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SYNTHESIS OF A MACROHETEROCYCLIC COMPOUND THROUGH PHOTHODECARBOXYLATION OF POTASSIUM ω-PHTHALIMIDOALKYNOATE[#]

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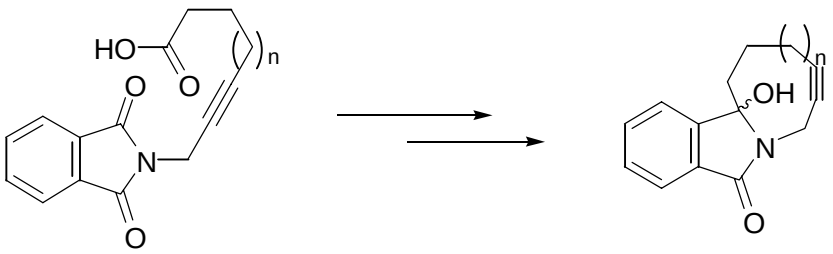
Abstract – A macroheterocyclic alkyne compound is prepared through photodecarboxylation of ω-phthalimidoalkynoates in moderate yield.

A facile synthesis of macrocyclic compounds has been a challenge to organic chemists for some time. Photochemical decarboxylation of ω-phthalimidoalkylcarboxylates gave aza-macrocycles in moderate to high yields offering an efficient route to the synthesis of macroheterocyclic compounds.[1-5]

Introduction of acetylene functional group into the heterocycle could be of importance in view of additional functional modification and geometrical restrictions. To evaluate the ring annulation methodology and to further widen the scope of the photodecarboxylation of ω-phthalimidoalkanoates, we have studied the decarboxylative cyclization of model substrates (**1a**, **1b**, and **1c**) (Figure 1). ω-Phthalimidoalkynoic acids (**1**) were selected since they possess a rigid and straight C≡C bond at γ position to avoid γ-hydrogen abstraction as well as the incorporation of the C≡C bond. The side chain connected with carboxylic acid moiety should have several methylene units to easily approach the imide carbonyl group for the photoinduced election transfer and subsequent cyclization.

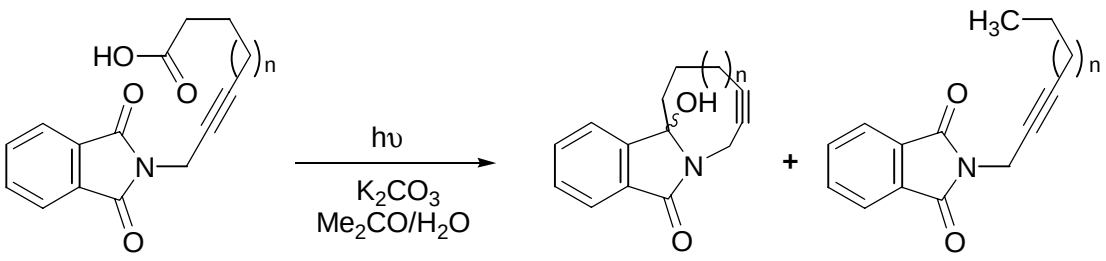


1a n = 0, **1b** n = 1, **1c** n = 8 **2**

Figure 1. Synthetic strategy

Photolysis of Potassium ω-Phthalimidoalkynoate:

Starting ω-phthalimidoalkynoic acid was deprotonated with potassium carbonate prior to photolysis in 1:1 (v/v) acetone and water solution (Scheme 1). There was no trace of ring compounds (**2a**, **2b**) when **1a** or **1b** was irradiated in 50% water/acetone under nitrogen atmosphere in a Rayonet photoreactor and only photoreduced product (**11a**) (76%) or (**11b**) (70%)[5b] was formed. However, the substrate (**1c**)[5a] with longer methylene chain yielded the corresponding annulation product (**2c**)[6] in 21% yield, accompanied by a trace amount of unidentified materials. The results indicated that a loss in conformational flexibility due to triple bond of the connecting hydrocarbon chain is not crucial for the efficiency of the ring formation. Large-ring hydroxy lactam was easily crystallized from acetone. Yoon *et al.*[7] have reported the formation of dimeric products in the photo-induced electron transfer (PET) macrocyclization using the (trialkylsilyl)methoxy group as an electron donor.[7a] However, neither dimeric products nor cross-



1a n = 0, **1b** n = 1
1c n = 8

2a,b : no detected
2c : 21%

11a : 76%, **11b** : 70%
11c : not obtained

Scheme 1. Products of photodecarboylation of ω-phthalimidoalkynoic acid (**1**)

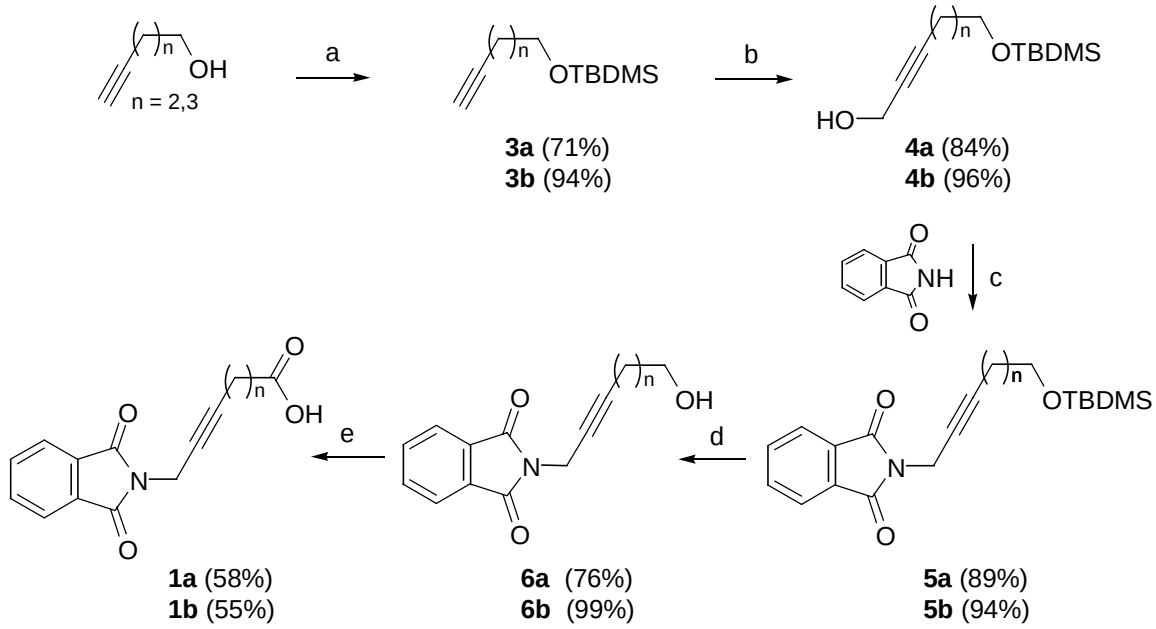
cyclization products were formed through photodecarboxylation as detected by NMR and MS spectral analysis. Epimerization at the stereogenic center of hydroxy lactams was shown in *ca*. 1:1 equilibrium as *N*-phthaloylvaline ester photolysis reported by Griesbeck.[2b]

The structural assignments for the photoproducts were made on the basis of spectroscopic data. IR spectra of major cyclized product (**2c**) showed characteristic absorption bands for the hydroxyl groups at 3100-3600 cm^{-1} and amide carbonyl group at 1678cm^{-1}. The ^{13}C-NMR spectra clearly showed resonances which correspond to quaternary carbon (C-3) at 91.3 ppm and internal acetylene carbon at 75.1 and 83.1 ppm. The GC/MS spectrum showed molecular ion peak at m/z 325 (M^+, 35%). These spectral data of the cyclization products are consistent with carbon-carbon bond formation between the phthalimide carbonyl carbon and α-carbon of potassium carboxylate.

Synthesis of ω-Phthalimidoalkynoic Acids:

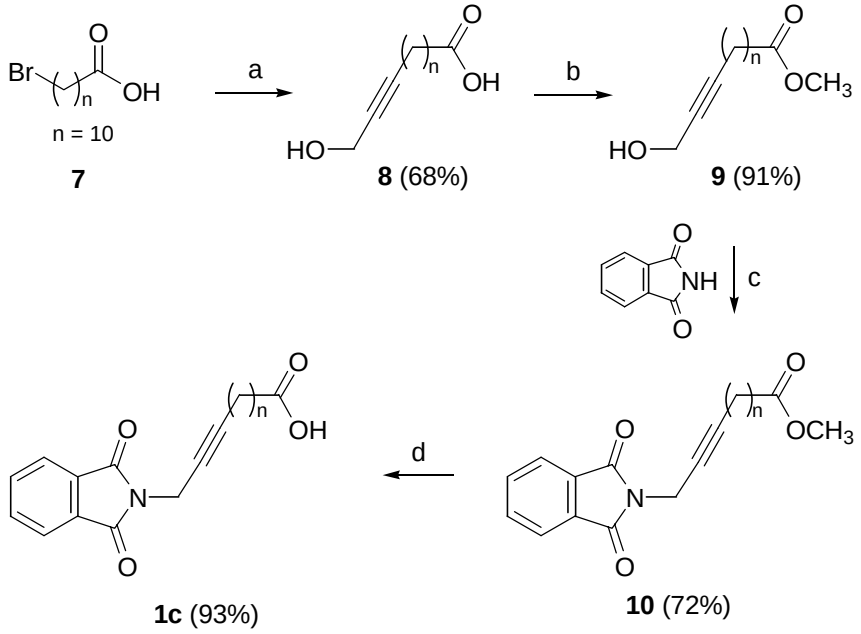
The short chain length phthalimidoalkynoic acid (**1a**,**b**) was prepared as described in Scheme 2. The primary hydroxyl group of ω-alkyn-1-ol was protected as *tert*-butyldimethylsilyl (TBDMS) ether and subsequently treated with *n*-butyllithium and paraformaldehyde to give **4** in 60-90% yields. Subsequent treatment of **4** with phthalimide, diethyl azodicarboxylate (DEAD), and triphenylphosphine by Mitsunobu reaction,[8] and then a deprotection of the silyl group with 0.5 M tetrabutylammonium fluoride/acetic acid buffer solution to avoid the ring opening of the phthalimide in the basic condition provided ω-phthalimido alcohol (**6**)[9] in 68-93% yields, which was then transformed to the desired ω-phthalimidoalkynoic acid (**1a**,**b**)[10] *via* PDC mediated oxidation in 58-55% yields.

The long chain length ω-phthalimidoalkynoic acid (**1c**) was prepared from 11-bromoundecanoic acid (**7**) as shown in Scheme 3. Compound (**8**)[11] was prepared in 68% yield by the reaction of **7** with propargyl alcohol, which is expected to proceed through nucleophilic addition of lithium acetylide in HMPA/THF.[12] Esterification of **8** with catalytic amount of sulfuric acid in methanol followed by Mitsunobu reaction[8] with phthalimide in the presence of DEAD and triphenylphosphine afforded methyl ω-phthalimidoalkynoate (**10**)[13] in 66% yield. Compound (**1c**)[14b] was easily obtained in 93% yield by treatment of **10** with a mixture of acetone, water, and conc. hydrochloric acid (*v/v/v* = 40:28:12) at reflux.[14a]



[α]The reaction conditions: a) TBDMSCl, imidazole, DMF, rt; b) *n*-BuLi, $(CH_2O)_n$, THF, -78 °C; c) DEAD, PPh_3, THF, rt; d) 0.5 M TBAF/HOAc, THF, rt; e) PDC, DMF, rt.

Scheme 2. Synthesis of ω-phthalimidoalkynoic acids (n = 2 and 3).[α]



[α]The reaction conditions: a) $CH{\equiv}CCH_2OH$, *n*-BuLi, HMPA, THF, -30 °C → rt; b) MeOH, H_2SO_4, rt; c) DEAD, PPh_3, THF, rt; d) conc. HCl/H_2O/acetone (*v/v/v*, 12:28:40), reflux.

Scheme 3. Synthesis of ω-phthalimidoalkynoic acid (n = 10).[α]

In conclusion, we have accomplished the first trial of photodecarboxylative cyclization of ω-phthalimidoalkynoic acid (**1**) having internal acetylene at γ position. Short methylene chain ω-phthalimidoalkynoic acids (**1a**) and (**1b**) produced only photoreduced compounds (**11a**) and (**11b**), but long chain ω-phthalimidoalkynoic acid (**1c**) afforded the corresponding heterocyclic ring compound (**2c**) in 21% yield.

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REFERENCES AND NOTES

[#]Dedicated to Professor Shô Itô on the occasion of his 77th birthday.

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5. Typical procedure for irradiation of **1a**-**1c**: A mixture of K_2CO_3 (0.28 g, 1.0 mmol) and the substrate (**1c**) (0.74 g, 2.0 mmol) in H_2O (2 mL) was heated to 60-70 ℃ for 1 min and dissolved in

H_2O/acetone 1:1 (*v/v*, 100 mL). The homogeneous solution obtained was irradiated (Rayonet photoreactor; 300 nm, 8 ×3000 Å lamps, *ca.* 800 W) in a Pyrex tube for 6 h while purging with a slow stream of nitrogen and cooling to *ca.* 20 °C. After evaporation of most of the acetone, the residual solution was extracted with $CHCl_3$ (3 ×100 mL). After drying over $MgSO_4$ and evaporation, the resulting product was chromatographed on silica gel (ethyl acetate/hexane = 1:1). (b) Selected physical and spectral data for the photoproduct (**11b**): mp 51-53 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.91 (t, 3H, *J* = 9.8 Hz), 1.46 (m, 2H), 2.05-2.14 (m, 2H), 4.40 (t, 2H, *J* = 2.9 Hz), 7.68-7.71 (m, 2H), 7.83-7.86 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.39, 20.57, 21.82, 27.46, 73.46, 83.58, 123.41, 132.11, 134.00, 167.19.

6. Selected physical and spectral data for the photoproduct **2c**: mp 135.5-138 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.18-1.32 (m, 12H), 1.33-1.40 (m, 2H), 2.13-2.24 (m, 4H), 2.71 (br s, 1H), 3.98 (dt, 1H, *J* = 17.6, 2.2 Hz), 4.31 (dt, 1H, *J* = 17.6, 2.2 Hz), 7.43-7.58 (m, 3H), 7.74 (d, 1H, *J* = 7.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.27, 22.59. 25.36, 25.55, 26.28. 26.35, 26.49, 27.13, 27.21, 27.62, 29.69, 30.90, 36.67, 75.05, 83.08, 91.28, 121.86, 123.53, 129.62, 131.05, 132.45, 146.81, 166.91; MS (m/z) 325 (M^+, 35%), 297 (24%), 281 (100%), 267 (31%), 223 (73%), 207 (44%), 160 (77%), 147 (43%); HRMS: calcd for $C_{21}H_{27}NO_2$ (325.2042), found (325.2041).
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9. Selected physical and spectral data for the products (**6a**): mp 129-130 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.66-1.72 (m, 2H), 1.70 (bs, 1H, OH), 2.24 (t, 2H, *J* = 6.8 Hz), 3.68 (t, 2H, *J* = 5.9 Hz), 4.38 (s, 2H), 7.68-7.70 (m, 2H), 7.82-7.84 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.18, 27.43, 30.94, 61.52, 73.96, 82.94, 123.45, 132.03, 134.07, 167.19; HRMS: calcd for $C_{14}H_{13}NO_3$ (243.0895), found (243.0868). **6b**: mp 88-90 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.51-1.61 (m, 4H), 2.12-2.16 (m, 2H), 3.60 (t, 2H, *J* = 6.1 Hz), 4.38 (t, 2H, *J* = 2.2 Hz), 7.68-7.71 (m, 2H), 7.81-7.84 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.36, 24.59, 27.44, 31.71, 62.20, 73.74, 83.39, 123.41, 132.06, 134.04, 167.17;

HRMS: calcd for $C_{15}H_{15}NO_3$ (257.1051), found (257.1082).

10. Selected physical and spectral data for the product (**1a**): mp 178-179.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.43-2.46 (m, 2H), 2.50-2.53 (m, 2H), 4.38 (s, 2H), 7.69-7.72 (m, 2H), 7.83-7.86 (m, 2H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 14.33, 27.41, 33.03, 74.49, 81.34, 123.57, 132.07, 134.19, 167.25. 177.43; MS (m/z) 82, 104, 130, 148, 160, 198, 215, 257; HRMS: calcd for $C_{14}H_{11}NO_4$ (257.0688), found (257.0690). **1b**: mp 117-119 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.73-1.80 (m, 2H), 2.13-2.22 (m, 2H), 2.41 (t, 2H, *J* = 7.2 Hz), 4.38 (s, 2H), 7.68-7.70 (m, 2H), 7.83-7.84 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.97, 23.22, 27.37, 32.59, 74.51, 82.21, 123.46, 132.04, 134.07, 167.18, 177.36; HRMS: calcd for $C_{15}H_{13}NO_4$ (271.0844), found (271.0832).
11. Selected physical and spectral data for the product (**8**): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.18-1.41 (m, 12H), 1.43-1.47 (m, 2H), 1.58-1.63 (m, 2H), 2.15-2.21 (m, 2H), 2.32 (t, 2H, *J* = 9.9 Hz), 4.23 (t, 2H, *J* = 2.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.10, 25.06, 28.95, 29.17, 29.38, 29.41, 29.52, 29.67, 29.73, 34.32, 51.81, 78.65, 87.05, 179.54.
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13. Selected physical and spectral data for the product **10**: mp 58-59 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.17-1.35 (m, 12H), 1.38-1.45 (q, 2H, *J* = 9.8 Hz), 1.55-1.60 (q, 2H, *J* = 10.0 Hz), 2.06-2.12 (m, 2H), 2.24-2.29 (t, 2H, *J* = 10.0 Hz), 3.63 (s, 3H), 4.39 (t, 2H, *J* = 2.8 Hz), 7.68-7.72 (m, 2H), 7.81-7.86 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.62, 24.94, 27.51, 28.40, 28.78, 29.01, 29.10, 29.19, 29.33, 29.35, 34.09, 51.38, 73.35, 83.81, 123.42, 132.17, 134.01, 167.18, 174.28.
14. (a) J. C. Sheehan, M. Goodman, and G. P. Hess, *J. Am. Chem. Soc*., 1952, **78**, 1367. (b) Selected physical and spectral data for the product (**1c**): mp 189 °C (decomp); ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.19-1.25 (m, 10H), 1.31-1.34 (m, 2H), 1.38-1.46 (m, 4H), 7.41-7.65 (m, 4H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 18.44, 24.94, 28.61, 28.66, 28.93, 28.95, 29.11, 29.25, 29.27, 34.19, 77.55, 82.59, 128.47, 129.55, 129.73, 168.36, 175.05; HRMS: calcd for $C_{22}H_{27}NO_4$ (369.1940), found (369.1936).