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Photolactamization: A Novel Synthetic Entry into Large Ring-Sized Lactams

Gerhard Quinkert*, Hans Peter Nestler, Bernd Schumacher, Michael del Grosso, Gerd Dürner, and Jan W. Bats

Institut für Organische Chemie der Universität, Niederurseler Hang,
D 6000 Frankfurt am Main 50

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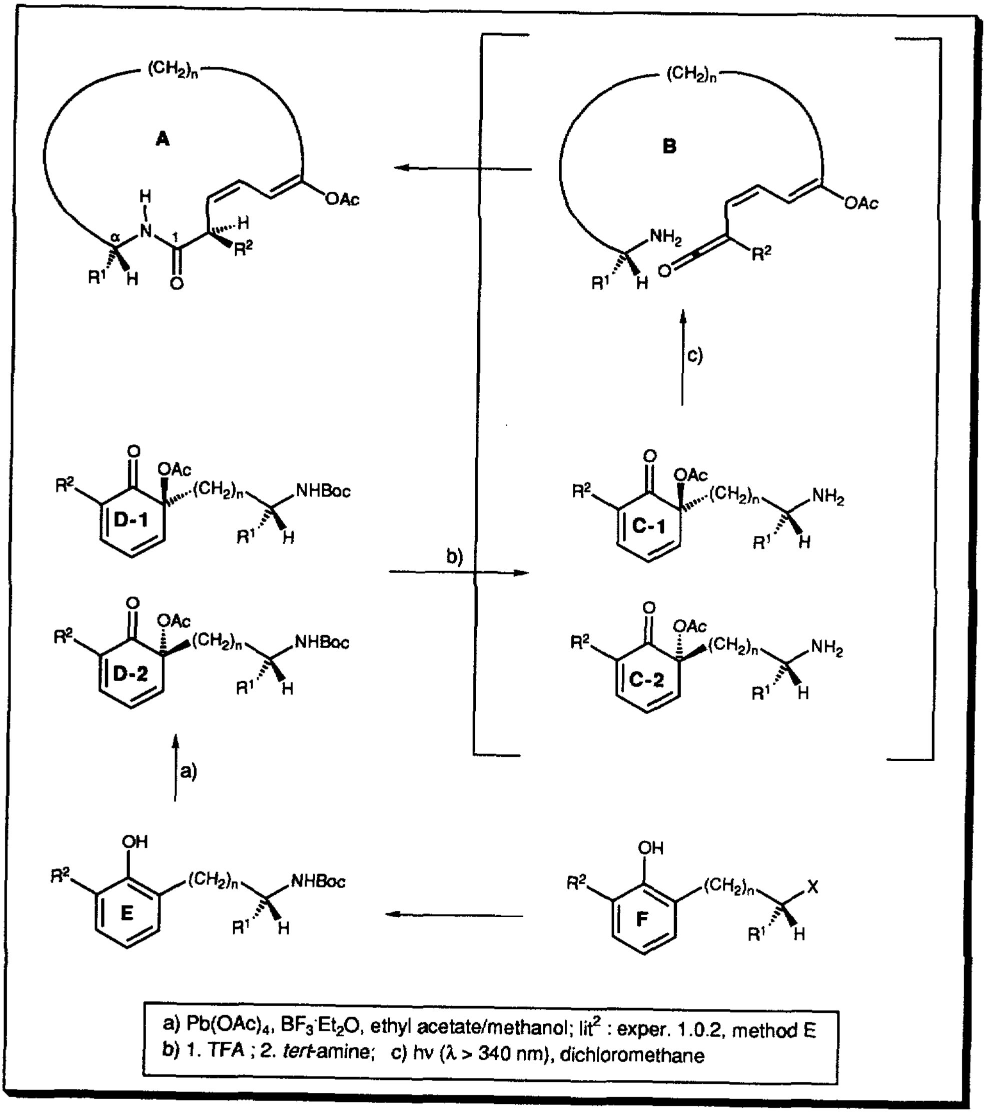
Abstract: *Diene ketenes smoothly accessible by photochemical ring cleavage of o-quinol acetates, in the presence of primary or secondary amines afford the corresponding amides. In an intramolecular version of this reaction macrocyclic lactams of type* **A** *are produced, if aminoalkylated o-quinol acetates of type* C *are used as photo reactants. These photo reactants are available on acid mediated removal of the Boc-protecting group from Wessely acetoxylation products of type* **D**, *easily formed via compounds of type* **E** *from aminoalkylated phenols of type* **F**.

Photolactamization[1] defines a new preparative way by which large ring-sized lactams of type **A** are photochemically accessible from aminoalkyl-substituted *ortho*-quinol acetates of type C via transient diene ketenes[3] of type **B**. As *ortho*-quinol acetates are usually reached by *Wessely* acetoxylation, the whole procedure begins with appropriately substituted phenols of type **E**, where the amino group in the side chain has been protected (by the *Boc*-group). On treatment with TFA carbamates of type **D** are converted into photo reactants of Type C. The latter, without isolation, are irradiated in the presence of an excess of a *tert*-amine.

According to *Table 1* the chemical yield (related to compounds of type **D**) becomes acceptable for lactams of type **A** with larger than 15-membered rings.

The structures of several of the photolactams have been determined by single crystal X-ray diffraction[5]. *Table 2* informs about torsions angles observed for lactams of type **A** in the crystalline state. The data fit well in the structural characteristics of the carboxylic amide group described by P. Chakrabarti and J.D. Dunitz[6].



a) $Pb(OAc)_4$, $BF_3 \cdot Et_2O$, ethyl acetate/methanol; lit[2] : exper. 1.0.2, method E
b) 1. TFA ; 2. *tert*-amine; c) hν (λ > 340 nm), dichloromethane

Aminoalkyl-substituted phenols of type **F** ($X = NH_2$; $n = p$ or $p+1$) were prepared from the corresponding hydroxyalkyl-substituted phenols **F** ($X = OH$; $n = p$)[2] on reaction of the phenoxyalkyl methanesulfonates **F** ($X = OSO_2CH_3$; $n = p$) with sodium azide or cyanide, respectively, in each case followed by $LiAlH_4$ reduction [7,8,9].

Table 1. Photolactams of Type **A** Formed in the Presence of *tert*-Amines

COMPD.	n	R^1	R^2	NMI^a	DABCO^a	TMEDA^a
Aa	5	H	H	23(17)	6(7)	4(12)
Ab	6	H	H	47(15)	17(18)	10(17)
Ac	7	H	H	48(5)	22(15)	15(17)
Ad	8	H	H	61(5)	42(13)	28(19)
Ae	9	H	H	52(11)	48(15)	33(14)
Af	10	H	H	69(7)	64(12)	57(17)
rac-**Ag**	10	H	Me	53(-)		
rac-**Ai**	10	H	PhSO$_2$	50(-)	49(-)	45(-)
rac-**Aj**	10	Me	H	62(-)		
Ak	11	H	H	63(15)	59(16)	54(13)
rac-**Al**	11	Ph	H	60(-)		
Al	11	Ph	H	48(-)		
Am	12	H	H	65(6)	61(11)	54(13)

a. The figures (in parentheses) indicate chemical yields (%) of monolides (diolides)

Table 2. Dihedral Angles of Photolactams of Type **A**

COMPD.	C(β)-C(α)-N-C(1)	C(α)-N-C(1)-C(2)	N-C(1)-C(2)-C(3)	C(1)-C(2)-C(3)-C(4)	C(3)-C(4)-C(5)-C(6)
Aa	-127.02(0.84)	172.94(0.71)	-59.90(0.89)	-60.51(1.04)	138.99(0.88)
Ac	101.80(0.20)	175.17(0.16)	99.27(0.17)	91.57(0.21)	159.62(0.20)
Ag^a	113(1) 124(1) 108(1)	176(1) -172(1) -178(1)	126(1) 116(1) 123(1)	-112(1) -108(1) -114(1)	173(1) -174(1) 179(1)
rac-**Ai**	-125.3(3)	-178.1(3)	-123.2(1)	130.9(3)	-173.9(3)
rac-**Al**	-115(1)	176(1)	-67(1)	-119(1)	176(1)
Am	-70.14(0.32)	179.60(0.21)	-101.87(0.25)	132.53(0.29)	174.99(0.28)

a. **Ag** was obtained from a solution of *rac*-**Ag** by spontaneous crystallization

REFERENCES AND NOTES

1. For photolactonization cf. *lit.*[2]
2. G. Quinkert, U.-M. Billhardt, H. Jakob, G. Fischer, J. Glenneberg, P. Nagler, V. Autze, N. Heim, M. Wacker, T. Schwalbe, Y. Kurth, J.W. Bats, G. Dürner, G. Zimmermann, H. Kessler, *Helv. Chim. Acta* **1987**, *70*, 771.
3. For diene ketenes from *ortho*-quinolacetates cf. *lit.*[4]
4. G. Quinkert, E. Kleiner, B.-J. Freitag, J. Glenneberg, U.-M. Billhardt, F. Cech, K.R. Schmieder, C. Schudok, H.-C. Steinmetzer, J.W. Bats, G. Zimmermann, G. Dürner, D. Rehm, *Helv. Chim. Acta* **1986**, *69*, 469.

5. The structures of compounds **Aa**, **Ac**, **Ag**, *rac*-**Ai**, *rac*-**Al**, and **Am** were determined by X-ray structure analyses: *Enraf-Nonius CAD4* diffractometer, Cu-K_α radiation, structure determination by direct methods, SDP program system. Complete results have been deposited and are available on request from Fachinformationszentrum Karlsruhe, Gesellschaft für wissenschaftliche Information mbH, D 7514 Eggenstein-Leopoldshafen 2, on quoting the depository number CSD-56055, the names of the authors and the journal citation.
   The crystals of **Aa** (dichloromethane/hexane, m.p. 134-135°) are monoclinic, $P2_1/n$ (No. 14), $a = 12.329(2)$, $b = 9.408(3)$, $c = 12.559(3)$ Å, $\beta = 98.64(2)°$; $V = 1440(1)$ Å^3; $Z = 4$; $\rho_{calc} = 1.159$ g/cm^3; hemisphere through $2\Theta = 120°$; 2140 independent reflections, 1725 with $I > 0$, 163 variables; $R(F) = 0.122$, $R_\omega(F) = 0.113$.
   The crystals of **Ac** (dichloromethane/hexane, m.p. 113.5-114°) are orthorhombic, Pcab (No. 61), $a = 9.210(2)$, $b = 13.745(1)$, $c = 25.590(1)$ Å; $V = 3240(1)$ Å^3; $Z = 8$; $\rho_{calc} = 1.146$ g/cm^3; quadrant through $2\Theta = 120°$; 2414 independent reflections, 2337 with $I > 0$, 282 variables; $R(F) = 0.044$, $R_\omega(F) = 0.035$.
   The crystals of **Ag** (ethyl acetate/hexane, m.p. 121-124°) are trigonal, $P3_1$ (No. 144), $a = b = 19.709(2)$, $c = 13.865(2)$ Å; $V = 4664(2)$ Å^3; $Z = 9$ (3 independent molecules); $\rho_{calc} = 1.075$ g/cm^3; sextant through $2\Theta = 44°$ (Mo-K_α radiation); 3815 independent reflections, 3452 with $I > 0$, 647 variables; $R(F) = 0.104$, $R_\omega(F) = 0.068$.
   The crystals of *rac*-**Ai** (ethyl acetate/hexane, m.p. 149-151.5°) are monoclinic, $P2_1/a$ (No. 14), $a = 9.6396(6)$, $b = 10.1300(7)$, $c = 21.791(2)$ Å, $\beta = 98.779(6)°$; $V = 2103.0(5)$ Å^3; $Z = 4$; $\rho_{calc} = 1.060$ g/cm^3; hemisphere through $2\Theta = 120°$; 3124 independent reflections, 2988 with $I > \sigma$, 218 variables; $R(F) = 0.075$, $R_\omega(F) = 0.058$.
   The crystals of *rac*-**Al** (ether/pentane, m.p. 122-123.5°) are monoclinic, $P2_1/n$ (No. 14), $a = 21.368(5)$, $b = 5.1233(6)$, $c = 23.266(7)$ Å, $\beta = 101.00(2)°$; $V = 2500(2)$ Å^3; $Z = 4$; $\rho_{calc} = 1.093$ g/cm^3; quadrant through $2\Theta = 100°$; 2550 independent reflections, 1445 with $I > 0$, 280 variables; $R(F) = 0.164$, $R_\omega(F) = 0.124$.
   The crystals of **Am** (dichloromethane/hexane, m.p. 104-105°) are monoclinic, $P2_1/c$ (No. 14), $a = 10.668(1)$, $b = 9.3520(9)$, $c = 21.917(2)$ Å, $\beta = 96.547(9)°$; $V = 2172.2(7)$ Å^3; $Z = 4$; $\rho_{calc} = 1.069$ g/cm^3; hemisphere through $2\Theta = 130°$; 3686 independent reflections, 3627 with $I > 0$, 227 variables; $R(F) = 0.076$, $R_\omega(F) = 0.066$.
6. P. Chakrabarti, J.D. Dunitz, *Helv. Chim. Acta* **1982**, *65*, 1555.
7. *General Procedure for Macrocyclization*: A 10-ml round-bottomed flask equipped with a magnetic stirring bar and a gas bubbler is charged with 1 mmol of the quinol acetates of type **D**, 2 ml of dry dichloromethane, and 0.8 ml (10 mmol; 10 eq) of TFA. The mixture is stirred at room temperature until the gas evolution ceases and poured into a 1 l cylindrical irradiation vessel charged with a solution of the tertiary amine in 1 l of dry dichloromethane. The obtained solution of quinol acetates of type **C** ($c = 10^{-3}$mol/l) is irradiated in a *Rayonet* reactor with ultraviolet light ($\lambda > 340$ nm) until no dienone remains (control by absorbance at $\lambda = 360$ nm). The solvent is removed in a rotary evaporator and the residue subjected to column chromatography using 20 g of silica gel. The typical amounts of the tertiary amine were 1.2 ml (15 mmol; 15 eq) of NMI, 1.14 g (7.5 mmol; 7.5 mmol) of DABCO, or 1.2 ml (7.5 mmol; 7.5 eq) of TMEDA.
8. The work reported here was generously supported by the Deutsche Forschungsgemeinschaft (Project Qu 15/25), the Fonds der Chemischen Industrie, the Bundesminister für Wirtschaft (Project 7882 AIF), and Hoechst AG.
9. Satisfactory spectroscopic and elemental analysis data were obtained using chromatographically purified and homogeneous samples of compounds of type **A**, type **D** (as mixtures), and type **E**.

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