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Palladium-Catalyzed Coupling of Alkenyl Iodides with Ethynyl Oxiranes: Synthesis of Epoxy Enediyne Core Intermediates Related to Neocarzinostatin Chromophore

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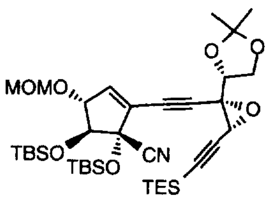
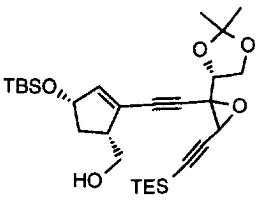
Abstract : Coupling of functionalized cyclopentenyl iodides with ethynyl oxiranes has been achieved by using catalytic amount of $Pd(CH_3CN)_2Cl_2$ and CuI in the presence of *i*-Pr_2NEt in moderate to good yields. Copyright © 1996 Elsevier Science Ltd

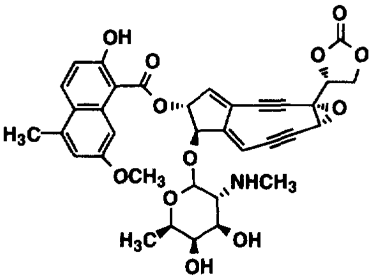
We previously developed a strategy for constructing nine- and ten-membered cyclic enediynes through nucleophilic 1,2-addition reactions of acetylides to cyclopentanone derivatives.[1,2] Recently we extended this approach to the coupling of diacetylenic moiety with substituted cyclopentenyl iodide derivatives using palladium catalyst.[3] However, we encountered difficulties when we applied this methodology to synthesize epoxy enediynes **1** and **2**, key intermediates in the total synthesis of enediyne anticancer antibiotics, neocarzinostatin chromophore **3**,[4,5] and N1999-A2.[6] The coupling reaction of functionalized cyclopentenyl iodides with ethynyl oxiranes did not proceed under the standard Sonogashira conditions[7a] though the relevant coupling of diacetylenic moiety without an epoxide worked smoothly.[3] To the best of our knowledge, such reactions involving ethynyl oxiranes have not been studied until recently.[2,7,8] Pale et al. have reported very recently a similar problem and they overcome the problem by changing a cocatalyst to silver salts from CuI.[8] We describe here our own solution for this problem.



1

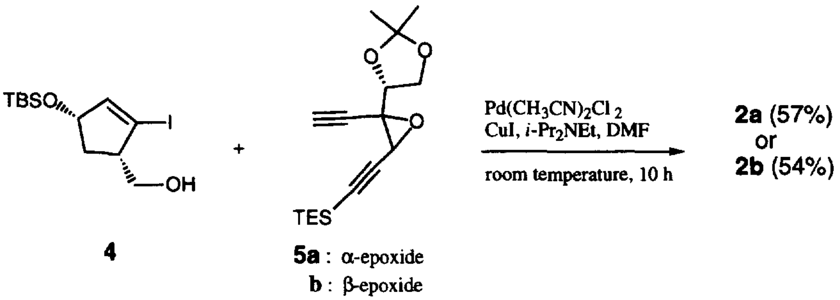


2a : α-epoxide
b : β-epoxide



3

When vinyl iodide **4**[9] was treated with the ethynyl oxirane **5**[10] in the presence of $Pd(PPh_3)_4$ (or $Pd(PPh_3)_2Cl_2$: 10-20 mole %), CuI (10-30 mole %) and Et_2NH (or *i*-Pr_2NEt: 3-5 eq.) in DMF, THF, or benzene at ambient temperature, no coupling product but merely decomposition of the starting oxiranes was observed. This is in agreement with the report by Pale et al.[8] After considerable experimentation, we found that a catalyst $Pd(CH_3CN)_2Cl_2$ (10-20 mole %) even in the presence of CuI (10-30 mole %) and *i*-Pr_2NEt (3-5 eq.) in DMF at ambient temperature afforded the desired coupling product in moderate to good yields. Thus, the treatment of **4** and **6**[9] with ethynyl oxiranes **5** (1.5 eq.) under these conditions gave rise to **2** and **1**, respectively, in 54-70% yields after silica gel flash chromatography.[11,12] When the reaction was performed under Stille's conditions[7b] the coupled products were obtained in only low yield (<20%).



4

5a : α-epoxide
b : β-epoxide

6

In summary, we have succeeded in coupling of the ethynyl oxiranes with the densely functionalized cyclpentenyl iodides using $Pd(CH_3CN)_2Cl_2$ in the presence of CuI. Further studies directing toward neocarzinostatin chromophore **3** and N1999-A2 through the above intermediates are in progress in our laboratory.

References and Notes

1. Hirama, M.; Fujiwara, K.; Shigematsu, K.; Fukazawa, Y. *J. Am. Chem. Soc.* **1989**, *111*, 4120-4122; Hirama, M.; Gomibuchi, T.; Fujiwara, K.; Sugiura, Y.; Uesugi, M. *J. Am. Chem. Soc.* **1991**, *113*, 9851-9853; Iida, K.; Hirama, M. *J. Am. Chem. Soc.* **1994**, *116*, 10310-10311.
2. For related approaches, see the reviews: (a) Hirama, M. "Synthesis and Chemistry of Neocarzinostatin Analogs," *In Recent Progress in the Chemical Synthesis of Antibiotics and Related Microbial Products, Vol 2;* Lukacs, G. Ed.; Springer-Verlag: Berlin, **1993**; pp. 293-329; (b) Nicolaou, K. C.; Dai, W.-M. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1387-1416; (c) Lhermitte, H.; Grierson, D. S.; *Contemp. Org. Synth.* **1996**, *3*, 93-124.
3. Sato, I.; Akahori, Y.; Iida, K.; Hirama, M. *Tetrahedron Lett.* **1996**, *37*, 5135-5138.
4. Ishida, N.; Miyazaki, K.; Kumagai, K.; Rikimaru, M. *J. Antibiot.* **1965**, *18*, 68-76; Edo, K.; Mizugaki, M.; Koide, Y.; Seto, H.; Furihata, K.; Otake, N.; Ishida, N. *Tetrahedron Lett.* **1985**, *26*, 331-334.
5. Hirama, M. *J. Syn. Org. Chem. Jpn.* (in English) **1994**, *52*, 980-991.
6. Ishii, M.; Ando, T.; Kajiura, T.; Kameyama, T.; Nihei, Y. *Jpn. Kokai Tokkyo Koho* JP 07291955; *Chem. Abst.* **1996**, *124*, 115564h.
7. (a) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, *50*, 4467-4470; (b) Stille, J. K.; Simpson, J. H. *J. Am. Chem. Soc.* **1987**, *109*, 2138-2152 and references cited therein.
8. Pale, P.; Bertus, P. *Tetrahedron Lett.* **1996**, *37*, 2019-2022.
9. Functionalized cyclpentenyl iodides were synthesized in a similar manner to our recent report.[3]
10. Synthesized from *D*-mannitol and the details will be reported separately.
11. All compounds were characterized by IR, ^1H-NMR, ^{13}C-NMR, and HRMS.
12 Ethynyl oxirane **5a** was added dropwise to the reaction mixture: the slow addition of **5a** increased the yield of **1**.

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