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A Highly Regio- and Stereoselective Carbocupration of Fluoroalkylated Internal Alkynes: A Short Total Synthesis of the Antiestrogenic Drug Panomifene

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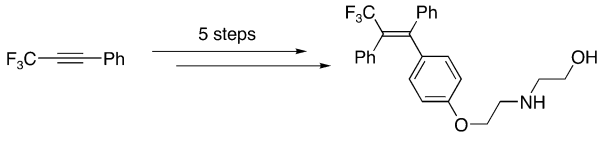
ABSTRACT



A highly regio- and stereoselective carbometalation reaction of fluoroalkylated internal alkynes with organocopper reagents is described. This reaction is utilized successfully in the short, stereoselective total synthesis of the antiestrogenic drug panomifene.

Panomifene[1] (EGIS-5656, GYKI-13504) **1** is a followup molecule of tamoxifen **2** (Nolvadex), the well-known triarylethylene-type antiestrogenic drug in the therapy of breast cancer and for the treatment of menstrual disorders (Figure 1).[2]

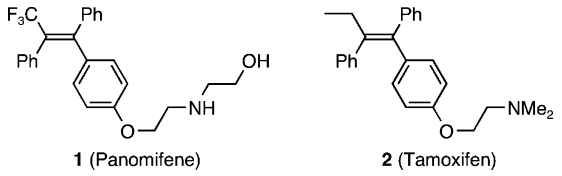


Figure 1. Panomifene and Tamoxifen.

Panomifene has proved to be superior to tamoxifen, especially in preventing the development of new tumors.[3] To date, several synthetic approaches to panomifene have been reported. In the patented synthesis of panomifene, the olefin was prepared by dehydrogenation of the corresponding alkane with dichlorodicyano-benzoquinone, which resulted in nonstereoselective access to panomifene.[4] The improved synthetic method by Simig et al. also involved the dehydration of the corresponding triarylethanol for constructing the double bond, leading to the moderate stereoselectivity (*E*-isomer:*Z*-isomer = 7.9:1). Additionally, the overall yield for ten steps starting from α,α,α-trifluoroacetophenone is quite low (12% yield).[4b]

The lack of high stereoselectivity as well as a short approach to **1** prompted us to examine the retrosynthesis of

(1) *Drugs Fut*. **1990**, *15*, 532−533.

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(3) (a) *Drugs Fut*. **1985**, *10*, 395. (b) *Drugs Fut*. **1986**, *11*, 426. (c) *Drugs Fut*. **1987**, *12*, 497. (d) *Drugs Fut*. **1988**, *13*, 480.

(4) (a) Ábrahám, G.; Horváth, T.; Toldy, L.; Borvendég, J.; Csányi, E.; Kiss, É.; Hermann-Szente, I.; Tory, K. (Gyógyszerkuntató Intézet). Hungarian Patent 17853, 1979. (b) Németh, G.; Kapiller-Dezsofi, R.; Lax, G.; Simig, G. *Tetrahedron* **1996**, *52*, 12821−12830.

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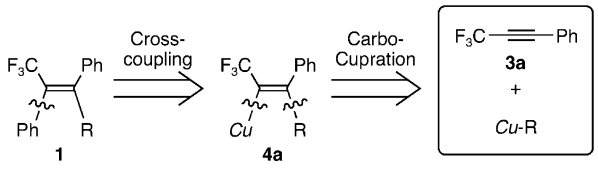
Scheme 1. Retrosynthesis of Panomifene



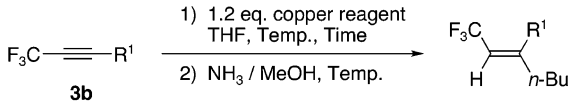
R = *p*-[HO(CH$_2$)$_2$NH(CH$_2$)$_2$O]C$_6$H$_4$

1 as illustrated in Scheme 1. Our strategy for the synthesis of **1** is based on the possibility of using a carbometalation reaction of trifluoromethylated internal alkyne **3a** with organocopper reagent, leading to the corresponding intermediate **4a**.[5] The successive stereospecific cross-coupling reaction of vinyl copper **4a** with phenyl halide would provide us with the target compound.[6]

In this communication, we wish to describe a highly regio- and stereoselective carbocupration reaction of fluoroalkylated internal alkynes and the following stereospecfic Suzuki−Miyaura cross-coupling reaction, the utilization of which realizes an efficient stereoselective total synthesis of panomifene **1**.

As preliminary studies, we examined the feasibility of the carbometalation reaction with a series of organocopper reagents (prepared from Grignard reagents) by using trifluoromethylated alkyne **3b**,[7] in order to determine the optimum linchpin (Table 1). Treatment of **3b** with *n*-butylcopper at −45 °C for 4 h furnished the carbometalation product *cis*-**5b** in only 5% yield, together with 48% of the starting material, after quenching the reaction with NH_3 (aq)/MeOH at −45 °C. The product proved to be a *cis*-adduct as a single isomer. This result encouraged us to investigate the reaction in more detail. Use of a lower-ordered dibutylcuprate, generated from butylmagnesium bromide and CuBr, significantly improved the yield of *cis*-**5b** from 5 to 58% (entry 2). Furthermore, the reaction at −78 °C was found to give the desired product *cis*-**5b** in 94% yield. Additional studies focused on a copper salt such as CuI and CuCN, both of which had proven to be good copper salts in our preliminary studies on the carbocupration reaction using organolithium reagents.[8] Thus, changing the copper salt from CuBr to CuI appreciably affected the yield (entry 4). Higher-ordered cyanocuprates realized the satisfactory reaction, resulting in the formation of *cis*-**5b** in 69% yield, although lower-ordered cyanocuprate did not lead to good results. In all cases, isomers such as *trans*-**5b**, *cis*-**6b**, and *trans*-**6b** were not detected at all (Figure 2).

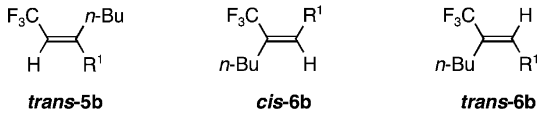
Table 1. Investigation of the Reaction Conditions for the Carbocupration



R^1 = *p*-ClC$_6$H$_4$

entry	copper reagent[a]	temp (°C)	time (h)	yield[b] of **5b** (%)	recovery[b] of **3b** (%)
1	*n*-BuCu	−45	4	5	48
2	*n*-Bu$_2$CuX	−45	4	58	0
3	*n*-Bu$_2$CuX	−78	2	94 (85)	0
4[c]	*n*-Bu$_2$CuX	−78	2	31	68
5	*n*-BuCu(CN)X	−78	2	24	76
6	*n*-Bu$_2$Cu(CN)X$_2$	−78	2	69	28

[a] Copper reagents were prepared from Grignard reagent (*n*-BuX, X = MgBr) and CuBr or CuCN, unless otherwise noted. [b] Determined by ^{19}F NMR. Value in parentheses is of isolated yield. [c] CuI was employed instead of CuBr.



R^1 = *p*-ClC$_6$H$_4$

Figure 2.

To examine the scope and limitation of this carbocupration, optimized reaction conditions were applied for various types of fluoroalkylated alkynes **3** as shown in Table 2.

Primary and secondary Grignard reagents such as *n*-BuMgBr and *s*-BuMgBr (entries 1 and 2), cyclohexyl, benzyl, and allyl Grignard reagents (entries 3−5) could participate well in the carbocupration reaction to give the corresponding adducts *cis*-**5** in good to excellent yields (69−86% isolated yields). However, the yield was somewhat eroded when vinyl Grignard reagent was employed (entry 6). Switching R in the Grignard reagent from aliphatic to aromatic groups had no discernible effect on the yield, although 2.4 equiv of copper reagents or CuCN instead of CuBr were required for the smooth reaction (entries 7 and

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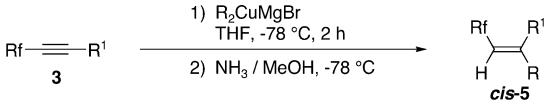
Table 2. Carbocupration Reaction of Fluoroalkylated Alkynes with Various Copper Reagents



entry	equiv of copper reagent	R	Rf	R^1	yield[a] of *cis*-**5** (%)
1	1.2	*n*-Bu	CF_3	*p*-ClC_6H_4	93 (83)
2	2.4	*s*-Bu	CF_3	*p*-ClC_6H_4	84 (69)
3	1.2	*c*-Hex	CF_3	*p*-ClC_6H_4	74
4[b]	1.2	Bn	CF_3	*p*-ClC_6H_4	quant. (69)
5[c]	1.2	allyl	CF_3	*p*-ClC_6H_4	98 (86)
6	2.4	vinyl	CF_3	*p*-ClC_6H_4	53 (41)
7	2.4	Ph	CF_3	*p*-ClC_6H_4	93
8	2.4	*p*-$MeOC_6H_4$	CF_3	*p*-ClC_6H_4	61[d]
9	2.4	*n*-Bu	CF_3	*m*-ClC_6H_4	90 (70)
10	1.2	*n*-Bu	CF_3	*o*-ClC_6H_4	89 (83)
11	1.2	*n*-Bu	CF_3	*p*-$MeOC_6H_4$	97 (93)
12	1.2	*n*-Bu	CF_3	*p*-MeC_6H_4	96 (90)
13	1.2	*n*-Bu	CF_3	*p*-$EtO_2CC_6H_4$	84 (80)
14	1.2	*n*-Bu	CF_3	(*p*-$MeOC_6H_4$)-CH_2	quant. (99)
15	1.2	*n*-Bu	HCF_2	*p*-ClC_6H_4	65 (55)

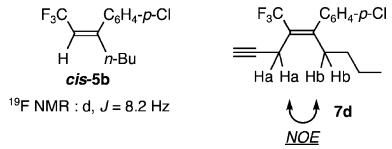
[a] Determined by ^{19}F NMR. Values in parentheses are of isolated yields. [b] Benzylmagnesium chloride was used for the preparation of copper reagent. [c] Allylmagnesium chloride was used for the preparation of copper reagent. [d] CuCN was employed instead of CuBr because the copper reagents prepared from Grignard reagent and CuBr did not give reproducible results.

8). Changing the aromatic substituent (R^1) of the alkynes **3** from *p*-chlorophenyl to *m*-chloro- or *o*-chlorophenyl also did not significantly affect the yield (entries 1, 9, and 10). In addition, no influence of the substituents in R^1 such as electron-donating (MeO, Me; entries 11 and 12) or electron-withdrawing groups (EtO_2C; entry 13) was observed on the yield. It is worth noting that the internal alkynes having an alkyl side chain as R^1 (entry 14) or a difluoromethyl moiety as Rf (entry 15) could also undergo the smooth carbocupration reaction to afford the corresponding adducts in good to high yields.

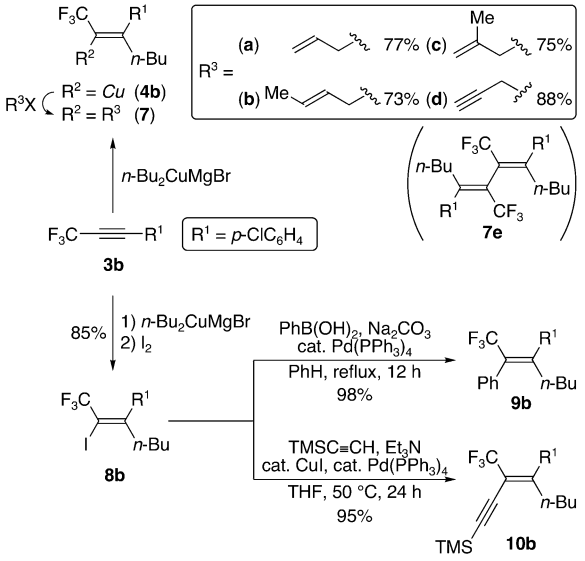
On the basis of the above-described results on the regio- and stereoselective carbometalation of the fluoroalkylated internal alkynes **3** with organocopper reagents, our interest was directed toward the cross-coupling reaction using the carbometalated adduct **4b** as a second key reaction for the total synthesis of panomifene (Scheme 2).

Treatment of **4b** with 4.0 equiv of allyl bromide, crotyl bromide, methallyl bromide, or propargyl bromide at −78 °C resulted in a smooth coupling reaction, affording the tetrasubstituted alkenes **7a**−**d** in high yields.[9] Surprisingly, other electrophiles such as benzyl bromide, ethyl chloroformate, ethyl bromoacetate, etc. were all unreacted, leading

(9) Stereochemistry in the carbocupration was determined as follows. Thus, the careful ^{19}F and ^1H NMR analysis of trisubstituted alkene *cis*-**5b** indicated that the hydrogen was attached with the carbon having a CF_3 group. In addition, a NOE between Ha and Hb in the NOESY experiment of **7d** shows that the compound has the *Z* configuration.

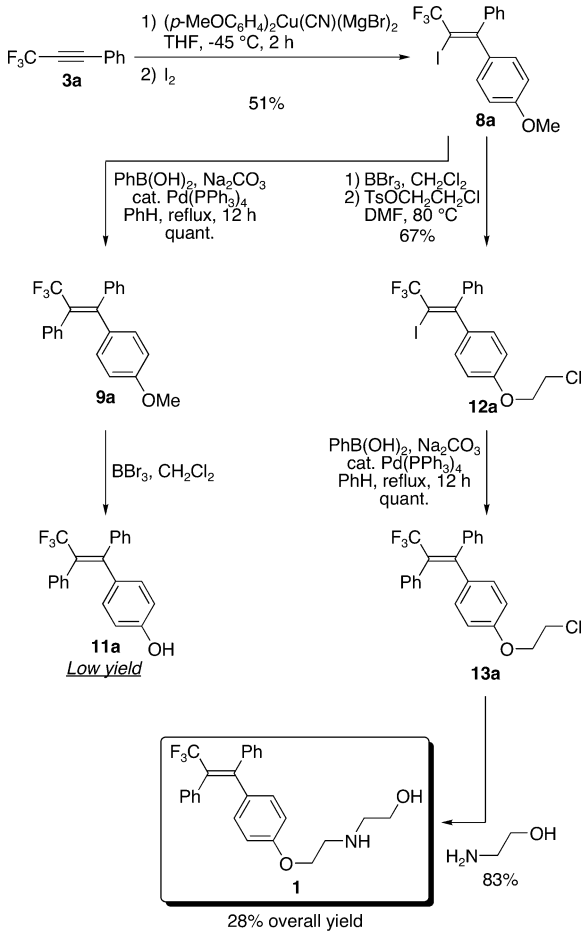


Scheme 2. Cross-Coupling Reaction



to the formation of trisubstituted alkene *cis*-**5b** after quenching the reaction with NH_3 (aq)/MeOH. The coupling reaction of **4b** with iodobenzene under the influence of palladium

Scheme 3. Short Synthesis of Panomifene



catalyst at 0 °C∼rt did not give any desired product due to decomposition of **4b**. Trimethylsilyl chloride and Tributylstannyl chloride were also found to be poor electrophiles, the desired tetrasubstituted alkenes being obtained in low yields, together with a large amount of *cis*-**5b** and the dimer **7e**. However, the reaction of **4b** with iodine took place readily to give the corresponding vinyl iodide **8b** in 85% yield. We then attempted the cross-coupling reaction of **8b** with organometallic reagents in the presence of a transition metal catalyst. Thus, the vinyl iodide **8b** was subjected to the Suzuki−Miyaura cross-coupling reaction[10] to form the adduct **9b** almost quantitatively. The Sonogashira coupling reaction,[11] on the other hand, afforded the corresponding enyne **10b** in 95% yield.

With the carbocupration and the Suzuki−Miyaura cross-coupling reactions, the synthesis of the antiestrogenic drug panomifene **1** was executed as follows (Scheme 3). Thus, alkyne **3a**[7] was exposed to the carbocupration reaction with $(p\text{-MeOC}_6\text{H}_4)_2\text{Cu(CN)(MgBr)}_2$ (1.2 equiv), −45 °C, 2 h, followed by addition of 2.4 equiv of iodine at −45 °C, to afford vinyl iodide **8a** in 51% yield. The ^{1}H, ^{13}C, and ^{19}F NMR and GLC analyses were indicative of no other stereoisomers being formed. The stereochemically pure **8a** was treated with 4.0 equiv of phenylboronic acid under the Suzuki−Miyaura cross-coupling reaction conditions, producing the triarylethylene derivative **9a** almost quantitatively with complete retention of the stereochemistry. Surprisingly, treatment of **9a** with BBr_3 gave **11a** in low yield. All attempts for improving this demethylation were unsuccessful. On the other hand, the demethylation of **8a** with BBr_3 proceeded readily to give the corresponding phenol derivative. The following nucleophilic substitution reaction between phenoxide and 2-chloroethyl tosylate in DMF at 80 °C gave rise to the desired ether **12a** in 67% yield. Suzuki−Miyaura cross-coupling reaction of **12a** with phenylboronic acid afforded the corresponding alkene **13a** quantitatively. Finally, on treatment of **13a** with ethanolamine in 2-methoxyethyleneglycol, the desired panomifene **1** was obtained in 83% yield (28% overall yield from **3a**).

In summary, we have investigated two key reactions: the carbocupration reaction of fluoroalkylated internal acetylene derivatives and the following cross-coupling reaction in search for the efficient total synthesis of antiestrogenic drug, panomifene. The carbocupration reaction of fluoroalkylated internal alkynes proceeded in a highly regio- and stereoselective manner to give the corresponding vinylcopper adduct. The vinylcopper reacted with only a few carbon electrophiles such as allyl halide and its derivatives, probably due to the low reactivity exerted by the electron-withdrawing CF_3 group. Treatment of vinylcopper with iodine gave a high yield of the corresponding vinyliodide, which was employed successfully for the total synthesis of panomifene **1** via stereospecific Suzuki−Miyaura cross-coupling reaction. As a result, we have attained a short and highly stereoselective total synthesis of panomifene (total yield for five steps: 28%).

Supporting Information Available: Experimental details and characterization for all new compounds (^{1}H NMR and ^{13}C NMR). This material is available free of charge via the Internet at http://pubs.acs.org.

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