Pergamon

Tetrahedron Letters, Vol. 38, No. 3, pp. 457-460, 1997
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0040-4039/97 $17.00 + 0.00

PII: S0040-4039(96)02325-8

A Novel Route to Disubstituted [7]Thiaheterohelicene via Biaryl- and Carbonyl-Coupling Reactions

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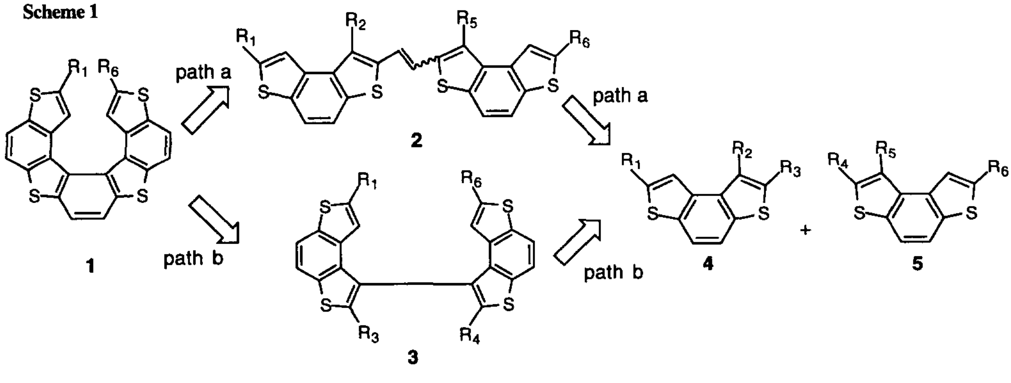
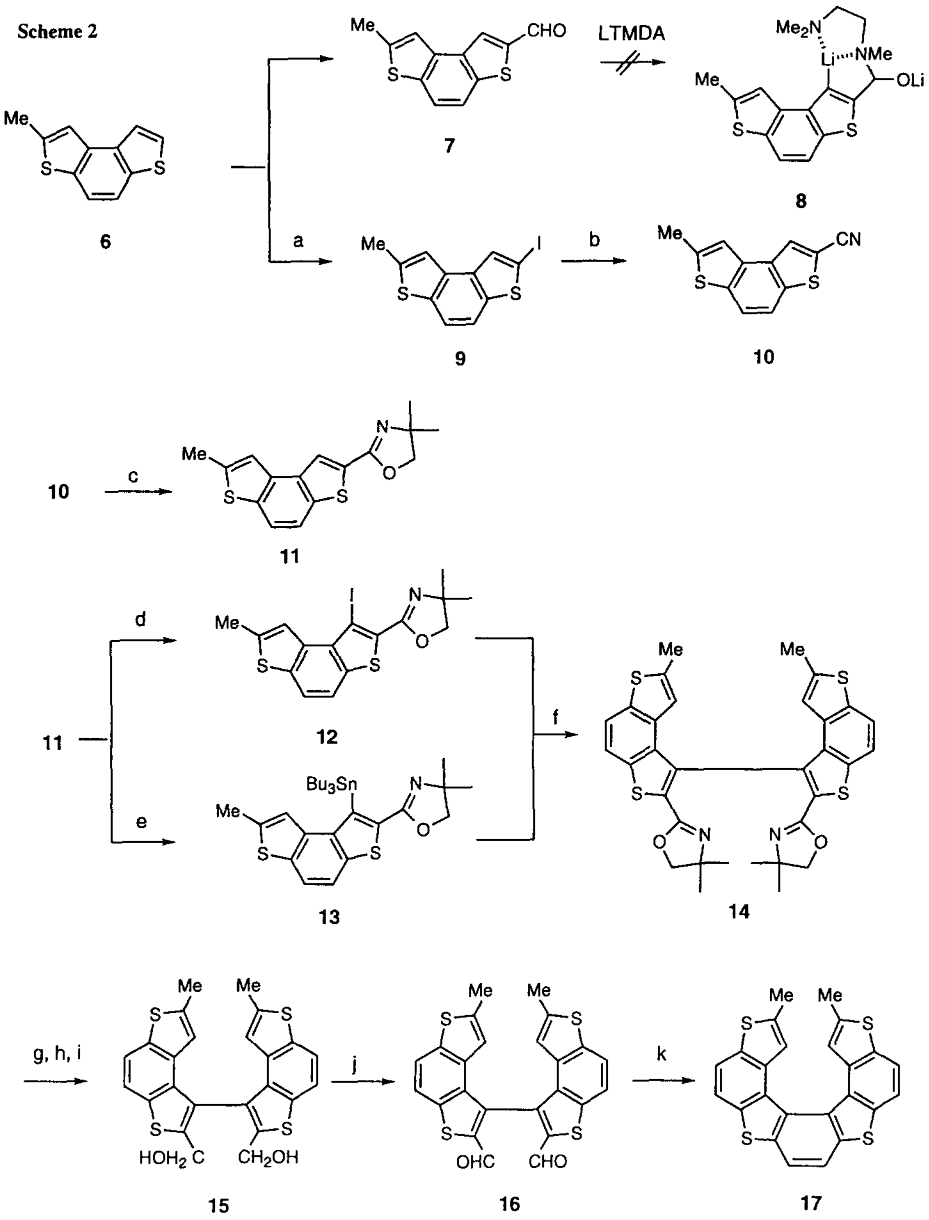
Abstract: A new non-photochemical synthesis of disubstituted heterohelicene is described. The directed metalation at the 1-position of 2-(4,4-dimethyloxazolin-2-yl)-7-methylbenzo[1,2-b:4,3-b']dithiophene was accomplished by the use of BuLi in ether to give the organolithium species which, upon treatment with iodine and chlorotributyltin, gave 2-(4,4-dimethyloxazolin-2-yl)-1-iodo-7-methylbenzo[1,2-b:4,3-b']-dithiophene and 2-(4,4-dimethyloxazolin-2-yl)-7-methyl-1-tributylstannylbenzo-[1,2-b:4,3-b']dithiophene in high yields. Palladium-catalyzed cross-coupling between them, followed by the intramolecular McMurry coupling reaction, gave 2,13-dimethyl[7]thiaheterohelicene in good yield.

Functionalized chiral helicenes and their heterocyclic analogs are of considerable interest in both materials research[1] and molecular recognition[2] due to their very high specific optical rotations and unique non-planar π-electron structures based on helicity.[3] In the synthesis of these overcrowding aromatic molecules, oxidative photocyclization is a crucial step, but the process has several drawbacks and limitations: the intense irradiation by UV light must be conducted in very dilute solutions (0.3-0.4 mM)[4] and is not always compatible with the presence of sensitive functional groups.[5] Although several non-photocyclization methods for helicenes have been reported, including the Friedel-Crafts acylation,[6] the intramolecular oxidative cyclization,[7] the cyclization of ammonium or phosphonium salts,[8] the acid or base-catalyzed condensation reactions,[9, 10, 11] and the Diels-Alder reactions of benzoquinone,[12] there is still a need for complementary methods which proceed under mild conditions and extend the range of application.

Scheme 1



Scheme 2



Reagents and conditions: (a) (i) BuLi, THF; (ii) iodine; (b) copper(I) cyanide, DMF, 74% from **6**; (c) 2-amino-2-methyl-1-propanol, cat. zinc chloride, chlorobenzene, 95%; (d) (i) BuLi, ether; (ii) iodine, 95%; (e) (i) BuLi, ether; (ii) chlorotributyltin , 91%; (f) cat. $PdCl_2(PPh_3)_2$, THF, 62%; (g) TFA , sodium sulfate, THF, H_2O; (h) acetic anhydride, pyridine; (i) $LiAlH_4$, THF, 71%; (j) PCC, CH_2Cl_2, 94%; (k) $TiCl_3{\cdot}DME_{1.5}$, Zn-Cu, DME, 78%.

This paper reports a non-photochemical route to disubstituted heterohelicene, which utilizes the palladium-catalyzed cross-coupling between two aryl units, **4** and **5**, and then the intramolecular McMurry coupling between the R_3 and R_4 substituents of the biaryl skeleton **3** (Scheme 1; path b). In the photochemical pathway (path a), the two aryl moieties are first connected at R_3 and R_4 by a vinylene bridge,[5] and the resulting 1,2-diarylethylene **2** is subjected to cyclization between the R_2 and R_5 groups.

Our initial experiments aimed at the lithiation of the 3-position of 2-formyl-7-methylbenzo[1,2-b:4,3-b']dithiophene[13] (**7**) using lithiated *N,N,N'*-trimethylethylenediamine (LTMDA)[14] were unsuccessful and the starting material was recovered (Scheme 2). However, we observed that the introduction of a strong ortho-directing oxazoline moiety[15] at the 7-position of 2-methyllbenzo[1,2-b:4,3-b']dithiophene (**6**) led to a facile generation of the organolithium species. The oxazoline **11** was prepared from the corresponding cyanide **10**, which was readily available in 74% overall yield from **6**. Treatment of **11** with BuLi in ether at -78 ℃, followed by trapping the lithium anion with iodine and chlorotributyltin, gave **12** and **13** in 95% and 91% yield, respectively.

The cross-coupling reaction[16] between **12** and **13** smoothly proceeded in the presence of 5 mol% of $PdCl_2(PPh_3)_2$ to afford the biaryl compound **14** in 62% yield. The oxazoline moiety was then transformed to the corresponding dialdehyde **16** via oxidation of **15** by PPC.[15] Finally, the intramolecular McMurry coupling reaction[17] using $TiCl_3$/Zn-Cu gave 2,13-dimethy[7]thiaheterohelicene **17** in 32% yield. The use of $TiCl_3 \cdot DME_{1.5}$/Zn-Cu[18] increased the yield to 78%. The protons (δ 6.43) on C(1) and C(14) of **17** resonate at higher field than the proton (δ 7.32) on C(1) of **6**. This implies that the former protons are in the region of a shielding zone exerted by the helical aromatic structure.[19]

In summary, we have developed a practical method for disubstituted thiaheterohelicene using as the key steps the Stille coupling and the McMurry coupling reactions. The methyl groups of **17** can be easily converted to other functionalities such as the bromomethyl moiety[13] and are thus very appropriate for further synthetic studies. If two different heterocycles having chiral oxazoline moieties could be subjected to the palladium-catalyzed cross-coupling, then a new practical advance in methodology for the asymmetric synthesis of helicenes should result. Work along these lines is in progress and will be reported in due course.

Acknowledgement. This work was supported by a Grant-in-Aid for Scientific Research on Priority Areas (No. 08236222), the Ministry of Education, Science, Sports and Culture, and a Grant-in-Aid for JSPS Fellows (No. 3089).

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(*Received in Japan* 28 *October* 1996; *revised* 22 *November* 1996; *accepted* 25 *November* 1996)