$, 300 MHz): δ 5.40 (sept, $J = 6.2$ Hz, 2 H), 1.56 (br s, 1 H), 1.34 (s, 2 H), 1.32 (d, $J = 6.0$ Hz, 12 H), 1.00 (s, 9 H), 0.98 (s, 6 H), 0.96 (s, 9 H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 199.9, 149.5, 74.0, 68.7, 58.6, 56.2, 39.0, 32.0, 31.8, 31.0, 26.2, 23.1, 23.0. Anal. Calcd for $C_{23}H_{41}NO_4$: C, 69.83; H, 10.45; N, 3.54; O, 16.18. Found: C, 69.96; H, 10.36; N, 3.52.

2-*tert*-Butyl-2-(*tert*-butylamino)-4,5-diisopropoxy-4-cyclopentene-1,3-dione (4c). A solution of *tert*-butyl isocyanide (125 μL, 1.11 mmol, 1.11 equiv) in ether (5.0 mL) was treated with *tert*-butyllithium (1.6 M in pentane, 0.75 mL, 1.20 mmol, 1.20 equiv) at −15 °C. As for **4a**, above, cannulation into a THF (5.0 mL) solution of diisopropyl squarate (198 mg, 1.00 mmol, 1.00 equiv) at −78 °C, quench after 30 min (0.5 mL saturated NH_4Cl), partition between ether (30 mL) and brine (20 mL), workup, and flash silica gel chromatography (0.5 in. × 4 in., 10% ethyl acetate in hexanes) gave 273 mg (0.80 mmol, 80%) of 2-*tert*-butyl-2-(*tert*-butylamino)-4,5-diisopropoxy-4-cyclopentene-1,3-dione (**4c**) as a yellow solid, mp = 42–43 °C, TLC (silica gel, 10% ethyl acetate in hexanes, $R_f = 0.34$). IR (CH_2Cl_2, NaCl, cm^{-1}): 3688 (w), 2985 (s), 1678 (s), 1613 (m), 1377 (s). ^1H NMR ($CDCl_3$, 300 MHz): δ 5.44 (sept, $J = 6.0$ Hz, 2 H), 1.50 (br s, 1 H), 1.33 (d, $J = 6.0$ Hz, 12 H), 0.99 (s, 9 H), 0.96 (s, 9 H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 199.7, 149.6, 74.1, 68.6, 51.7, 38.7, 31.8, 25.9, 23.2, 23.1. Anal. Calcd for $C_{19}H_{33}NO_4$: C, 67.22; H, 9.80; N, 4.13; O, 18.85. Found: C, 67.29; H, 9.80; N, 4.18.

2-*n*-Butyl-2-(*tert*-butylamino)-4,5-diisopropoxy-4-cyclopentene-1,3-dione (4d). A solution of *tert*-butyl isocyanide (130 μL, 1.15 mmol, 1.16 equiv) in ether (5.0 mL) was treated with *n*-butyllithium (2.4 M in hexanes, 0.55 mL, 1.32 mmol, 1.33 equiv) at −15 °C. As for **4a**, above, cannulation into a THF (5.0 mL) solution of diisopropyl squarate (195 mg, 0.99 mmol, 1.00 equiv) at −78 °C, quench after 30 min (0.5 mL saturated NH_4Cl), partition between ether (30 mL) and brine (20 mL), workup, and flash silica gel chromatography (0.5 in. × 4 in., 10%–30% ethyl acetate in hexanes) gave 292 mg (0.86 mmol, 87%) of 2-*n*-butyl-2-(*tert*-butylamino)-4,5-diisopropoxy-4-cyclopentene-1,3-dione (**4d**) as a yellow oil, TLC (silica gel, 20% ethyl acetate in hexanes, $R_f = 0.50$). IR (CH_2Cl_2, NaCl, cm^{-1}): 2966 (s), 2932 (s), 2872 (m), 1682 (s), 1602 (m), 1463 (m), 1380 (s), 1370 (m), 1300 (m), 1093 (m). ^1H NMR ($CDCl_3$, 300 MHz): δ 5.49 (sept, $J = 6.0$ Hz, 2 H), 1.63 (m, 2 H), 1.45 (br s, 1 H), 1.35 (d, $J = 6.0$ Hz, 12 H), 1.20 (m, 2 H), 1.04 (m, 2 H), 1.01 (s, 9 H), 0.82 (t, $J = 7.5$ Hz, 3 H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 199.6, 149.8, 74.2, 64.5, 52.0, 38.4, 31.9, 25.6, 23.0, 22.9, 22.7, 13.5. Anal. Calcd for $C_{19}H_{33}NO_4$: C, 67.22; H, 9.80; N, 4.13; O, 18.85. Found: C, 67.36; H, 9.83; N, 4.19.

2-*n*-Butyl-4-isopropoxy-5-phenyl-2-[(1,1,3,3-tetramethylbutyl)amino]-4-cyclopentene-1,3-dione (4e). A solution of 1,1,3,3-tetramethylbutyl isocyanide (175 μL, 1.00 mmol, 1.12 equiv) in ether (5.0 mL) was treated with *n*-butyllithium (2.4 M in hexanes, 0.45 mL, 1.08 mmol, 1.21 equiv) at −15 °C. As for **4a**, above, cannulation into a THF (5.0 mL) solution of 3-isopropoxy-4-phenyl-3-cyclobutene-1,2-dione (192 mg, 0.89 mmol,

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1.00 equiv) at −78 °C, quench after 30 min (0.5 mL saturated NH_4Cl), partition between ether (30 mL) and brine (20 mL), workup, and flash silica gel chromatography (0.5 in. × 4 in., 6% ethyl acetate in hexanes) gave 245 mg (0.59 mmol, 66%) of 2-*n*-butyl-4-isopropoxy-5-phenyl-2-[(1,1,3,3-tetramethylbutyl)amino]-4-cyclopentene-1,3-dione (**4e**) as a red oil, TLC (silica gel, 10% ethyl acetate in hexanes, $R_f = 0.35$). IR (CH_2Cl_2, NaCl, cm^{-1}): 3151 (w), 2958 (s), 2935 (s), 1685 (s), 1582 (m), 1463 (m), 1372 (s), 1310 (m). ^1H NMR ($CDCl_3$, 300 MHz): δ 7.96 (dd, $J = 1.8$, 8.4 Hz, 2 H), 7.40 (m, 3 H), 5.83 (sept, $J = 6.0$ Hz, 1 H), 1.68 (m, 2 H), 1.63 (br s, 1 H), 1.39 (d, $J = 6.0$ Hz, 6 H), 1.20 (pent, $J = 7.2$ Hz, 2 H), 1.10 (m, 2 H), 1.05 (d, $J = 2.7$ Hz, 6 H), 1.02 (s, 9 H), 1.01 (s, 2 H), 0.80 (t, $J = 7.2$ Hz, 3 H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 204.0, 202.8, 162.2, 132.9, 129.6, 129.4, 129.0, 128.2, 75.3, 65.2, 57.6, 56.5, 39.2, 31.9, 31.8, 31.3, 25.7, 23.5, 23.3, 22.9, 13.7. Anal. Calcd for $C_{26}H_{39}NO_3$: C, 75.50; H, 9.50; N, 3.39; O, 11.60. Found: C, 75.52; H, 9.52; N, 3.38.

2-*n*-Butyl-2-(*tert*-butylamino)-4-isopropoxy-5-phenyl-4-cyclopentene-1,3-dione (4f). A solution of *tert*-butyl isocyanide (130 μL, 1.15 mmol, 1.15 equiv) in ether (5.0 mL) was treated with *n*-butyllithium (2.4 M in hexanes, 0.55 mL, 1.32 mmol, 1.32 equiv) at −15 °C. As for **4a**, above, cannulation into a THF (5.0 mL) solution of 3-isopropoxy-4-phenyl-3-cyclobutene-1,2-dione (216 mg, 1.00 mmol, 1.00 equiv) at −78 °C, quench after 30 min (0.5 mL saturated NH_4Cl), partition between ether (30 mL) and brine (20 mL), workup, and flash silica gel chromatography (0.5 in. × 4 in., 6% ethyl acetate in hexanes) gave 271 mg (0.76 mmol, 76%) of 2-*n*-butyl-2-(*tert*-butylamino)-4-isopropoxy-5-phenyl-4-cyclopentene-1,3-dione (**4f**) as a red oil, TLC (silica gel, 10% ethyl acetate in hexanes, $R_f = 0.30$). IR (CH_2Cl_2, NaCl, cm^{-1}): 3680 (w), 3150 (w), 2965 (s), 1690 (s), 1372 (s), 1091 (m). ^1H NMR ($CDCl_3$, 300 MHz): δ 7.97 (dd, $J = 1.5$, 8.1 Hz, 2 H), 7.42 (m, 3 H), 5.84 (sept, $J = 6.0$ Hz, 1 H), 1.68 (m, 2 H), 1.62 (br s, 1 H), 1.39 (d, $J = 6.0$ Hz, 6 H), 1.19 (pent, $J = 7.5$ Hz, 2 H), 1.04 (m, 11 H), 0.80 (t, $J = 6.9$ Hz, 3 H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 203.7, 202.4, 162.4, 133.3, 129.6, 129.5, 128.9, 128.2, 75.4, 65.1, 52.3, 38.9, 32.0, 25.6, 23.4, 23.3, 22.8, 13.6. Anal. Calcd for $C_{22}H_{31}NO_3$: C, 73.92; H, 8.74; N, 3.92; O, 13.43. Found: C, 74.01; H, 8.72; N, 3.85.

2,5-Di-*n*-butyl-4-isopropoxy-2-[(1,1,3,3-tetramethylbutyl)amino]-4-cyclopentene-1,3-dione (4g). A solution of 1,1,3,3-tetramethylbutyl isocyanide (175 μL, 1.00 mmol, 1.11 equiv) in ether (5.0 mL) was treated with *n*-butyllithium (2.4 M in hexanes, 0.45 mL, 1.08 mmol, 1.20 equiv) at −15 °C. As for **4a**, above, cannulation into a THF (5.0 mL) solution of 3-*n*-butyl-4-isopropoxy-3-cyclobutene-1,2-dione (176 mg, 0.90 mmol, 1.00 equiv) at −78 °C, quench after 30 min (0.5 mL saturated NH_4Cl), partition between ether (30 mL) and brine (20 mL), workup, and flash silica gel chromatography (0.5 in. × 4 in., 10% ethyl acetate in hexanes) gave 158 mg (0.40 mmol, 44%) of 2,5-di-*n*-butyl-4-isopropoxy-2-[(1,1,3,3-tetramethylbutyl)amino]-4-cyclopentene-1,3-dione (**4g**) as a red oil, TLC (silica gel, 20% ethyl acetate in hexanes, $R_f = 0.70$). IR (CH_2Cl_2, NaCl, cm^{-1}): 2962 (s), 2871 (s), 1685 (s), 1608 (m), 1466 (m), 1367 (s), 1098 (m). ^1H NMR ($CDCl_3$, 300 MHz): δ 5.64 (sept, $J = 6.0$ Hz, 1 H), 2.26 (t, $J = 7.5$ Hz, 2 H), 1.50 (m, 5 H), 1.32 (m, 10 H), 1.15 (m, 4 H), 0.99 (s, 9 H), 0.96 (s, 6 H), 0.90 (t, $J = 7.5$ Hz, 3 H), 0.78 (t, $J = 7.2$ Hz, 3 H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 204.0, 203.7, 164.0, 140.3, 74.0, 65.1, 57.4, 56.3, 38.9, 31.8, 31.2, 31.1, 29.2, 25.7, 23.4, 23.2, 22.8, 22.7, 21.4, 13.68, 13.67. Anal. Calcd for $C_{24}H_{43}NO_3$: C, 73.24; H, 11.01; N, 3.56; O, 12.19. Found: C, 73.49; H, 11.02; N, 3.67.

2,4,5-Tri-*n*-butyl-2-[(1,1,3,3-tetramethylbutyl)amino]-4-cyclopentene-1,3-dione (4h). A solution of 1,1,3,3-tetramethylbutyl isocyanide (200 μL, 1.14 mmol, 1.14 equiv) in ether (5.0 mL) was treated with *n*-butyllithium (2.4 M in hexanes, 0.55 mL, 1.32 mmol, 1.32 equiv) at −15 °C. As for **4a**, above, cannulation into a THF (5.0 mL) solution of 3,4-di-*n*-butyl-3-cyclobutene-1,2-dione (195 mg, 1.00 mmol, 1.00 equiv) at −78 °C, quench after 30 min (0.5 mL saturated NH_4Cl), partition between ether (30 mL) and brine (20 mL), workup, and flash silica gel chromatography (0.5 in. × 4 in., 20% ethyl acetate in hexanes) gave 205 mg (0.52 mmol, 52%) of 2,4,5-tri-*n*-butyl-2-[(1,1,3,3-tetramethylbutyl)amino]-4-cyclopentene-1,3-dione (**4h**) as a red oil, TLC (silica gel, 10% ethyl acetate in hexanes, $R_f = 0.47$). IR (CH_2Cl_2, NaCl, cm^{-1}): 2959 (s), 2932 (s), 1691 (s), 1464 (m), 1345 (s), 1225 (m). ^1H NMR ($CDCl_3$, 300 MHz): δ 2.43 (t, $J = 7.2$ Hz, 4 H), 1.40 (m, 13 H), 1.30 (s, 2 H), 1.13 (pent, $J = 7.2$ Hz, 2 H), 0.98 (s, 6 H), 0.91 (t, $J = 7.2$ Hz, 6 H), 0.90 (s, 9 H), 0.76 (t, $J = 7.2$ Hz, 3 H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 208.3, 156.5, 63.2, 57.3, 56.3, 39.0, 31.8, 31.1, 29.9, 25.7, 23.9, 23.0, 22.8, 13.7, 13.6. Anal. Calcd for $C_{25}H_{45}NO_2$: C, 76.67; H, 11.58; N, 3.58; O, 8.17. Found: C, 76.47; H, 11.41; N, 3.65.

2,4-Di-*n*-butyl-5-methyl-2-[(1,1,3,3-tetramethylbutyl)amino]-4-cyclopentene-1,3-dione (4i). A solution of 1,1,3,3-tetramethylbutyl isocyanide (200 μL, 1.14 mmol, 1.14 equiv) in ether (5.0 mL) was treated with *n*-butyllithium (2.4 M in hexanes, 0.55 mL, 1.32 mmol, 1.32 equiv) at −15 °C. As for **4a**, above, cannulation into a THF (5.0 mL) solution of 3-*n*-butyl-4-methyl-3-cyclobutene-1,2-dione (152 mg, 1.00 mmol, 1.00 equiv) at −78 °C, quench after 30 min (0.5 mL saturated NH_4Cl), partition between ether (30 mL) and brine (20 mL), workup, and flash silica gel chromatography (0.5 in. × 4 in., 10% ethyl acetate in hexanes) gave 153 mg (0.44 mmol, 44%) of 2,4-di-*n*-butyl-5-methyl-2-[(1,1,3,3-tetramethylbutyl)amino]-4-cyclopentene-1,3-dione (**4i**) as a red oil, TLC (silica gel, 10% ethyl acetate in hexanes, $R_f = 0.30$). IR (CH_2Cl_2, NaCl, cm^{-1}): 2957 (s), 2935 (s), 2871 (m), 1695 (s), 1460 (m), 1380 (s), 1219 (m). ^1H NMR ($CDCl_3$, 300 MHz): δ 2.44 (t, $J = 7.2$ Hz, 2 H), 2.00 (s, 3 H), 1.45 (m, 7 H), 1.35 (m, 2 H), 1.29 (s, 2 H), 1.12 (pent, $J = 7.2$ Hz, 2 H), 0.97 (s, 6 H), 0.90 (t, $J = 7.2$ Hz, 3 H), 0.89 (s, 9 H), 0.76 (t, $J = 7.5$ Hz, 3 H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 208.4, 208.0, 156.8, 152.9, 63.1, 57.3, 56.3, 38.8, 31.8, 31.1, 29.5, 25.6, 23.8, 22.9, 22.9, 13.7, 13.6, 9.3. Anal. Calcd for $C_{22}H_{39}NO_2$: C, 75.59; H, 11.25; N, 4.01; O, 9.15. Found: C, 75.70; H, 11.20; N, 4.01.

2-*n*-Butyl-4,5-dimethyl-2-[(1,1,3,3-tetramethylbutyl)amino]-4-cyclopentene-1,3-dione (4j). A solution of 1,1,3,3-tetramethylbutyl isocyanide (200 μL, 1.14 mmol, 1.14 equiv) in ether (5.0 mL) was treated with *n*-butyllithium (2.4 M in hexanes, 0.55 mL, 1.32 mmol, 1.32 equiv) at −15 °C. As for **4a**, above, cannulation into a THF (5.0 mL) solution of 3,4-dimethyl-3-cyclobutene-1,2-dione (110 mg, 1.00 mmol, 1.00 equiv) at −78 °C, quench after 30 min (0.5 mL saturated NH_4Cl), partition between ether (30 mL) and brine (20 mL), workup, and flash silica gel chromatography (0.5 in. × 4 in., 6% ethyl acetate in hexanes) gave 38 mg (0.12 mmol, 12%) of 2-*n*-butyl-4,5-dimethyl-2-[(1,1,3,3-tetramethylbutyl)amino]-4-cyclopentene-1,3-dione (**4j**) as an orange solid, mp = 47−48 °C, TLC (silica gel, 20% ethyl acetate in hexanes, $R_f = 0.48$). IR (CH_2Cl_2, NaCl, cm^{-1}): 2955 (m), 1696 (s), 1643 (m), 1606 (m), 1465 (m), 1385 (m), 1321 (m). ^1H NMR ($CDCl_3$, 300 MHz): δ 2.02 (s, 6 H), 1.50 (m, 3 H), 1.30 (s, 2 H), 1.14 (m, 2 H), 1.01 (m, 8 H), 0.92 (s, 9 H), 0.80 (t, $J = 7.5$ Hz, 3 H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 208.1, 153.2, 63.1, 57.4, 56.3, 38.6, 31.8, 31.0, 25.6, 22.9, 13.6, 9.4. Anal. Calcd for $C_{19}H_{33}NO_2$: C, 74.22; H, 10.82; N, 4.56; O, 10.41. Found: C, 74.13; H, 10.76; N, 4.50.

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