Effective Synthesis of Tamoxifen Using Nickel-Catalyzed Arylative Carboxylation

Kazuya Shimizu,[a] Masanori Takimoto,[b] Miwako Mori,*[c] Yoshihiro Sato*[a]

[a] Graduate School of Pharmaceutical Sciences, Hokkaido University, Sapporo 060-0812, Japan

[b] Organometallic Chemistry Laboratory, RIKEN (The Institute of Physical and Chemical Research), 2-1 Hirosawa, Wako, Saitama 351-0198, Japan

[c] Health Sciences University of Hokkaido, Ishikari-Tobetsu 061-0293, Japan
Fax +81(11)7064982; E-mail: mori@pharm.hokudai.ac.jp

Received 2 May 2006

Dedicated to Professor Richard F. Heck for his contributions to organopalladium chemistry

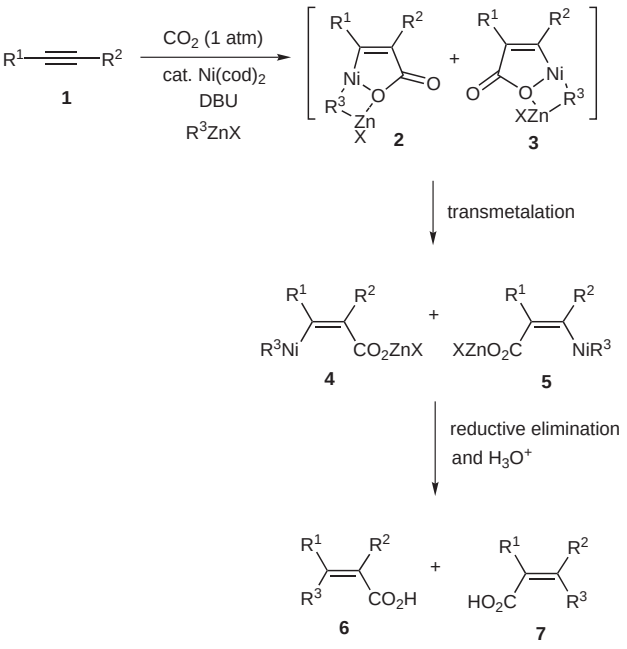
Abstract: Tamoxifen was synthesized using a nickel-catalyzed arylative carboxylation developed by our group. The key compound, tetrasubstituted alkene, was synthesized from disubstituted alkyne using a catalytic amount of Ni(0) and DBU in the presence of Ph_2Zn under an atmosphere of carbon dioxide. The reaction proceeded smoothly in a regio- and stereoselective manner, and the resultant tetrasubstituted alkene was converted into tamoxifen.

Key words: tetrasubstituted alkenes, nickel catalyst, zinc reagent, tamoxifen, carbon dioxide

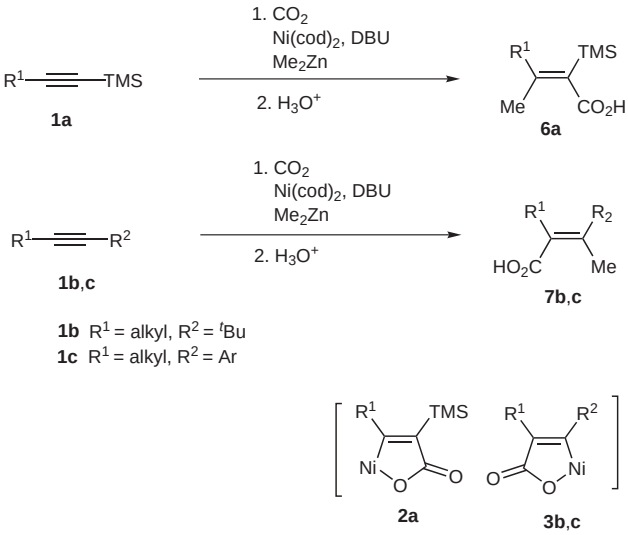
Tamoxifen[1] is an antiestrogenic anticancer drug that is effective for the treatment of metastatic breast cancer. The structure of tamoxifen, which has tetrasubstituted alkene, prompted us to synthesize[2] this compound in a regio- and stereoselective manner because we have developed a novel method for synthesizing tetrasubstituted alkene from disubstituted alkyne, CO_2, a zinc reagent and DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) using a catalytic amount of Ni(0).[3a]

The reaction proceeded through the formation of oxanickelacycle **2** and/or **3** by oxidative cyclization of alkyne **1**, CO_2 and Ni(0) followed by transmetalation of **2** and/or **3** with a zinc reagent and then reductive elimination from alkylnickel complex **4** and/or **5** to give tetrasubstituted alkene **6** and/or **7** (Scheme 1).

To realize the regioselective synthesis of tetrasubstituted alkene, the effect of the substituent on an alkyne is very important. That is, alkyne **1a** having a trimethylsilyl group gave tetrasubstituted alkene **6a** predominantly via oxanickelacycle **2a**, but the alkynes **1b** and **1c** having a *t*-Bu group and an aryl group gave tetrasubstituted alkenes **7b** and **7c** predominantly in high yields via oxanickelacycles **3b** and **3c**, respectively (Scheme 2). Presumably, an oxanickelacycle made thermodynamically more stable by conjugation of the carboxyl group with the substituent R^1 or R^2 on the oxanickelacycle would give a major tetrasubstituted alkene.



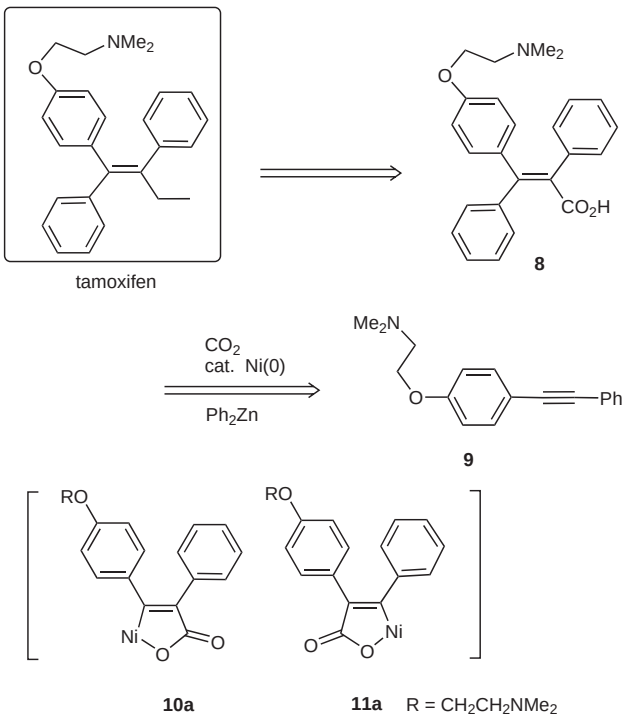
Scheme 1 Synthesis of tetrasubstituted alkenes using nickel-catalyzed alkylative carboxylation



Scheme 2 Electronic effects on the regioselectivity of nickel-catalyzed carboxylation

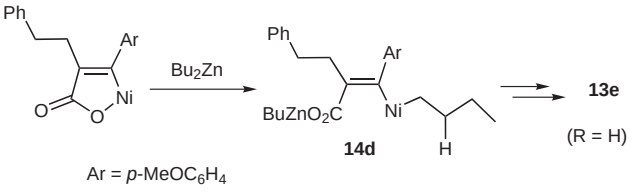
SYNLETT 2006, No. 18, pp 3182–3184
Advanced online publication: 25.10.2006
DOI: 10.1055/s-2006-951517; Art ID: S10206ST

Our retrosynthetic analysis of tamoxifen is shown in Scheme 3. Tamoxifen would be synthesized from tetrasubstituted alkene **8**, which would be obtained from disubstituted alkyne **9**, CO_2 and Ph_2Zn in the presence of a catalytic amount of nickel complex.



Scheme 3 Retrosynthetic analysis of tamoxifen using nickel-catalyzed phenylative carboxylation

To examine whether other zinc reagents can be used for this reaction, various zinc reagents were examined and the results are shown in Table 1. The use of Ph_2Zn and Bn_2Zn gave the corresponding tetrasubstituted alkenes **13b** and **13c** in high yields, respectively (entries 2 and 3). In the case of Bu_2Zn, tetrasubstituted alkene **13d** was obtained in 79% yield along with trisubstituted alkene **13e** (R = H) in 19% yield (entry 4). The latter compound **13e** should be formed by transmetalation of oxanickelacycle with Bu_2Zn followed by β-hydrogen elimination from butyl nickel complex **14d** and reductive elimination of hydride nickel complex (Scheme 4).

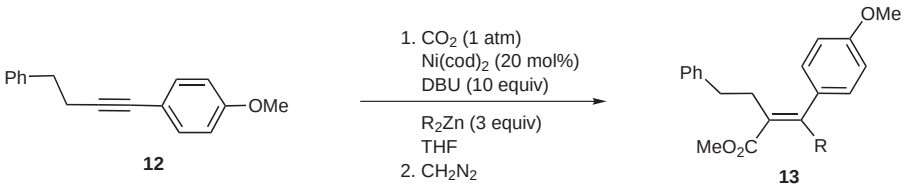


Scheme 4

In the synthesis of tamoxifen, oxanickelacycle **10a** should be formed predominantly because oxanickelacycle **10a** is more stable than **11a** due to the conjugation of the *p*-alkoxyphenyl group with the carboxyl group in **10a** and compound **8** would be obtained as a major product from **10a**. To confirm this, synthesis of tetrasubstituted alkene was examined using a model compound **15**. When a THF solution of alkyne **15** and Ph_2Zn in the presence of 20 mol% of $Ni(cod)_2$ and 10 equivalents of DBU was stirred under an atmosphere of carbon dioxide at 40 °C for 17 hours, desired tetrasubstituted alkene **16** was obtained in 67% yield along with **17** in 27% yield (Scheme 5). As expected, oxanickelacycle **10a** (R = Me) was preferentially formed as an intermediate.

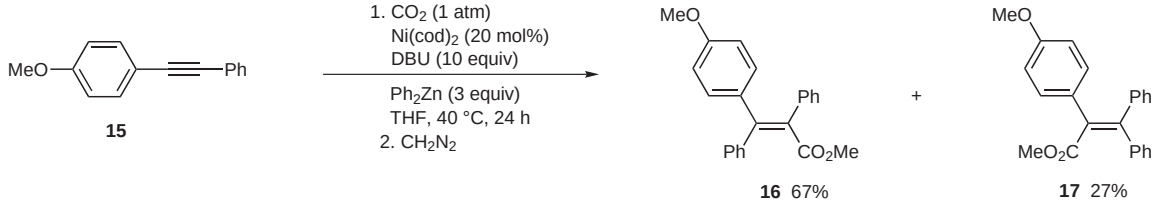
The synthesis of starting disubstituted alkyne **9** was carried out. Alkylation of *p*-iodophenol gave **18**,[2o] which was condensed with phenylacetylene in the presence of a palladium catalyst to afford desired alkyne **9**. When a reaction of **9**, CO_2, and Ph_2Zn was carried out in a manner similar to that for the synthesis of **16**, desired tetrasubstituted alkene **19** was obtained in 63% yield along with **20** in 22% yield. Reduction of the ester group of **19** with DIBAL-H gave alcohol **21**, which was already converted into tamoxifen by Fallis (Scheme 6).[2o] According to the

Table 1 Nickel-Catalyzed Carboxylation in the Presence of Various Zinc Reagents

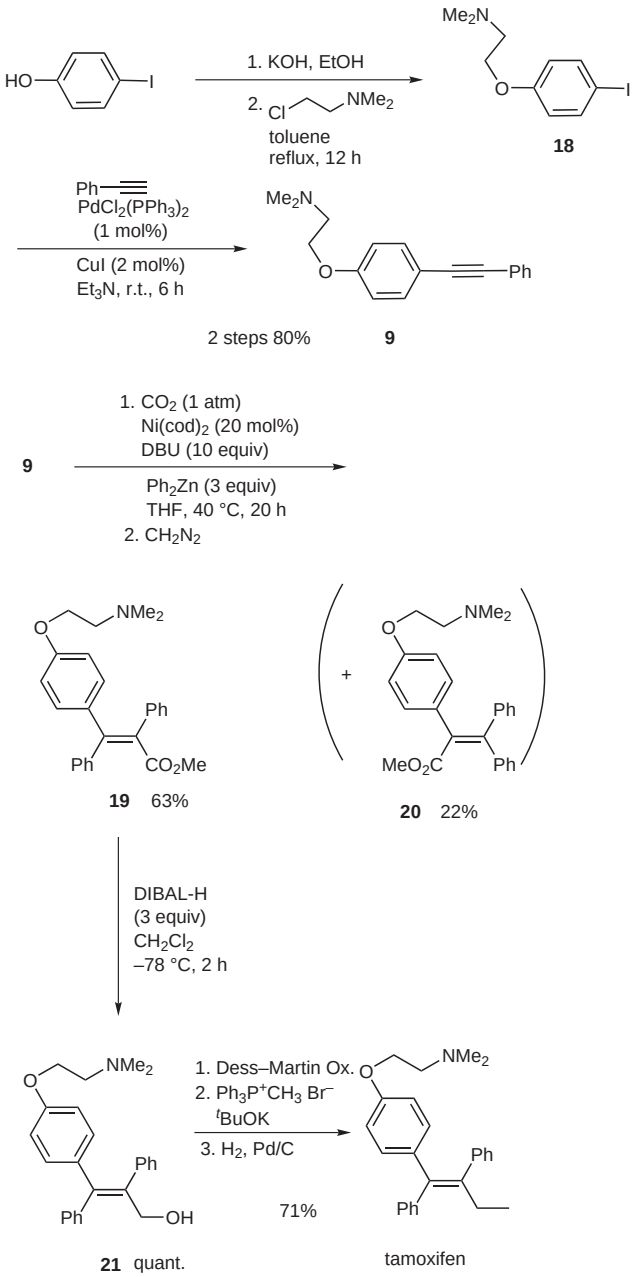


Entry	R_2Zn	Temp	Time (h)	R	Product	Yield (%)
1	Me_2Zn	r.t.	18	Me	**13a**	quant.[a]
2	Ph_2Zn	40 °C	15	Ph	**13b**	97
3	Bn_2Zn	40 °C	12	Bn	**13c**	90
4	Bu_2Zn	r.t.	18	Bu	**13d**	79[b]

[a] Previously reported.
[b] Trisubstituted alkene **13e** (R = H) formed by β-hydrogen elimination was obtained in 19% yield.



Scheme 5 Model study for the synthesis of tamoxifen



Scheme 6 Synthesis of tamoxifen

Fallis' procedure, Dess–Martin oxidation of **21** followed by Wittig reaction and then hydrogenation afforded tamoxifen, whose spectral data agreed with those reported in the literature.[2p] Thus, the synthesis of tamoxifen was achieved in 36% overall yield over eight steps.

Synthesis of tamoxifen was achieved using nickel-catalyzed arylative carboxylation. In this synthesis, carbon dioxide and an aryl group were introduced into diarylated alkyne regioselectively. Carbon dioxide is a useful resource in synthetic organic chemistry. Further study for utilization of carbon dioxide is now in progress.

References

(1) Harpor, M. J. K.; Richardson, D. N.; Walpole, A. L. GB 1013907, **1965**; *Chem. Abstr.* **1965**, *62*, 10374e.

(2) For recent syntheses of tamoxifen, see: (a) Miller, R. B.; Al-Hassan, M. I. *J. Org. Chem.* **1985**, *50*, 2121. (b) Al-Hassan, M. I. *Synth. Commun.* **1987**, *17*, 1247. (c) Al-Hassan, M. I. *Synthesis* **1987**, 816. (d) Coe, P. L.; Scriven, C. E. *J. Chem. Soc., Perkin Trans. 1* **1986**, 475. (e) Potter, G. A.; McCague, R. *J. Org. Chem.* **1990**, *55*, 6184. (f) Stüdemann, T.; Knochel, P. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 93. (g) Stüdemann, T.; Ibrahim-Ouali, M.; Knochel, P. *Tetrahedron* **1998**, *54*, 1299. (h) Brown, S. D.; Armstrong, R. W. *J. Org. Chem.* **1997**, *62*, 7076. (i) Yus, M.; Ramón, D. J.; Gómez, I. *Tetrahedron* **2003**, *59*, 3219. (j) Itami, K.; Kamei, T.; Yoshida, J. *J. Am. Chem. Soc.* **2003**, *125*, 14670. (k) Shiina, I.; Suzuki, M.; Yokoyama, K. *Tetrahedron Lett.* **2004**, *45*, 965. Formal syntheses of tamoxifen: (l) Zhou, C.; Emrich, D. E.; Larock, R. C. *Org. Lett.* **2003**, *5*, 1579. (m) Shindo, M.; Matsumoto, K.; Shishido, K. *Synlett* **2005**, 176. (n) Shimizu, M.; Nakamaki, C.; Shimono, K.; Scelper, M.; Hiyama, T. *J. Am. Chem. Soc.* **2006**, *127*, 12506. (o) Tessier, P. E.; Penwell, A. J.; Souza, F. E. S.; Fallis, A. G. *Org. Lett.* **2003**, *5*, 2989. (p) Zhou, C.; Larock, R. C. *J. Org. Chem.* **2005**, *70*, 3765.

(3) Synthesis of tetrasubstituted alkene, see; (a) Shimizu, K.; Takimoto, M.; Sato, Y.; Mori, M. *Org. Lett.* **2005**, *7*, 195. Other CO_2 fixation reaction developed by our group, see: (b) Takimoto, M.; Mori, M. *J. Am. Chem. Soc.* **2001**, *123*, 2895. (c) Takimoto, M.; Shimizu, K.; Mori, M. *Org. Lett.* **2001**, *3*, 3345. (d) Takimoto, M.; Mori, M. *J. Am. Chem. Soc.* **2002**, *124*, 10008. (e) Shimizu, K.; Takimoto, M.; Mori, M. *Org. Lett.* **2003**, *5*, 2323. (f) Takimoto, M.; Kawamura, M.; Mori, M. *Org. Lett.* **2003**, *5*, 2599. (g) Takimoto, M.; Kawamura, M.; Mori, M. *Synthesis* **2004**, 791. (h) Takimoto, M.; Nakamura, Y.; Kimura, K.; Mori, M. *J. Am. Chem. Soc.* **2004**, *126*, 5956. (i) Takimoto, M.; Kawamura, M.; Mori, M.; Sato, Y. *Synlett* **2005**, 2019. (j) Takimoto, M.; Mizuno, T.; Sato, Y.; Mori, M. *Tetrahedron Lett.* **2005**, *46*, 5173.