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Synthesis of a Novel Conjugate of Bromoarene and Polyamide Containing N-Methylimidazoles

Dan LIU, Gu YUAN*

Department of Chemical Biology, The Key Laboratory of Bioorganic Chemistry and Molecular Engineering of Ministry of Education, College of Chemistry, Peking University, Beijing 100871

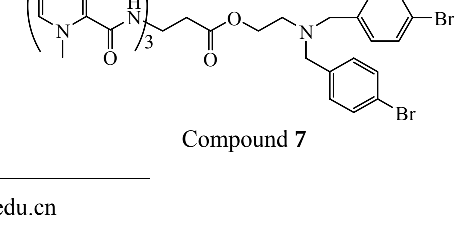
Abstract: A novel DNA cleavage conjugate of bromoarene and polyamide containing three N-methylimidazole rings was synthesized by the chloroform reaction and the DCC/HOBT coupling reaction.

Keywords: DNA cleavage, bromoarene, polyamide, chloroform reaction.

DNA-photocleavage agents have generated considerable attention in chemistry, biology and medicine[1, 2], because their DNA-cleavage activities can be easily controlled by photoirradiation. In the past decade, several DNA-cleavage agents have been successfully attached to polyamide[3, 4], to obtain new conjugates with higher and specific DNA-cleavage activities. Most of them contain only one photocleavage group to induce single-strand breaks, and the conjugates inducing double-strand breaks have been rarely reported. Comparing with single-strand breaks, double-strand breaks are more biologically significant, because they are more difficult to be repaired. In this research, our purpose is to combine two photocleavage groups in one terminal of polyamide for inducing the double-strand breaks of DNA (**Figure 1**). Bromoarene was selected as the photocleavage group due to the active, stable and synthetically accessible structure[5]; polyamide contained N-methylimidazole (Im) rings can specially recognize G•C rich region in the minor groove of DNA[6].

In the synthesis (**Scheme 1**), ethanolamine and 4-bromobenzyl bromide **1** are vital reagents to construct this novel photocleavage agents. The highly active 4-bromobenzyl bromide could be linked to NH_2 group of ethanol amine in 2:1 mode within one step, and

Figure 1



Compound **7**

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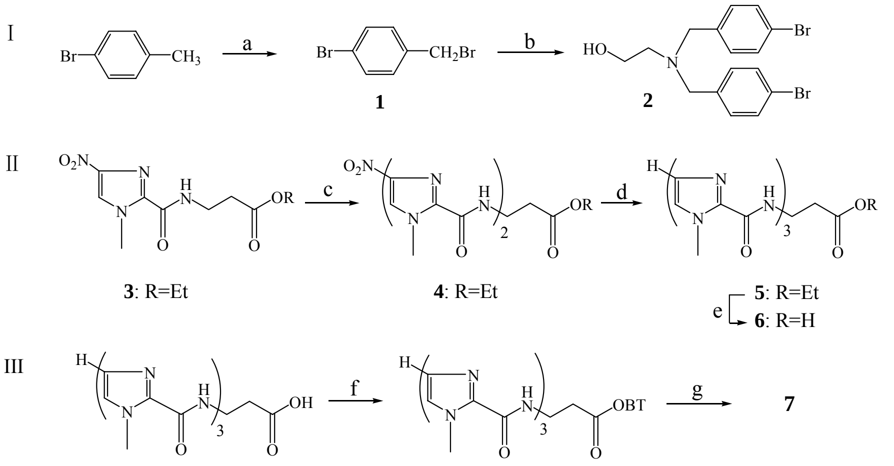
[*] E-mail: guyuan@pku.edu.cn

Scheme 1



Reagents: a. NBS, BPO, CCl_4, 76 % yield; b. $HOCH_2CH_2NH_2$, Et_3N, EtOAc, 55 % yield; c. H_2, Pd-C/EtOAc, $NO_2ImCOCCl_3$, 80 % yield; d. H_2, Pd-C/DMF, $ImCOCCl_3$, 55 % yield; e. NaOH, H_2O, EtOH, and HCl, pH=2, 90 % yield; f. HOBT, DCC, DMF; g. Compound **2,** 28 % yield.

the formed tertiary amine is important and necessary to increase the polarity of the polyamide. ImImImβOEt **5** was synthesized by a convenient chloroform reaction[7] without complicated separation. In the last step, ImImImβCOOH and compound **2** was conjugated to produce the photocleavage agent **7** by the DCC/HOBT coupling reaction.

Experimental

To the solution of 100 mg (0.22 mmol) Compound **6** in 2 mL DMF, was added 31 mg (0.22 mmol) HOBT and 46 mg (0.22 mmol) DCC, and the mixture was stirred for 12 h. Then, Compound **2** (90 mg, 0.22 mmol) was added to this mixture. After stirred for 12 h, the mixture was filtered, and the filtrate was concentrated *in vacuo.* The crude product was purified by flash chromatography to give a yellow solid **7** (52 mg, 28 % yield). ^{1}H-NMR (200 MHz, $CDCl_3$, δ ppm): 9.51 (s, 1H, -CO-NH-), 9.23 (s, 1H, -CO-NH-), 7.63 (t, 1H, J=6.2 Hz, -CO-NH-CH_2-), 7.50 (s, 1H, Im-H), 7.42 (s, 1H, Im-H), 7.41 (d, 4H, J=8.2 Hz, Ph-H), 7.25 (d, 4H, J=8.2 Hz, Ph-H), 7.09 (s, 1H, Im-H), 7.03(s, 1H, Im-H), 4.22 (t, 2H, J=5.8 Hz, -O-CH_2-CH_2-), 4.14 (s, 3H, >N-CH_3), 4.11 (s, 3H, >N-CH_3), 4.08 (s, 3H, >N-CH_3), 3.66 (m, 2H, -NH-CH_2-CH_2-), 3.57 (s, 4H, >N-CH_2-Ph ×2), 2.73 (t, 2H, J=5.8 Hz, -CH_2-CH_2-N<), 2.61 (t, 2H, J=6.2 Hz, -CH_2-CH_2-CO-); ESI-MS: calcd. for (M+H$^+$), 827 ($C_{34}H_{37}N_{10}O_5{}^{81}Br_2$, 51%), 825 ($C_{34}H_{37}N_{10}O_5{}^{81}Br^{79}Br$, 100 %) and 823 ($C_{34}H_{37}N_{10}O_5{}^{79}Br_2$, 62 %), found 827, 825 and 823.

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