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Bioorganic & Medicinal Chemistry Letters 18 (2008) 934–937
Bioorganic & Medicinal Chemistry Letters

Photoactivated enediynes as targeted antitumoral agents: Efficient routes to antibody and gold nanoparticle conjugates

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Received 29 October 2007; revised 18 December 2007; accepted 19 December 2007
Available online 7 January 2008

Dedicated to Professor Elias J. Corey on the occasion of his 80th birthday.

Abstract—Efficient syntheses of a series of functionalized aryl enediynes have been developed. The building blocks were used to effect conjugation to carrier PEG templates which allowed subsequent coupling to a cardiac targeted monoclonal antibody. Immunocompetence of the enediyne-Mab conjugates was demonstrated by ELISA, and both parent enediynes and bioconjugates underwent successful photo-Bergman cyclization. Finally, surface modified (Au) nanoparticle conjugates were prepared and size confirmed by TEM analysis. Application as long-circulating photoactivated prodrugs is anticipated.

The enediynes are a class of potent antitumoral agents isolated from soil bacteria.[1] Over 20 of this class are now known, two of which have entered clinical evaluation. One of these (Mylotarg®) represents the first ever monoclonal antibody–cytotoxin conjugate to be approved by the FDA and is currently used for treatment of acute myeloid leukemia (AML).[2] The natural enediynes use a variety of elaborate triggering mechanisms which activate the pharmacophore **1** via a cascade process ultimately involving Bergman cycloaromatization, to produce cytotoxic diyl radicals **2**, which abstract H atoms from cellular and nuclear macromolecules en route to arenes **3** (Scheme 1).[3] There has been considerable interest in the preparation of designed enediynes, including the potential for photoactivated prodrugs. The latter process, commonly referred to as the photo-Bergman cyclization, has been studied in some depth,[4] and parameters affecting photoconversion delineated.[5] In order to extend the versatility of the enediynes as controlled cytotoxins, we became interested in the possibility of assembling photo-Bergman precursors that could be routinely derivatized, specifically for bioconjugation chemistry.

Accordingly, a differentially substituted aryl enediyne **4** was firstly prepared from 1,2-di-iodobenzene via sequential coupling–deprotection (Scheme 2).[6] Palladium mediated coupling with 4-iodobenzyl alcohol then gave enediyne **5**, reactions readily scaleable through multigram level. The viability of **5** as a photo-Bergman substrate was confirmed (vide infra) as was its shelf-life, fidelity preserved at room temperature over a period of weeks. With this building block in hand we elected to demonstrate versatility via formation of bioconjugates under established coupling methods. We firstly investigated preparation of a C-16 PEG conjugate **6**. PEGylation has become a commonly used strategy for the delivery of various lipophilic drug candidates.[7] Enhanced circulatory capacity coupled with reported affinity for specific tumor neovasculature suggest such conjugates hold promise in a number of clinical applications.[7] Conjugate **6** was formed in good yield via carbodiimide coupling of the PEG diacid, and displayed marked solubility in buffered organic and aqueous solutions. One of the expected properties of the conjugate (**6**) was facile derivatization to form three component drug-linker-antibody conjugates, and this was exemplified by coupling to an available cardio-myosin targeting antibody (2-G4) viz. **7** via NHS coupling.[8] The immunocompetence and fidelity of the enediyne bioconjugate **7** was confirmed by ELISA (Fig. 1). To demonstrate versatility of the enediyne building blocks we also developed a three component approach involving reductive

Keywords: Enediyne; Photo-Bergman; Bioconjugation; Antibody conjugate; Nanoparticles.
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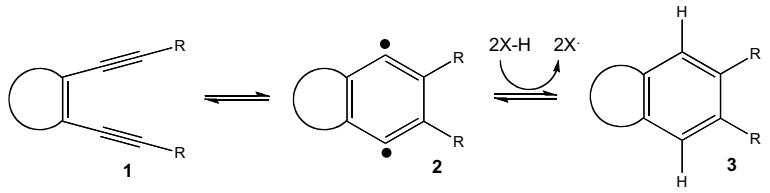
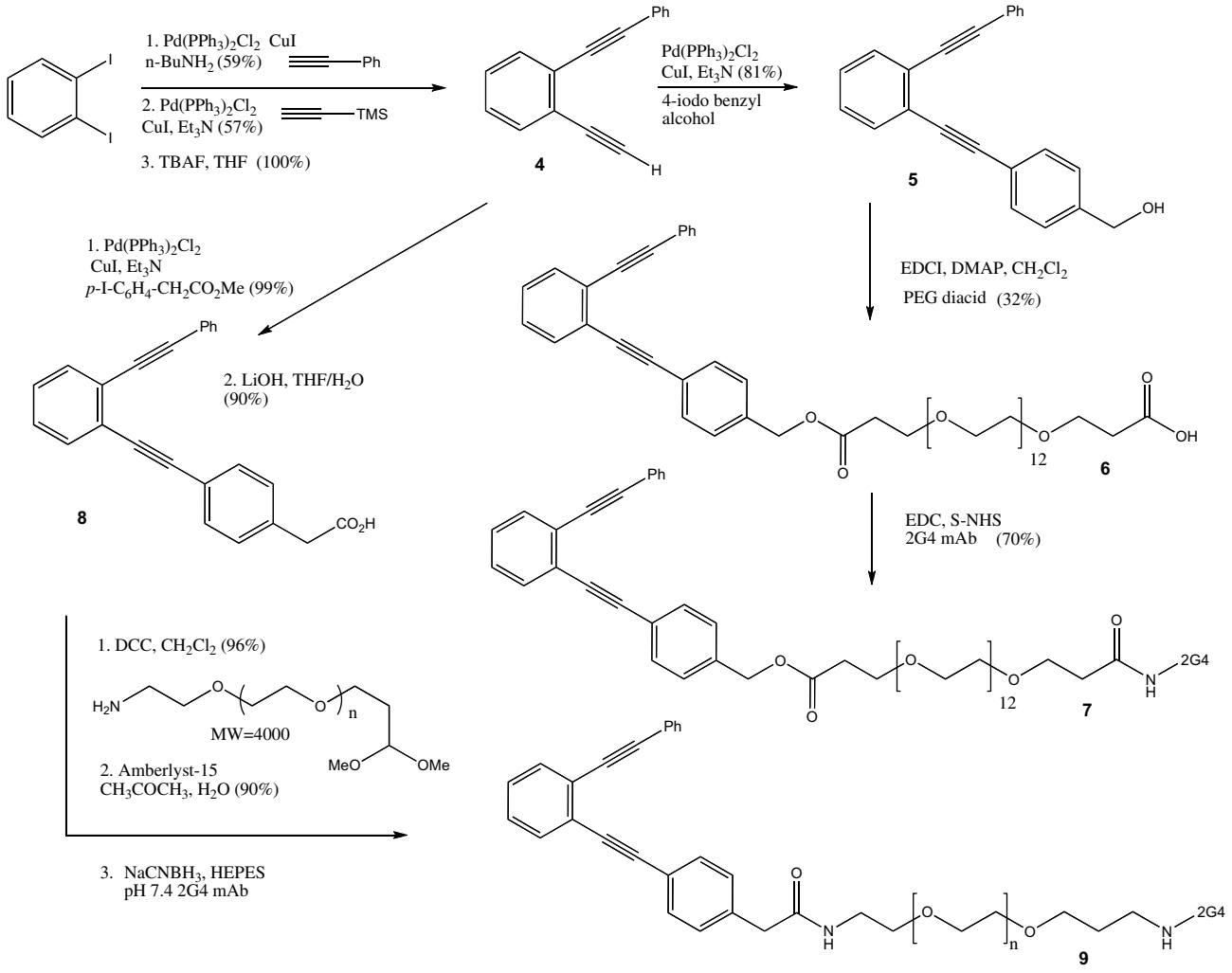
doi:10.1016/j.bmcl.2007.12.045



Scheme 1. The Bergman cycloaromatization of 3-hexene-1,5-diynes.



Scheme 2. Preparation, PEGylation, and bioconjugation of aryl enediyne photo-prodrugs.

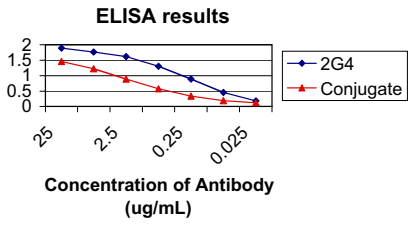


Figure 1. Relative immunoaffinity (**7**).

amination. Specifically **4** was coupled to a phenylacetic ester, and the (revealed) carboxylate **8** amidated with a differentially substituted (α-amino-ω-acetal) PEG with MW of approx 4000.[9] The carboxaldehyde was liberated using Amberlyst resin, then reductive amination of the product in the presence of the 2G4 mAb produced bioconjugate **9** in >50% yield (based on recovered aldehyde). Identical strategy was successfully used to prepare the bioconjugate of the related mAb 2G5 and immunocompetency confirmed by ELISA.[8]

With the parent enediynes and two bioconjugates in hand we were able to assess the impact of derivatization on photo-Bergman cyclization. Gratifyingly, simple irradiation of either **5**, **6**, **7**, **8** or **9** resulted in smooth