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A CONVENIENT METHOD FOR THE SYNTHESIS OF 1,8-*BIS*(PYRIDIN-3-OXY)OCT-4-ENE-2,6-DIYNE

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ABSTRACT

A convenient and rapid synthesis of the title compound is described. The key step in the procedure is the Stephens Castro coupling of 3-prop-2-ynyloxy-pyridine with *cis*-1,2-dichloroethylene and subsequent column purification in the final stage.

Key Words: Enediyne; Metal binding enediyne; Pyridylene-diyne; Metalloenediyne

Syntheses of enediynes have received much attention after the discovery of the natural product anticancer molecules such as esperamicin,[1] calicheamicin,[2] dynemicin,[3] neocarzinostatin,[4] and C 1027 chromophore.[5] The key feature of these natural products is the 1,5-diyne-3-ene unit that undergoes Bergman cyclization in the presence of biological reducing equivalents to generate benzene-1,4-diradicals[6] that abstract the hydrogen atom from the sugar phosphate backbone of DNA, leading to strand cleavage and, finally, cell death.[7]

The ability to control formation of the 1,4-benzenoid diradical intermediate of the enediyne antitumor antibiotics leads to the potential for

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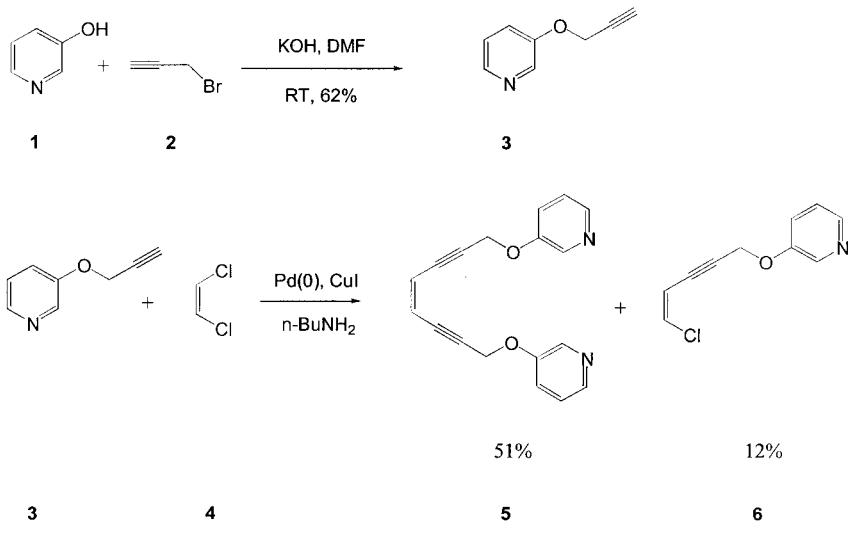
designing new chemical entities with pharmacological utility.[8] A number of unique synthetic,[9] photochemical,[10] and electrochemical[11] approaches have been explored to initiate Bergman cyclization of organic enediynes in a controlled manner.

The recent discovery that enediyne cyclization can be promoted at reduced temperatures by the addition of metal salts has inspired the use of transition metals for influencing Bergman cyclization reactions.[12–17] Recently we have reported the synthesis and thermal properties of a novel metal chelating enediyne ligand, namely, 1,8-*bis*(pyridin-3-oxy)oct-4-ene-2,6-diyne (**5**), which upon complexation with copper, cyclizes at a very moderate temperature.[16] These copper complexes also cyclize photochemically and show DNA cleaving activity.[18] We have synthesized this metal chelating ligand (**5**) using 1,8-dibromooct-4-ene-2,6-diyne[19] as a starting material, which was prepared by the coupling of tetrahydro-2-(2-propynyloxy)-2H-pyran with *cis*-1,2-dichloroethylene, followed by bromination. Unfortunately, this method is very tedious, requires toxic reagents, is uneconomical, and takes three days to prepare the desired compound.

In light of our ongoing study on metalloenediynes, we have developed a simple and more facile method for the synthesis of this novel compound. This new approach involves the use of 3-hydroxypyridine (**1**) and propargyl bromide (**2**) as starting materials to prepare 3-prop-2-ynyloxy-pyridine (**3**) in 62% yield. Only two references are found in the scientific[20,21] and patent[21] literature which actually describe the preparation of (**3**) (41% yield). In our



scheme, Stephens Castro[22] coupling of 3-prop-2-ynyloxy-pyridine (**3**) with *cis*-1,2-dichloroethylene (**4**) in the presence of Pd(0) and CuI led to the formation of the desired product (**5**) in 51% yield. The monochloro product (**6**)[23] is also produced in the reaction and can be easily separated by flash chromatography. It is important to note that at room temperature this reaction was very slow, while at 45°C, the reaction proceeds to complete in 4 h. However, at higher temperatures (60–65°C), the alkyne decomposes within 2 h. Progress of the reaction was monitered by NMR and TLC.

We conclude that the above-described synthesis of (**5**) is convenient, economical, and provides rapid access to (**5**) in two steps. This synthesis does not mandate preparation of 1,8-dibromooct-4-ene-2,6-diyne, which is lachrymatic and requires bromine as a key reagent.

EXPERIMENTAL

Synthesis of 3-Prop-2-ynyloxy-pyridine (3)

To a mixture of 3-hydroxypyridine (5.0 g, 50 mmol) and KOH (8.8 g, 158 mmol) in DMF (30 ml), a solution of propargyl bromide (7.5 g, 63 mmol) in 10 ml DMF was added at 5–10°C. The reaction mixture was stirred for 15 min and the product extracted with dichloromethane. The organic layer was washed with excess of water to remove the DMF and stirred with activated charcoal (5%) for 30 min. The dichloromethane layer was filtered through a celite bed and the solvent removed. The pale yellow product thus obtained did not require purification by column chromatography. Yield: 4.3 g (62%); b.p. 185–186°C; ^{1}H NMR (400 MHz, $CDCl_3$): 2.65 (s, 1H, CH), 4.72 (s, 2H, OCH_2), 7.22–7.27 (m, 2H), 8.25 (m, 1H), 8.37 (s, 1H); ^{13}C NMR ($CDCl_3$): 56.32 (OCH_2), 76.36 (CH), 78.0 (Cquart), 121.88 (CH), 123.98 (CH), 138.67 (CH), 143.19 (CH), 156.0 (Cquart); Mass; *m*/*z*: 133 (M^+), 95; HR-MS (EI) *m*/*z*: 133.14269 [M^+ calcd for C_8H_7NO: 133.14942]; IR (neat, cm^{-1}): 3056, 2120, 1575, 1476, 1427, 1278, 1220, 1050, 925, 797, 705.

Synthesis of 1,8-*Bis*(Pyridin-3-oxy)oct-4-ene-2,6-diyne (5)

3-Prop-2-ynyloxy-pyridine (3.0 g, 22 mmol) in 20 ml benzene was added dropwise to a suspension of *cis*-1,2-dichloroethylene (1.0 g, 10 mmol), $Pd(PPh_3)_4$ (0.69 g, 0.59 mmol), CuI (0.23 g, 1.2 mmol), *n*-butylamine (3.76 g, 50 mmol) and benzene (50 ml) at 45°C and reaction mixture was stirred for 4 h at that temperature. The solvent was removed and the

residue chromatographed (flash chromatography) on silica gel (10% ether/dichloromethane) to yield 51% of the desired product (**5**) along with 12% of the chloro compound (**6**). Spectral data for (**5**); Cyclization temperature 136°C (DSC); ^{1}H NMR (400 MHz, $CDCl_3$): 4.89 (s, 4H, OCH_2), 5.90 (s, 2H, CH), 7.24–7.30 (m, 4H), 8.20 (d, 2H), 8.40 (d, 2H); ^{13}C NMR ($CDCl_3$): 56.7 (OCH_2), 84.6 (Cquart), 90.9 (Cquart), 119.8 (CH), 121.9 (CH), 123.8 (CH), 138.6 (CH), 142.8 (CH), 153.7 (Cquart); Mass; *m*/*z*: 290 (M^+); HR-MS (EI) *m*/*z*: 290.10427 [M^+ calcd for $C_{18}H_{14}N_2O_2$: 290.1411]; IR (neat, cm^{-1}): 3056, 2216, 1576, 1475, 1375, 1180, 1130, 1001, 798, 706, 619.

Synthesis of 3-(5-Chloro-pent-4-en-2ynyloxy)-pyridine (6)

Yield: 12%; b.p. 211–212°C; ^{1}H NMR (400 MHz, $CDCl_3$): 4.95 (s, 2H, OCH_2), 5.90 (d, $J = 8$ Hz, 1H, CH), 6.46 (d, $J = 8$ Hz, 1H, CH), 7.25–7.33 (m, 2H), 8.27 (m, 1H), 8.42 (s, 1H); ^{13}C NMR ($CDCl_3$): 56.95 (OCH_2), 82.0 (Cquart), 91.23 (Cquart), 111.28 (CH), 121.94 (CH), 123.98 (CH), 130.97 (CH), 138.70 (CH), 143.05 (CH), 153.94 (Cquart); Mass: *m*/*z*; 195 (M^++2), 193 (M^+), 158, 130; HR-MS (EI) *m*/*z*: 193.02900 [M^+ calcd for $C_{10}H_8ClNO$: 193.02944]; IR (neat, cm^{-1}): 3084, 2213, 1574, 1475, 1427, 1276, 1219, 1128, 1048, 1001, 796, 705.

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