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AN EFFICIENT SYNTHESIS OF ENEDIYNE AND ARENEDIYNE LACTAMS

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ABSTRACT: Enediyne and arenediyne lactams are easily synthesized from (*Z*)-dichloroethylene and *o*-dibromobenzene.

The synthesis of conjugated enediynes has recently received much attention since this structural moiety is found in a novel class of antitumoral antibiotics[1] (*esperamicins, calicheamicins and dynemicin).* This structure is at the origin of the high biological activity of these substances. Simple and stable model compounds are thus of interest in connection with the development of related compounds.

We describe herein an efficient and simple synthesis of yet unknown stable enediyne (**1a**) and *o*-benzenediyne (**1b**) lactams.

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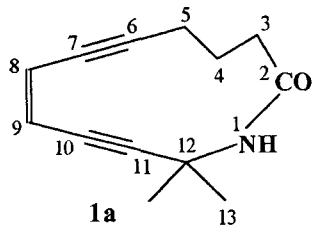
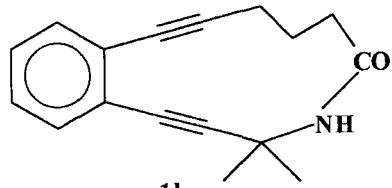
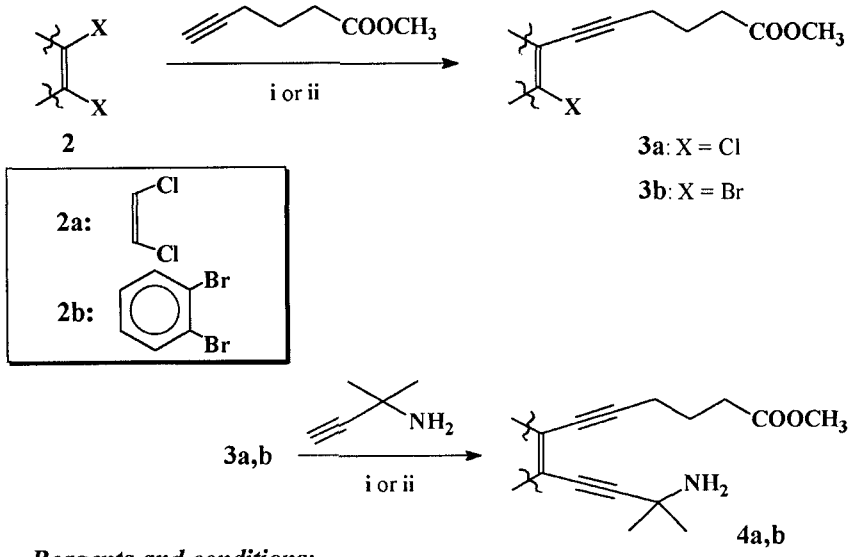


1a



1b

Key compounds for the synthesis of these lactams were the amino-esters **4a,b**. They are easily obtainable by a two step procedure involving sequential palladium-catalyzed coupling reactions of (*Z*)-1,2-dichloro-ethylene, (or *o*-dibromobenzene) with methyl 5-hexynoate and 1,1-di-methyl-2-propynylamine (Scheme 1).



Reagents and conditions:

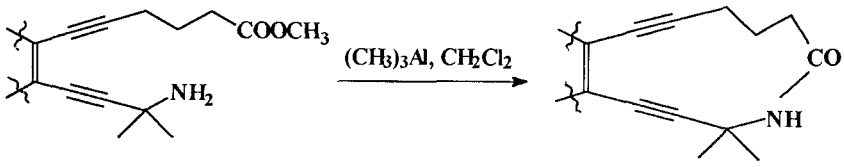
i (for **a**): 0.05 equiv $Pd(PPh_3)_4$, 0.1 equiv CuI, n-$BuNH_2$, C_6H_6, r.t.
ii (for **b**): 0.05 equiv $Pd(PPh_3)_4$, 0.1 equiv CuI, Et_3N, 80°C.

Scheme 1

Thus, when (*Z*)-1,2-dichloroethylene (**2a**, 1.5 equiv) was treated with methyl 5-hexynoate (1 equiv) in the presence of $Pd(PPh_3)_4$ (0.05 equiv) and copper (I) iodide (0.1 equiv) in benzene containing *n*-$BuNH_2$ (2 equiv) at room temperature for 6h[2], the chloroester **3a** was obtained in 89% yield. When coupled with 1,1-dimethyl-2-propynylamine (2 equiv) under the same reaction conditions, **3a** afforded **4a** in 97% yield. Similarly, *o*-dibromobenzene **2b** (1.1 equiv) was coupled with methyl 5-hexynoate (1 equiv) in Et_3N in the presence of the same catalysts to afford after stirring for 5h at 80°C the bromoester **3b** in 70% yield. The second step, carried out with 1,1-dimethyl-2-propynylamine (2 equiv) under the same reaction conditions for 11h gave the aminoester **4b** (73%).

We have studied two routes for the synthesis of the lactams **1a,b**: *a*) cyclization of the aminoesters **4a,b** and *b*) cyclization of the aminoacids **5a,b**.

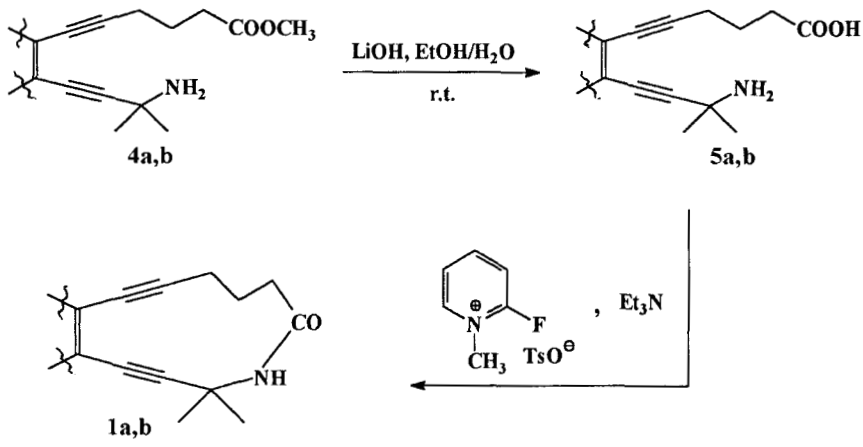
The route *a*) proved to be not only the more direct but also the more convenient one. Thus, treatment of the aminoesters **4a,b** with trimethylaluminium (2.1 equiv)[3,4] in dry methylene chloride (Scheme 2) for several hours (6h for **1a**, 11h for **1b**) at reflux led to the desired lactams in good yields: **1a**, 72% and **1b**, 79%.



4a,b **1a,b**

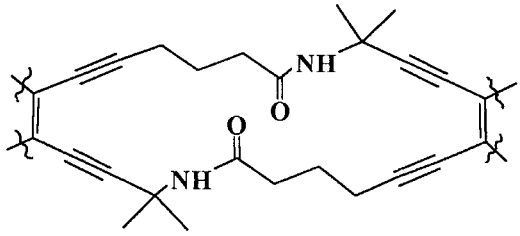
Scheme 2

The cyclization of the aminoacids **5a,b,** obtained by alkaline hydrolysis of the corresponding aminoesters **4a,b**, was achieved by employing 2-fluoro-1-methylpyridinium tosylate as carboxylic acid activating agent[5] (Scheme 3)



Scheme 3

In order to avoid formation of the products of dimerizing cyclization **6a,b**, it was necessary to carry out the cyclization step by slow addition of high diluted solutions of the aminoacids **5a,b** to the reagent. Thus, when the pyrididinium salt (1,5 equiv) was added in one portion at room temperature to a stirred suspension of **5a** (1 equiv) and triethylamine (2 equiv), concentration *ca.* 15.10^{-3} mol/l in methylene chloride, the cyclization reaction was practically finished (90% yield) within 15 min, but the product contained *ca.* 10% of **6a**[6]. However, pure **1a** was obtained by a slow addition of a diluted (*ca.* 4.10^{-3} mol/l) solution of **5a** and Et_3N to a suspension of the pyridinium salt.



6a,b

Similar trend was obserwed in the case of **1b.** Pure lactam **1b** was obtained when the reaction was carried out at 40°C and the warm diluted ($1.5.10^{-4}$ mol/l) solution of **5b,** containing the 2 equiv of Et_3N was introduced slowly to the suspention of the pyridinium salt.

It should be noted that lactams **1a** and **1b** exist in solution as two interconvertable species as revealed by the broad and temperature depending signals in the proton NMR spectra. More detailed analysis was done on **1a** in $CDCl_3$. The carbon NMR spectrum showed two sets of signals, the ratio major/minor being approximatively 75:25. The 2D phase sensitive CH-hetero-correlation experiment allowed interpretation and unambiguous assignement of the proton NMR spectra. The main difference between the two conformers was obserwed for the methylene group neighbouring to the carbonyl group - in the minor conformer these protons are deshielded by 0.90 ppm.

In conclusion, the palladiun-catalyzed reaction of 1-alkynes with (*Z*)-dichloroethylene and *o*-dibromobenzene has been proved efficient for the synthesis of enediyne and arenediyne lactams.

Experimental:

All melting points are uncorrected. IR-spectra were recorded on a Bruker IFS 113V Fourier Spectrometer. The ^1H-(250 MHz) and ^{13}C-(62.9

MHz) NMR spectra were measured on a Bruker WM-250 and AVANCE DRX-250 with TMS as internal standard, chemical shifts (δ) in ppm, coupling constants J in Hz. Most of the ^{1}H- and ^{13}C-NMR spectra were measured in $CDCl_3$. The exceptions will be duly precised. CI-MS were obtained on a Jeol IMS D-300 spectrometer, reactant gas 2-methyl-propane, (10^{-5} Torr, emission 100 μA). All reactions, except the hydrolysis of **4**, were carried out in anhydrous conditions under inert atmosphere. Qualitative TLC investigations were carried out on silica gel 60 F_{254} (aluminium sheets "Merck") The products were purified by column chromatography on silica gel 60 (230-400 mesh, ASTM "Merck")

$Pd(PPh_3)_4$ was freshly prepared according to ref.[7]. The *n*-$BuNH_2$ and the Et_3N were distilled and stored over KOH. The 1,1-dimethyl-2-propynylamine (Aldrich) was distilled before use. The methyl ester of 5-hexynoic acid was prepared by oxydation of 5-hexyn-1-ol[8] followed by esterification of the corresponding acid.

Preparation of 3a: A solution of (*Z*)-1,2-dichloroethylene (1.46 g, 15 mmol) in benzene (12 ml) was stirred at room temperature for 15 min with $Pd(PPh_3)_4$ (0.58 g, 0.5 mmol), then methyl 5-hexynoate (1.26 g, 10 mmol) dissolved in benzene (3 ml), *n*-$BuNH_2$ (2 ml, 20 mmol) and CuI (0.19 g, 1 mmol) were successively added. After stirring for 6h at room temperature, saturated aq. solution of NH_4Cl was added and the mixture was extracted with ether. The organic layer was washed (brine) and dried ($MgSO_4$). After the removal *in vacuo* of the solvent, the crude product was purified by column chromatography (ethylacetate/petroleum ether 1/5, R_f=0.34); yield 1.65 g, 89%, oil. ^{1}H-NMR: 6.32 (d, 1H, J=7.4), 5.86 (dt, 1H, J=7.4 and 2.3), 3.69 (s, 3H), 2.48 (m, 4H), 1.90 (quint, 2H, J=7.1); ^{13}C-NMR: 173.41, 127.18, 112.19, 97.64, 75.42, 51.46, 32.59, 23.58, 18.99; CI-MS: m/z=187 $[M+1]^+$; IR ($CDCl_3$): 2218, 1732 cm^{-1}.

Preparation of 4a: A solution of **3a** (1.40 g, 7.5 mmol) in benzene (9 ml) and $Pd(PPh_3)_4$ (0.435 g, 0.375 mmol) was stirred for 15 min. 1,1-dimethyl-2-propynylamine (1.24 g, 15 mmol) dissolved in benzene (4 ml), *n*-$BuNH_2$ (1.5 ml, 15 mmol) and CuI (0.14 g, 0.75 mmol) were added. The reaction mixture was stirred at room temperature for 6h. Work up as above. Purification of the crude product by column chromatography[9] (methylene chloride/methanol 9/1, R_f=0.45); yield 1.79 g, 97%, oil. ^{1}H-NMR: 5.72

(s, 2H), 3.64 (s, 3H), 2.74 (m, 4H), 1.86 (quint, 2H), 1.74 (br s, 2H), 1.42 (s, 6H); ^{13}C-NMR: 173.34, 119.03, 119.72, 104.35, 96.49, 78.95, 77.53, 51.46, 45.68, 32.69, 31.43, 23.71, 19.04, 15.32; IR ($CHCl_3$): 3368, 3302, 2217, 2201, 1732; CI-MS: m/z=234 $[M+1]^+$.

Preparation of 3b: To a stirred mixture of 1,2-dibromobenzene (1.30 g, 5.5 mmol), triethylamine (10 ml) and $Pd(PPh_3)_4$ (0.29 g, 0.25 mmol) at 60°C was added methyl 5-hexynoate (0.63 g, 5 mmol) dissolved in triethylamine (4 ml) and CuI (95 mg, 0.5 mmol). After stirring of the reaction mixture for 5h at 75-80°C, Et_3N was removed *in vacuo*, the reaction was quenched with saturated solution of NH_4Cl and extracted with methylene chloride. The organic layer was washed with brine and dried over $MgSO_4$. After the solvent removal, the residue was purified by column chromatography (ether/petroleum ether 1/2, R_f=0.66) to give **3b**: 0.976 g, 69.5%, oil. ^{1}H-NMR: 7.55 (dd, 1H, *J*=1.3 and 7.9), 7.41 (dd, 1H, *J*=1.8 and 7.4), 7.22 (dt, 1H, *J*=7.7 and 1.3), 7.11 (dt, 1H, *J*=1.8 and 7.9), 3.69 (s, 3H), 2.57 (t, 2H, *J*=7.2), 2.55 (t, 2H, *J*=6.7), 1.97 (quint, 2H, *J*=7.2); ^{13}C-NMR: 173.39, 133.16, 132.16, 128.71, 126.77, 125.36, 93.87, 80.13, 51.39, 32.69, 23.65, 18.90.

Preparation of 4b: To a mixture of **3b** (1.12 g, 4 mmol), triethylamine (8 ml) and $Pd(PPh_3)_4$ (0.23 g, 0.2 mmol), stirred at 60°C was added a solution of 1,1-dimethyl-2-propynylamine (0.66 g, 8 mmol) in 3 ml of triethylamine. The reaction mixture was stirred at 75-80°C for 11h. Work up as above. The crude reaction product was purified by column chromatography[9] (ethylacetate/petroleum ether/methanol 23/76/1; R_f=0.19) to give **4b**, 0.825 g, 73%, oil. ^{1}H-NMR: 7.35-7.41 (m, 2H), 7.17-7.20 (m, 2H), 3.68 (s, 3H), 2.52-2.58 (m, 4H), 2.07 (br.s, 2H), 1.96 (quint, 2H, *J*=7.2), 1.55 (s, 6H); ^{13}C-NMR: 173.35, 131.84, 131.72, 127.83, 127.24, 125.99, 124.60, 92.96, 81.21, 79.89, 51.42, 46.73, 32.77, 29.58, 23.76, 18.84; IR (KBr): 3450, 2220, 1739 cm^{-1}.

Preparation of 5. General procedure:

A solution of **4** (5 mmol) in ethanol (10 ml) was added to LiOH (0.5 g) dissolved in a 1:1 mixture of water/ethanol (10 ml). After stirring at room temperature for 1h, the reaction mixture was neutralyzed with saturated aq. solution of NaH_2PO_4. The ethanol was removed *in vacuo* and the residue was treated as follows:

Compound **5a**: This residue was extracted thoroughly with methylene chloride. After drying ($MgSO_4$) the solvent was removed and the crude product (0.89 g), recrystallized from methanol/anhydrous ether gave pure **5a**, 0.78 g (71%), m.p. 159-160°C (with decomposition, measured in a sealed capillary); ^{1}H-NMR (CD_3OD): 5.92 (dt, 1H, *J*=10.9 and 2.2), 5.82 (d, 1H, *J*=10.9), 2.47 (dt, 2H, *J*=2.2 and 6.6), 2.42 (t, 2H, *J*=7.3), 1.82 (quint, 2H, *J*=7.0); 1.65 (s, 6H).

Compound **5b**: The residue was diluted with water (5 ml), stirred for several minutes, the solid was filtered off and washed two times with water. The product, 1.28 g, recrystallized from methanol/ether yielded pure **5b**: 0.97 g (72%); m.p. 194.5-196°C (with decomposition, measured in a sealed capillary); ^{1}H-NMR (CD_3OD): 7.23-7.39 (m, 2H), 7.41-7.45 (m, 2H), 2.54 (t, 2H, *J*=6.7), 2.46 (t, 2H, *J*=7.3),1.89 (quint, 2H, *J*=7.0); IR (KBr): 3450, 2250, 1615, 1531 cm^{-1}; R_f=0.38 (CH_2Cl_2/methanol 7/1)).

Synthesis of the lactams 1.

a) From the aminoesters **4**:

To a stirred solution of 4.2 mmol of trimethylaluminium (2.1 ml, 2M in *n*-hexane) in dry methylene chloride (10 ml), a solution of **4** (2 mmol) in methylene chloride (5 ml) was added dropwise within 1h at room temperature. After stirring under gentle reflux (6h for **4a**, 11h for **4b**), the reaction mixture was cooled, acidified carefully with diluted HCl and extracted thoroughly with methylene chloride. In the case of lactam **1b** which is very poorly soluble, the last two extractions were carried out with chloroform. The combined extract was dried ($MgSO_4$), filtered, and the solution was passed through a very small column packed with silica gel (*ca.* 250 mg.). The latter was washed with 10-15 ml anhydrous ether. After removal *in vacuo* of the solvents, the residue was washed 3 times with portions of 4-5 ml anhydrous ether to give pure crystaline lactam **1**. Additional small amounts of **1a,b** could be obtained by column chromatography of these ethereal "washings".

Compound **1a**: yield 0.290 g (72%), m.p. 172-173°C (from methylene chloride/petroleum ether, measured in a sealed capillary). ^{1}H-NMR: major conformer: 5.80 (d, 1H-8), 5.66 (d, 1H-9), 2.50 (br s, 2H-5), 2.23 (br s, 2H-3), 1.99 (br s, 2H-4) 1.63 (s, 6H-13); minor conformer: 5.80 (m, 2H-8,9), 3.13 (br s, 2H-3), 2.50 (br s, 2H-5), 1.99 (br s, 2H-4), 1.63 (s, 6H-13).

^{13}C-NMR: major conformer: 171.66 (C-2), 121.96(C-8), 118.45 (C-9), 100.80 (C-11), 97.17 (C-6), 79.77 and 79.32 (C-7,10), 48.05 (C-12), 36.76 (C-3), 28.68 (C-13), 22.85 (C-4), 20.21 (C-5); minor conformer: 175.10 (C-2), 121.97 (C-8), 119.81 (C-9), 98.87 and 98.50 (C-6,11), 86.02 and 81.26 (C-7,10), 47.71 (C-12), 30.97 (C-13), 30.41 (C-3), 21.90 (C-4), 17.94 (C-5). IR ($CHCl_3$): 3239, 2269, 2204, 1644; CI-MS: m/z 202 $[M+1]^+$; Anal. calcd for $C_{13}H_{15}NO$ (201.3): C, 77.58; H, 7.51; N, 6.96 %. Found C, 77.49; H, 7.46; N, 6.85%.

Compound **1b:** yield 0.397 g (79%), m.p. 274-275°C, taken on a Kofler hot-stage microscope; ^{1}H-NMR: major conformer (*ca.* 60%): 7.35-7.14 (m, 4H), 5.72 (s, 1H), 2.59 (t, 2H), 2.27 (t, 2H), 2.05 (m, 2H), 1.69 (s, 6H); minor conformer: (*ca.* 40%): 5.77 (s, 1H), 3.16 (t, 2H); IR (KBr): 3340, 2243, 2219, 1660 cm^{-1}. CI-MS: m/z 252 $[M+1]^+$; Anal. calcd for $C_{17}H_{17}NO$ (251.33): C, 81.24; H, 6.82; N, 5.57%. Found C, 81.09; H, 6.82; N, 5.43%.

b) From the aminoacids **5**

Compound **1a**: To a stirred suspension of 2-fluoro-1-methylpyridinium tosylate (0.22 g, 0.75 mmol) in methylene chloride (10 ml) was added at room temperature for a period of 1h a solution of **5a** (0.11 g, 0.5 mmol) and triethylamine (0.14 ml, 1 mmol) in methylene chloride (115 ml). After stirring for an additional 1h the homogenuous solution was filtered through a column packed with silica gel (*ca.* 10 g). Pure **1a** (40 mg, 40%, m.p. 172-173°C) was isolated by elution with ether/ethanol 13/1.

Compound **1b**: A warm (35-40°C) solution of **5b** (0.107 g, 0.4 mmol) and triethylamine (0.11 ml, 0.8 mmol) in methylene chloride (270 ml) was added slowly (5.5h) to a srirred at 40°C suspension of 2-fluoro-1-methylpyridinium tosylate (0.17 g, 0.6 mmol) in methylene chloride (10 ml). After additional stirring for 1h at the same temperature the cooled solution was filtered through a very small column packed with silica gel (3 g). Elution of the adsorbed crude product with chloroform/ether (4/1) gave pure **1b,** 50 mg (50%), m.p. 274-275°C.

Acknowledgement: We are grateful to Dr Svetlana Simova for the interpretation and the assignement of the NMR spectra of **1a** and to Mr. Rumen Christov for the mass spectral analyses.

References and Notes

1. For a review see: a) Nicolaou, K.C. and Smith, A.L., *Acc. Chem. Res.*, **1992**, *25*, 497. b) Nicolaou, K.C., *Chemistry in Britain*, **1994**, *30*, 33.
2. Ratovelomanana, V. and Limstrumelle, G., *Tetrahedron Lett.*, **1981**, 315.
3. Basha, A., Lipton, M. and Weinreb, S.M., *Tetrahedron Lett.*, **1977**, *48*, 4171.
4. Vorbrüggen, H. and Woodward, R.B., *Tetrahedron*, **1993**, *49*, 1625.
5. For a review on the use of onium salts as carboxyl activating agents see Mukaiyama, T., *Angew. Chem. Int. Ed. Engl.*, **1979**, *18*, 707.
6. The ^{1}H NMR spectra of the products **1a** and **6a**, resp. **1b** and **6b** are indistinguishable, the latter can be distinguished only by mass spectral analysis.
7. Coulson, D.R., *Inorg. Synth.*, **1972**, *13*, 121.
8. Katritzky, A.R., Khan, G.R. and Leahy, D.E., *J. Org. Chem.*, **1984**, *49*, 4784.
9. For packing the column a solvent containing *ca.* 0.5 vol % of Et_3N was used.

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