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Formation of (*S*)-5-Cyclohexyl-5-phenyl-1,3-dioxolane-2,4-dione: A Key Intermediate in the Synthesis of (*S*)-Oxybutynin Hydrochloride†

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Abstract:

The synthesis of the drug candidate (*S*)-oxybutynin hydrochloride 1 is described. The procedure involves initial activation of (*S*)-cyclohexylmandelic acid 2, using isobutylchloroformate, followed by reaction of the resulting intermediate with 4-(diethylamino)but-2-yn-1-ol, 3. In this reaction, (*S*)-5-cyclohexyl-5-phenyl-1,3-dioxolane-2,4-dione 7 was identified as a key transient intermediate leading to 1. On the basis of the *in situ* IR spectroscopy data collected, the sequence of chemical events involved in the formation of intermediate 7, and its conversion to product and byproducts are described.

Introduction

Urge urinary incontinence (UUI) is caused by hyperactivity of the detrusor muscle and is widely treated by muscarinic receptor antagonists, particularly acting at the M_3 subtype. However, side effects such as dry mouth, tachycardia, and mydriasis often result from the nonselective binding with other M subtypes or with M_3 subtypes, which are not bladder specific such as those located in the salivary glands and pupils.[1] Enantiopure (*S*)-oxybutynin[2] **1** (Figure 1) has the potential to reduce urinary frequency and incontinence episodes while reducing the side effects associated with the racemic compound.

Results and Discussion

An efficient and scalable coupling protocol for the synthesis of multikilogram quantities of the target molecule **1** has been developed, starting from carboxylic acid **2**. The two-step, one-pot procedure involves the initial activation of **2** using isobutylchloroformate (IBCF) and *N*-methylpiperidine (NMP) in toluene, at ambient temperature. The resulting intermediate is subsequently reacted with 4-(diethylamino)but-2-yn-1-ol **3** over

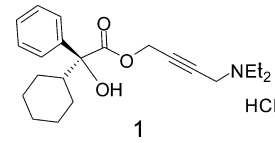

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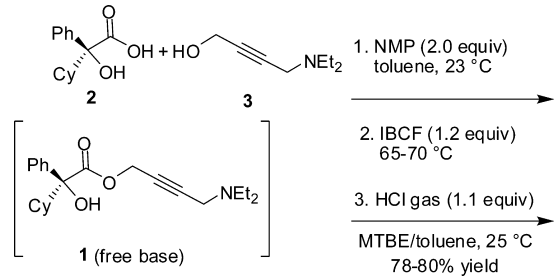
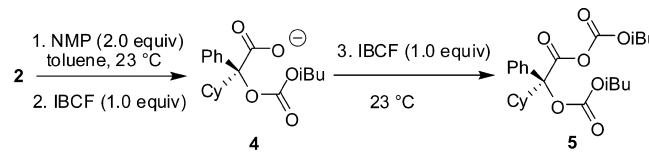
Figure 1. **(*S*)-Oxybutynin hydrochloride.**

Scheme 1. **Synthesis of 1**



Scheme 2. **Reaction of 2 with IBCF**



6−8 h, at 65−70 °C, to afford **1** (83−85% assay yield). After aqueous workup, the organic layer containing **1** as the free base, is distilled to remove isobutyl alcohol and water prior to crystallization. Product **1** is isolated as the HCl salt in 78−80% yield from **2** by crystallization from MTBE/toluene (Scheme 1).

A number of other activating reagents such as DCC, CDI, $SOCl_2$, phosphoryl chloride, and 2-fluoro-1-methylpyridinium *p*-toluenesulfonate were also evaluated in the laboratory. However, IBCF was selected as the reagent of choice on the basis of reaction performance, cost, stability, and commercial availability. In order to track and obtain a better understanding of the chemical events throughout the course of this reaction, we sought to monitor the activation of **2** with IBCF as well as the formation of **1** using HPLC and *in situ* IR spectroscopy.

The reaction of **2** with NMP (2 equiv) and IBCF (1 equiv) at 23 °C affords intermediate **4** (along with 2−3 area % **5**) as detected by HPLC and by *in situ* IR spectroscopy[3] (Scheme 2). All attempts to isolate a pure sample of intermediate **4** were unsuccessful due to its inherent instability resulting in partial

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(2) (a) Shuji, M.; Suzuki, M.; Kanai, M.; Shibasaki, M. *Tetrahedron Lett.* **2002**, *43*, 8647. (b) Gupta, P.; Fernandes, R. A.; Kumar, P. *Tetrahedron Lett.* **2003**, *24*, 351. (c) Shuji, M.; Suzuki, M.; Kanai, M.; Shibasaki, M. *Tetrahedron Lett.* **2004**, *60*, 10497. (d) Trost, B. M.; Xu, J.; Reichle, M. *J. Am. Chem. Soc.* **2007**, *129*, 282. For the synthesis of (*S*)-cyclohexylmandelic acid see: (e) Senanayake, C. H.; Fang, K.; Grover, P. T.; Bakale, R. P.; Vandenbossche, C. P.; Wald, S. A. *Tetrahedron Lett.* **1999**, *40*, 819. (f) Grover, P. T.; Bhongle, N. N.; Wald, S. A.; Senanayake, C. H. *J. Org. Chem.* **2000**, *65*, 6283. (g) Tokuda, O.; Kano, T.; Gao, W.; Ikemoto, T.; Maruoka, K. *Org. Lett.* **2005**, *7*, 5103. (h) Roy, S.; Sharma, A.; Chattopadhyay, N.; Chattopadhyay, S. *Tetrahedron Lett.* **2006**, *47*, 7067.

(3) *In situ* IR spectra were obtained using a ReactIR 1000 instrument, from ASI Applied Systems, equipped with a SiComp probe.

(4) (a) Rhee, S. W.; Ryan, K. J.; Tracy, M.; Kelson, A. B.; Clizbe, L. A.; Chang, M.-H.; Park, J.-S.; Roh, J.-K.; Kong, J.-Y.; Yang, J.; Kim, W.-B.; Ok, K.-D. *J. Label. Compds. Radiopharm.* **1997**, *39*, 773. (b) Kim, H.; Olsen, R. K.; Choi, O. *J. Org. Chem.* **1987**, *52*, 4531.

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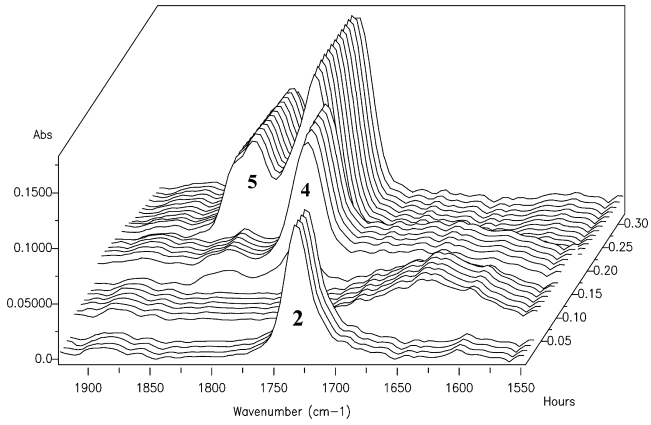


Figure 2. **Three-dimensional waterfall plot (solvent subtracted) of the reaction depicted in Scheme 2, monitored over time by *in situ* IR. Absorptions: 2 1733 cm^{-1} (C═O); 2 carboxylate 1644 cm^{-1} (C═O); 4 1752 and 1652 cm^{-1} (C═O); 5 1829, 1811, and 1760 cm^{-1} (C═O).**

decomposition of **4** to **2** and isobutyl alcohol as evident by crude ^{1}H and ^{13}C NMR. Instead, intermediate **4** was trapped as the methyl ester, using diazomethane, was isolated, and was fully characterized.

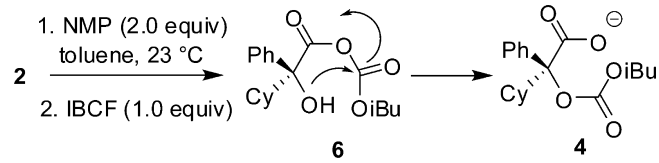
The addition of a second equivalent of IBCF (2 equiv total) afforded exclusively intermediate **5** as evident by HPLC and by IR. This intermediate was isolated and fully characterized. Intermediates similar to **5**, resulting from the reaction of α-hydroxy acids with IBCF (2 equiv), have been proposed by Rhee[4a] et al. for the ^{14}C-radiolabeled synthesis of anthracycline, an anticancer agent, and employed as intermediates by Olsen et al. for the preparation of β-keto esters.[4b]

In situ IR spectroscopy was utilized to observe the conversion of **2** to intermediates **4** and **5** (Figure 2). Accordingly, NMP (2 equiv) was added to a suspension of **2** in toluene at 23 °C, resulting in a homogeneous solution. The deprotonation of **2** resulting from the addition of the amine base to afford the carboxylate salt can be observed. The absorption at 1733 cm^{-1} **2**, carboxylic acid (C═O stretch) disappears upon addition of the base, while the broad absorption at 1644 cm^{-1} (carboxylate salt C═O stretch), subsequently appears. Addition of IBCF (1 equiv) at 23 °C resulted in a thin suspension by activation of the carboxylate salt, resulting in the formation of intermediate **4** as evidenced by the appearance of the absorption at 1752 cm^{-1} (carbonate C═O stretch) along with retention of the broad absorption at 1652 cm^{-1} (carboxylate salt C═O stretch). Likewise, addition of a second equivalent of IBCF (2 equiv total), resulting in the formation of intermediate **5**, was also observed. The two absorptions at 1752 cm^{-1} and 1652 cm^{-1} corresponding to intermediate **4** disappear, while the absorptions at 1829, 1811, and 1760 cm^{-1} (C═O stretches) simultaneously appear, resulting from the formation of intermediate **5**. Similar mixed anhydrides[5] of this type are reported to absorb at 1827−1810 and 1775−1750 cm.$^{-1}$

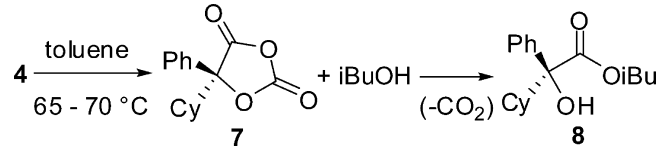
Formation of intermediate **4** is believed to proceed through the mixed anhydride intermediate **6** (Scheme 3); however, no sign of this intermediate **6** was observed by *in situ* IR

(5) Colthup, N. B.; Daly, L. H.; Wiberley, S. E. *Introduction to Infrared and Raman Spectroscopy*, 3rd ed.; Academic Press: San Diego, CA, 1990; p 312.

Scheme 3. **Formation of intermediate 4**



Scheme 4. **Conversion of intermediate 4 to the transient intermediate 7**



spectroscopy under the reaction conditions nor at −78 °C with a collection rate of three spectra per second. Initial formation of the mixed anhydride **6**, followed by the rapid intramolecular transfer of the isobutoxycarbonyl moiety to the α-hydroxyl, is believed to be the mechanism leading to the formation of intermediate **4**. This is based on the finding that the methyl ester of **2** has been found to remain unreacted when subjected to the same reaction conditions.

Intermediate **4**, when heated to 65−70 °C in toluene, was observed to slowly undergo intramolecular ring closure to afford the 5-cyclohexyl-5-phenyl-1,3-dioxolane-2,4-dione intermediate **7** and isobutyl alcohol (Scheme 4). This conversion is evident by the appearance of the absorption at 1815 cm^{-1} (C═O stretch) and 1900 cm^{-1} (carbonate C═O stretch), followed by the corresponding decrease in absorptions related to the disappearance of intermediate **4** (Figure 3).

The *in situ* IR absorptions observed for intermediate **7** were found to be consistent with the IR spectrum of a synthetic sample prepared from **2** using trichloromethylchloroformate.[6] Intermediate **7** appears to be the final intermediate along the pathway to forming product **1**. Conversely, by allowing the reaction to proceed further at 65−70 °C in the absence of **3**, consumption of the two carbonyl stretches resulting from reaction of intermediate **7** with isobutyl alcohol is observed along with the simultaneous increase in the absorption at 1725 cm^{-1}, resulting in the formation of the byproduct, isobutyl ester[7]

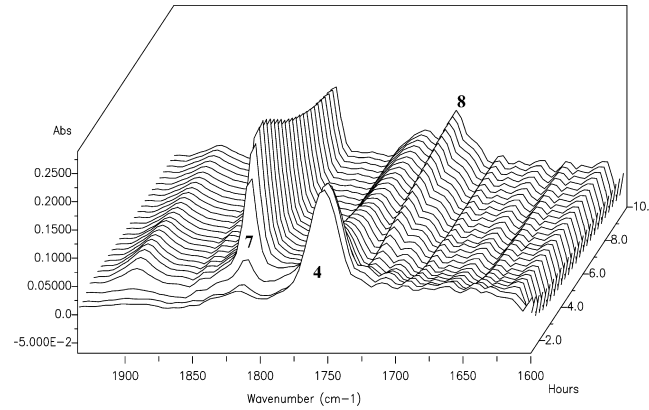
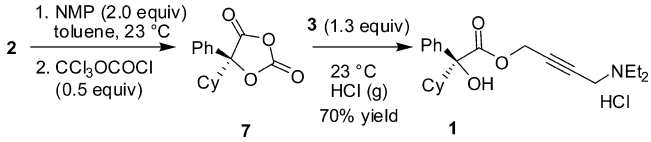


Figure 3. **Three-dimensional waterfall plot (solvent subtracted) of the partially completed reaction, depicted in Scheme 4, monitored over time by *in situ* IR. Absorptions: 4 1752, and 1652 cm^{-1} (C═O); 7 1900, and 1815 cm^{-1} (C═O); 8 1725 cm^{-1} (C═O).**

Scheme 5. **Generation of intermediate 7 using trichloromethylchloroformate**



8 (Figure 3). This is consistent with the literature report about that dioxalane-2,4-diones, similar to **7**, though less hindered, were prepared and converted to esters by Grieco and Deng.[8]

The use of trichloromethylchloroformate as an alternative reagent was also evaluated for this coupling process. The benefit of using this reagent, over IBCF, was the possible gain in yield resulting from the reduction in the amount of the isobutyl ester **8** produced (Scheme 5). Formation of the same reactive intermediate **7** was observed at 23 °C by *in situ* IR when trichloromethylchloroformate was used as an activating reagent instead of IBCF. The reaction trending profile (Figure 4) clearly indicates the formation of **2** carboxylate anion, which is consumed by formation and build up of intermediate **7.** When intermediate **7** is treated with **3** (at ~3 h) it undergoes reaction to produce **1** (free base). Despite the advantage in yield increase due to elimination of byproduct **8**, major concerns regarding safety, cost, and scalability prohibited the consideration of trichloromethylchloroformate for further development and scale up.

The cyclization of **4** to cyclic intermediate **7** occurs only at or above 40 °C when isobutylchloroformate is used as evident by *in situ* IR, but **7** can be made and subsequently converted to **1** at room temperature when trichloromethylchloroformate is used instead. Also, under the standard reaction conditions, upon heating intermediate **4** in the presence of 1.3 equiv of **3**, no observable level of intermediate **7** is detected by *in situ* IR. However, only by starving the reaction mixture of **3**, at 65−70 °C, allowed sufficient quantity of intermediate **7** to be detected in order to confirm its presence in the reaction mixture. On the basis of these findings it is concluded that among the series of chemical events in the synthesis of **1** from **2** (Scheme 6), the formation of **7** from **4** may be the rate-limiting step.

The fate of intermediate **5**, generated using 2.0 equiv of IBCF, throughout the course of the coupling reaction was also investigated. Under these conditions, a significant increase in the amount of the undesirable byproduct, isobutyl ester **8**, was produced upon reaction completion (15 vs 5 area % by HPLC under reaction conditions, when 1.0 equiv of IBCF was used). In this case, intermediate **4** is formed along with carbonate

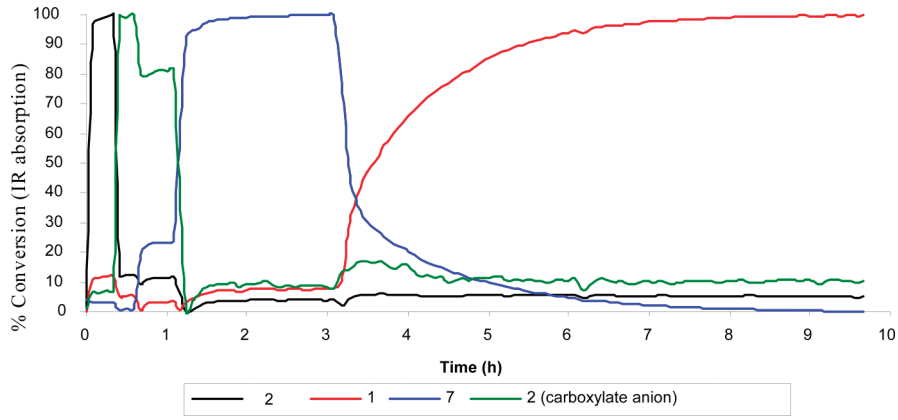
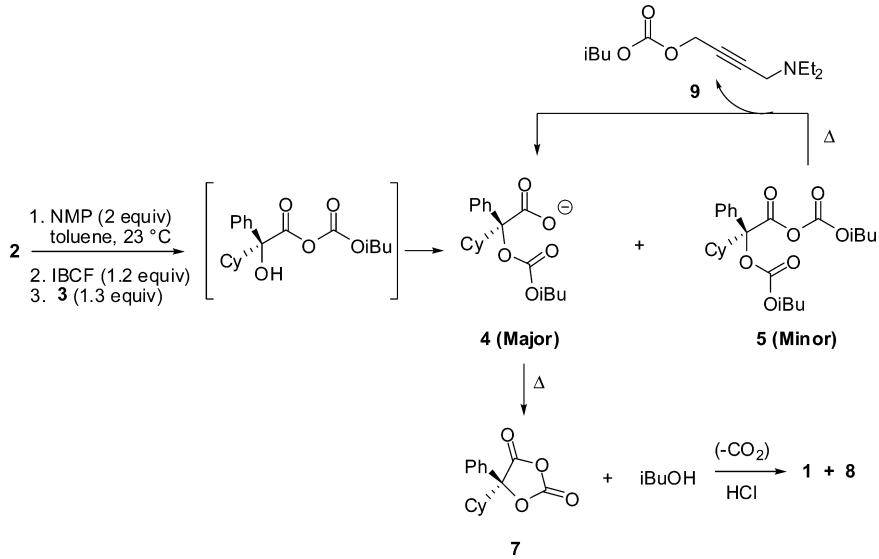


Figure 4. **Absorption profile for the reaction depicted in Scheme 5, as determined by *in situ* IR spectroscopy.**

Scheme 6. **Proposed reaction mechanism**



byproduct[9] **9** by the reaction of intermediate **5** with **3** (Scheme 6). Formation of byproduct **9** ultimately diminishes the amount of available **3** in solution. In the absence of a sufficient amount of **3**, the isobutyl alcohol (generated from the formation of intermediate **7** from **4**), reacts with **7**, resulting in a significant increase of the isobutyl ester **8** along with **1**. Since all three pathways are irreversible and the products of each are not interconvertible, the relative distribution of products is kinetically controlled.

Conclusion

In summary, *in situ* IR spectroscopy combined with HPLC was found to be an effective tool for determining and tracking the chemical events of this reaction. Using *in situ* IR allowed for a better understanding of the chemical process. The formation and build up of transient intermediates, starting material disappearance, and product and byproduct formation were effectively followed during the course of the reaction using both techniques. This process has been scaled up to produce multiton quantities of **1**. Presumably, other α-hydroxy acids react with chloroformates in a similar manner to afford esters and amides.

Experimental Section

General. A Water 2690 HPLC system equipped with Waters 2487 UV detector was used for in-process assays. The HPLC data were reported in area % and were not adjusted to weight %. The formation of intermediates **4** (17.8 min) and **5** (19.9 min), from **2** (13.6 min), and product **1** (8.8 min) were monitored using gradient HPLC @ 220 nm (Zorbax RX C-8, mobile phase: A = 0.05 M NaH_2PO_4 (pH 2.5)/methanol (40:60, v/v), B = methanol). Linear ramp from 100% A to 100% B from 0 to 10 min; held at 100% B for 10 to 25 min; re-equilibration with 100% A for 15 min prior to next injection. Typically, up to 2−3 HPLC A% of **5** along with **4** was observed even when only 1.0 equiv of IBCF was used.

5-Cyclohexyl-5-phenyl-1,3-dioxolane-2,4-dione, 7. NMP (0.7 mL, 10.2 mmol. 2.0 equiv) was added over 30 s to a stirred solution of **2** (1.17 g, 5.0 mmol) in anhydrous THF (10 mL) at ambient temperature. After 10 min, trichloromethylchloroformate (0.7 mL, 5.8 mmol, 1.2 equiv) was added dropwise over one minute while maintaining the reaction temperature ≤30 °C. After being stirred for 12 h at room temperature, the reaction mixture was concentrated to a viscous oil under reduced pressure. Hexanes (20 mL) was added to the oil, and the mixture was allowed to stand at 5 °C for 2 h. The resulting solid (amine salt) was filtered and washed with hexane (10 mL). The hexane solution was concentrated, and the crude product was purified by flash chromatography using hexane eluent to give pure product **7** (1.0 g, 79% yield). IR (film) 1807, 1900 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.14 to 1.46 (m, 6H), 1.70 to 1.89 (m, 4H), 2.20 to 2.28 (m, 1H), 7.4 to 7.6 m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 25.6, 25.7, 25.9, 26.7, 46.4, 92.8, 124.7, 129.1, 129.6, 132.9, 148.0, 168.3. HRMS Calcd for $C_{15}H_{16}O_4$ $(M + Na)^+$ 283.0946; found 283.0942.

(*S*)-4-(Diethylamino)but-2-ynyl 2-cyclohexyl-2hydroxy-2-phenyl Acetate Hydrochloride, 1. To a suspension of compound **2** (30.0 g, 128 mmol) in toluene (180 mL) under argon was added NMP (25.3 g, 256 mmol, 2.0 equiv) at 23 °C. Isobutylchloroformate was added over 10 min (17.5 g, 128 mmol, 1.0 equiv) at 23 °C. The reaction mixture was stirred at ambient temperature for 30 min before 4-(diethylamino)but-2-yn-1-ol, **3** was added (23.6 g, 166 mmol, 1.3 equiv), and the reaction mixture was stirred at 70 °C for 4 h. A second portion of isobutyl chloroformate (3.8 g, 25.6 mmol, 0.2 equiv) was added at 70 °C, and the reaction mixture was stirred at 70 °C for 3 h. At this point, HPLC analysis showed starting material **2** and intermediate **4** each were less than 1 area %. The reaction mixture was cooled to ambient temperature and quenched by the addition of NaH_2PO_4 (10%, 192 g) before separating the organic layer. The organic layer was washed with NaH_2PO_4 (10%, 192 g) and DI water (192 g). HPLC analysis showed the desired product was obtained in 86% assay yield (39.4 g). The resulting yellow solution was subjected to azeotropic distillation to remove isobutanol and lower the water content of the mixture to <0.2% by weight. The batch was concentrated to a final volume of 110 mL, and diluted to a final volume of 250 mL with fresh toluene. MTBE (184 mL) was added as cosolvent. Hydrogen chloride gas (4.4 g) was added via subsurface addition over 20 min at 25 °C. The clear solution was heated to 50 °C, and crystallization was initiated by seeding. After seeding, the resulting slurry was allowed to stir at 50 °C for 2 h. The batch was cooled to ambient temperature over 1 h and agitated, at 20−25 °C, for 2 h. The slurry was filtered through a glass filter, and the cake was washed with MTBE (157 g) and oven-dried at 40−45 °C, under reduced pressure, for 12 h to afford **1** (40.2 g, 80.0% yield) as white needles, mp 117−118 °C. ^1H NMR (400 MHz, DMSO-d_6): δ 0.9 to 1.1 (m, 4H), 1.1 to 1.2 (m, 7H), 1.3 (m, 1H), 1.4 (m, 1H), 1.6 (m, 2H), 1.7 (m, 1H), 2.9 (d, 4H), 4.1 (s, 2H), 4.8 (s, 2H), 5.7 (s, 1H), 7.2 (m, 1H), 7.3 (m, 2H), 7.5 (m, 2H), 11.4 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 8.9, 25.2, 25.1, 25.8, 25.9, 25.9, 40.5, 45.7, 46.8, 52.4, 75.4, 80.9, 83.8, 125.7, 127.2, 127.9, 141.1, 173.5.

Cyclohexyl-isobutoxycarbonyloxy-phenyl Acetic Acid Methyl Ester. NaOH (5 N, 19.8 mL) was added dropwise to a solution of 1-methyl-1-nitroso-1-nitro guanidine (4.4 g, 30 mmol) (*caution! diazomethane is potentially toxic and carcinogenic; all operations should be carried out in fumehood)* in diethyl ether (100 mL) and H_2O (16.5 mL) at 0 °C. The two-phase reaction mixture was allowed to stir for approximately 2 h at 0 °C. The bottom aqueous layer was separated and discarded. The bright-yellow organic layer was maintained at 0 °C prior to use (solution A). To a suspension of compound **2** (5.0 g, 21.3 mmol) in toluene (30 mL) under argon was added NMP (5.2 mL, 42.6 mmol, 2.0 equiv) at 23 °C. Isobutyl chloroformate (2.7 mL, 21.3 mmol, 1.0 equiv) was added over approximately 10 min at 23 °C. The reaction mixture was allowed to stir at ambient temperature for 1 h and was then quenched with aqueous NaH_2PO_4 (10%, 75 mL) and diluted

(6) Toyooka, K.; Takeuchi, Y.; Kubota, S. *Heterocycles* **1989**, *29*, 975.
(7) Mndzhoyan, A. L.; Bagdasaryan, E. R. *Arm. Khim. Zh.* **1970**, *23*, 617.
(8) Moher, E. D.; Grieco, P. A.; Collins, J. L. *J. Org. Chem.* **1993**, *58*, 3789. Grieco, P. A.; Collins, J. L.; Moher, E. D.; Thomas, J. F.; Gross, R. S. *J. Am. Chem. Soc.* **1993**, *115*, 6078. Tang, L.; Deng, L. *J. Am. Chem. Soc.* **2002**, *124*, 2870.
(9) For a review article on organic carbonates see: Shaikh, A.-A.; Sivaram, S. *Chem. Rev.* **1996**, *96*, 951.

with toluene (30 mL). The organic phase (solution B) was separated and washed with DI water (50 mL). Solution A was added dropwise to solution B at 0 °C, resulting in a colorless solution. The reaction mixture was allowed to stir at 0 °C for 1 h and then at ambient temperature overnight. The organic layer was concentrated under reduced pressure to afford a yellow oil. The crude product was purified using flash chromatography; Rf = 0.33 (eluent: 93:7 hexane/EtOAc) to afford the desired product as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.86 to 1.30 (m (2d, J = 2.7 and 3.0 Hz), 11H), 1.50 to 2.25 (m, 7H), 3.80 (s, 3H), 3.95 (dd, J = 8.9, 6.9 Hz, 2H), 7.28 to 7.39 (m, 3H), 7.56 to 7.60 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 19.0, 26.2, 26.4, 26.3, 27.5, 28.0, 28.1, 47.4, 52.4, 74.4, 88.2, 126.4, 127.8, 127.9, 137.4, 154.0, 170.4. HRMS Calcd for $C_{20}H_{28}O_5$ (M + Na) 371.1834; found 371.1850.

Cyclohexylisobutyloxycarbonyloxyphenyl Acetic Acid Isobutylcarbonic Anhydride, 5. To a suspension of **2** (5.0 g, 21.3 mmol) in cyclohexane (100 mL) was added triethylamine (7.4 mL, 53.3 mmol, 2.5 equiv) and isobutylchloroformate (5.5 mL, 42.6 mmol, 2.0 equiv) while maintaining the reaction temperature between 20−30 °C. The reaction mixture was allowed to stir at ambient temperature for 1 h and was then quenched with aqueous NaH_2PO_4 (10%, 50 mL). The organic phase was separated and washed with aqueous NaH_2PO_4 (10%, 50 mL) and DI water (50 mL). The organic layer was dried over anhydrous $MgSO_4$, concentrated in vacuo, and purified using flash chromatography; R_f = 0.20 (eluent: 95:5 hexane/EtOAc) to afford the desired product (2.5 g, 27% yield unoptimized) as a colorless oil. IR (film) 1825, 1809, 1761, 1273 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.94 (d, J = 6.9 Hz, 6H), 0.99 (d, J = 6.9 Hz, 6H), 1.10 to 2.40 (m, 13H), 3.94 (dd, J = 10.5, 6.3 Hz, 1H), 3.99 (dd, J = 10.5, 6.3 Hz, 1H), 4.09 (d, J = 6.9 Hz, 2H), 7.27 (m, 3H), 7.58 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 18.7, 25.9, 26.1, 26.2, 26.8, 27.6, 27.7, 46.7, 74.6, 75.6, 87.3, 126.1, 127.9, 128.0, 135.7, 148.5, 153.6, 164.4. HRMS Calcd for $C_{24}H_{34}O_7$, (M + Na) 457.2205; found 457.2176.

Isobutyl 2-cyclohexyl-2-hydroxy-2-phenylacetate, 8. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.85 to 1.0 (m, 6H), 1.0 to 1.40 (m, 6H), 1.45 (m, 2H), 1.65 (m, 2H), 1.83 (m, 1H), 1.99 (m, 1H), 2.25 (m, 1H), 3.98 (m, 2H), 7.27 to 7.40 (m, 3H), 7.68 to 7.70 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.2, 25.7, 26.4, 26.5, 26.6, 27.6, 27.8, 45.9, 72.6, 81.1, 126.2, 127.5, 128.2, 141.0, 175.9.

4-(Diethylamino)but-2-yn-1-ol Isobutyl Carbonate, 9. Authentic sample of **9** was prepared by reacting **3** with isobutylchloroformate (1.2 equiv) in the presence of triethylamine (1.2 equiv) in toluene at room temperature for 12 h. The product, as an oil, was isolated in 48% yield after removal of toluene under vacuum followed by flash chromatography using 20% (v/v) ethyl acetate in hexane. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.95 (m, 6H), 1.05 (m, 6H), 2.0 (m, 1H), 2.55 (q, J = 7.5 Hz, 4H), 3.48 (br s, 2H), 3.98 (d, J = 3 Hz, 2H), 4.85 (br s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 12.8, 19.1, 28.0, 41.1, 47.4, 55.9, 74.6, 78.4, 82.8, 155.1. Anal. Calcd for $C_{13}H_{23}NO_3$: C, 64.70; H, 9.61; N, 5.80. Found: C, 64.56; H, 9.79; N, 5.70.

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Supporting Information Available

Experimental procedures and spectral data of all new compounds described in the paper (^{1}H, ^{13}C NMR, and FTIR if applicable). This material is available free of charge via the Internet at http://pubs.acs.org.

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