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Novel Synthesis of Heterocycles Having a Functionalized Carbon Center via Nickel-Mediated Carboxylation: Total Synthesis of Erythrocarine

Kazuya Shimizu, Masanori Takimoto, and Miwako Mori*

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

mori@pharm.hokudai.ac.jp

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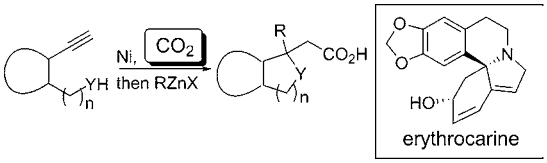
ABSTRACT

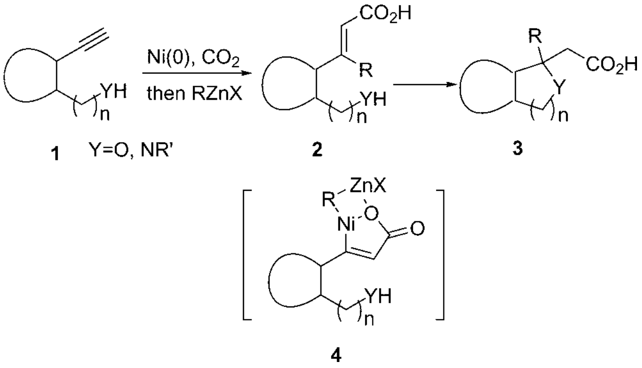


Novel synthetic procedure of heterocycles was developed using nickel-mediated alkylative carboxylation, and the total synthesis of erythrocarine was achieved using this method and RCM of dienyne as the key steps.

Carbon dioxide is a useful carbon 1-unit source for synthetic organic chemistry, and the reaction of Grignard reagent and carbon dioxide has been used as a method for converting an aryl or alkyl halide into carboxylic acid. Transition-metal-mediated or -catalyzed carboxylation is a promising reaction because carbon−carbon bond formation is induced between carbon−oxygen double bond of carbon dioxide and multiple bonds by the transition metals.[1] Recent reports[2] of nickel-mediated and -catalyzed carboxylation reactions to alkyne are very interesting because the reaction conditions are very mild. During the course of our study[3] of nickel-mediated carboxylation to alkyne,[3b] we planned for the synthesis of heterocycles using this method. Our plan is shown in Scheme 1. If alkyne **1** having a heteroatom in a tether is treated with Ni(0) under carbon dioxide, oxanickelacycle **4** should be formed.

Transmetalation of an alkyl group of a zinc reagent into nickel[4] followed by reductive elimination should give trisub-

Scheme 1. Plan for Synthesis of Heterocycles



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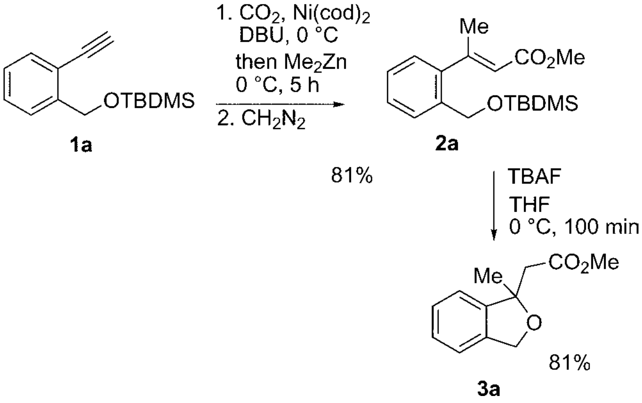
[1] Reviews: (a) Behr, A. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 661. (b) Braunstein, P.; Matt, D.; Nobel, D. *Chem. Rev.* **1988**, *88*, 747. (c) Gibson, D. H. *Chem. Rev.* **1996**, *96*, 2063. (d) Leitner, W. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2207.

[2] (a) Hoberg, H.; Burkhart, G. *Angew.* Chem., *Int. Ed. Engl.* **1982**, *21*, 76. (b) Hoberg, H.; Schaefer, D. *J. Organomet. Chem.* **1982**, *238*, 383. (c) Hoberg, H.; Schaefer, D.; Burkhart, G.; Krüger, C.; Romao, M. J. *J. Organomet. Chem.* **1984**, *266*, 203. (d) Saito, S.; Nakagawa, S.; Koizumi, T.; Hirayama, K.; Yamamoto, Y. *J. Org. Chem.* **1999**, *64*, 3975. Recent reports of catalytic reactions involving a related coupling process: (e) Inoue, Y.; Itoh, Y.; Kazama, H.; Hashimoto, H. H. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 3329. (f) Tsuda, T.; Morikawa, S.; Hasegawa, N.; Saegusa, T. *J. Org. Chem.* **1990**, *55*, 2978. (g) Dèrien, S.; Clinet, J.-C.; Duñach, E.; Pèrichon, J. *J. Am. Chem. Soc.* **1991**, *113*, 8447. (h) Louie, J.; Gibby, J. E.; Farnworth, M. V.; Tekavec, T. N.; *J. Am. Chem. Soc*. **2002**, *124*, 15189.

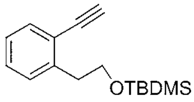
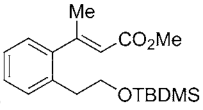
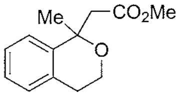
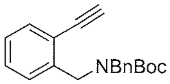
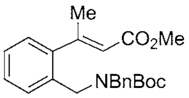
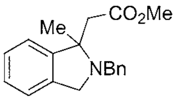
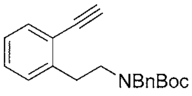
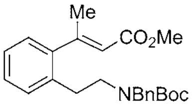
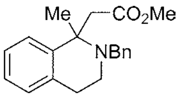
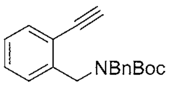
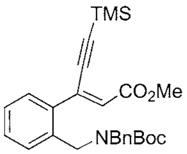
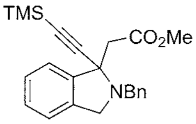
10.1021/ol034670w CCC: $25.00

Scheme 2. Synthesis of Isobenzofuran



stituted alkene **2** after hydrolysis. Michael addition of a heteroatom in a tether of **2** to an α,β-unsaturated carboxyl moiety would give heterocycles **3**.

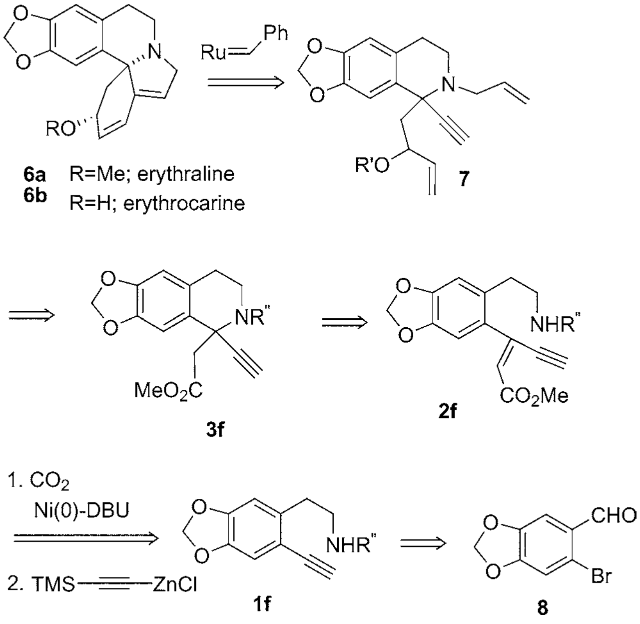
Table 1. Synthesis of Heterocycles Using Nickel-Mediated Carboxylation Followed by Michael Reaction

run	alkyne	alkylative carboxylation product	heterocycle
1	 **1b**	 **2b** 67%	 **3b**[a] 81%
2	 **1c**	 **2c** 75%	 **3c**[b] 83%
3	 **1d**	 **2d** 76%	 **3d**[c] 79%
4	 **1c**	 **2e** 71%	 **3e**[d] 85%

[a] Treatment of **2b** with TBAF at room temperature for 3 h. [b] A CH$_2$Cl$_2$ solution of **2c** was refluxed in the presence of CF$_3$CO$_2$H for 2 h. [c] A CH$_2$Cl$_2$ solution of **2d** was refluxed in the presence of CF$_3$CO$_2$H for 1 h, and then a MeOH solution of amine was refluxed for 2 h. [d] A CH$_2$Cl$_2$ solution of **2e** was refluxed in the presence of CF$_3$CO$_2$H for 5 h, and then a MeOH solution of amine was refluxed for 14 h.

TMS—≡—ZnCl **5**

Scheme 3. Retrosynthetic Analysis of Erythrina Alkaloid



On the basis of this idea, a THF solution of compound **1a** was stirred in the presence of Ni(cod)$_2$ (1.1 equiv) and DBU (2.2 equiv) under carbon dioxide (1 atm) at 0 °C for 1 h, and then Me$_2$Zn was added. The solution was stirred at 0 °C for 5 h, and after hydrolysis, the crude product was treated with CH$_2$N$_2$ to give ester **2a** in 81% yield. Deprotection of a silyl group afforded the desired isobenzofuran **3a** in 81% yield (Scheme 2).

Subsequently, alkyne **1b**, whose one carbon in a tether was elongated, was treated in a similar manner to give ester **2b**, which was treated with TBAF at room temperature to give isobenzopyran **3b** in 81% yield (Table 1, run 1). Synthesis of isoindoline **3c** or isoquinoline derivative **3d** was also achieved in a similar manner in high yield (runs 2 and 3). Furthermore, alkynylzinc reagent **5** could be used as a zinc reagent for this reaction, and isoindoline **3e** having a highly functionalized carbon center could be synthesized (run 4).

Encouraged by these results, we planned for the synthesis of erythrina alkaloid,[5] which is a widely distributed family of structurally interesting and biologically active natural products that each possess a tetracyclic framework. Our retrosynthetic analyses of erythraline **6a**[6a−c] and erythrocarine **6b**[6d] are shown in Scheme 3. They would be synthesized from dienyne **7** by a ruthenium-catalyzed metathesis reaction.

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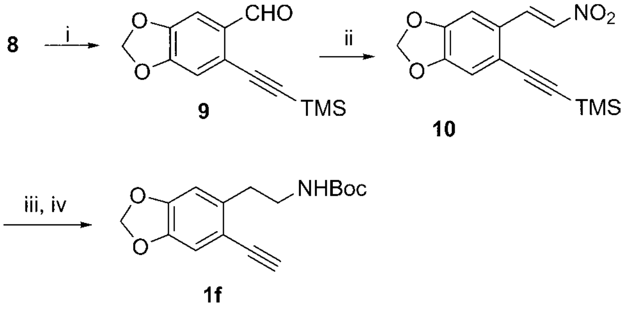
(3) (a) Takimoto, M.; Mori, M. *J. Am. Chem. Soc.* **2001**, *123*, 2895. (b) Takimoto, M.; Shimizu, K.; Mori, M. *Org. Lett.* **2001**, *3*, 3345. (c) Takimoto, M. Mori, M. *J. Am. Chem. Soc.* **2002**, *124*, 10008.

(4) Transmetalation of alkylzinc reagent to nickel, See: (a) Ikeda, S.; Kondo, K.; Sato, Y. *Chem. Lett.* **1999**, 1227. (b) Ikeda, S.; Kondo, K.; Sato, Y. *J. Org. Chem.* **1996**, *61*, 8248. (c) Oblinger, E.; Montgomery, J. *J. Am. Chem. Soc.* **1997**, *119*, 9065. (d) Sato, Y.; Takanashi, T.; Mori, M. *Organomet.* **1999**, *18*, 4891.

(5) (a) Hill, R. K. *The Alkaloids*; Manske, R. H. F., Ed.; Academic Press: New York, 1967; Vol. 9, p 281. (b) Dyke, S. F.; Quessy, S. N. *The Alkaloids*; Manske, R. H. F., Ed.; Academic Press: New York, 1981; Vol. 18, p 1.

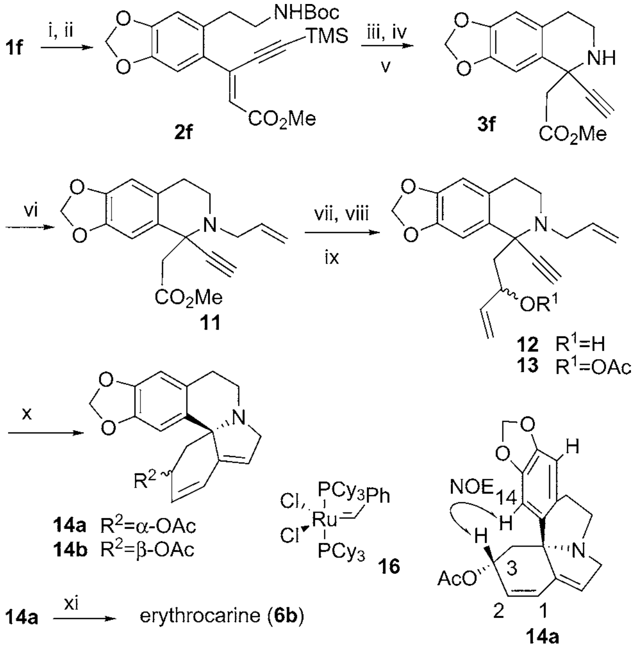
(6) Isolation of erythraline: (a) Folkers, K.; Koniuszy, F. *J. Am. Chem. Soc.* **1940**, *62*, 436. Total synthesis of erythraline: (b) Sano, T.; Toda, J.; *Heterocycles* **1982**, *18*, 229. (c) Sano, T.; Toda, J.; Kashiwaba, N.; Ohshima, T.; Tsuda, Y. *Chem. Pharm. Bull.* **1987**, *35*, 479. Erythrocarine, isolation: (d) Chawla, A. S.; Redha, F. M. J.; Jackson, A. H. *Phytochemistry* **1985**, *24*, 1821.

Scheme 4. Synthesis of Alkyne **1f**[a]



[a] Key: (i) trimethylsilylacetylene, $PdCl_2(PhCN)_2$, PPh_3, Et_3N, reflux, 30 min, quant; (ii) CH_3NO_2, NH_4OAc, AcOH, 100 °C, 7 h, 85%; (iii) $LiAlH_4$, THF−Et_2O (1:1), rt, 3 h; (iv) $(Boc)_2O$, Et_3N, 61% from **10**.

Scheme 5. Total Synthesis of Erythrocarine[a]



[a] Key: (i) CO_2, $Ni(cod)_2$ (1.1 equiv), DBU (3.3 equiv), THF, 0 °C , 1 h, then **5** (3 equiv), 0 °C, 24 h; (ii) CH_2N_2, 69% from **1f**; (iii) CF_3CO_2H, rt, 3 h; (iv) MeOH, reflux, 18 h; (v) TBAF, 76% from **2f**; (vi) allyl bromide, K_2CO_3; (vii) $LiAlH_4$; (viii) $(COCl)_2$, DMSO, Et_3N and then vinylmagnesium bromide; (ix) Ac_2O, Et_3N, DMAP, 70% from **3f**; (x) HCl then 10 mol % of **16** in CH_2Cl_2, rt, 18 h, quant; (xi) K_2CO_3, MeOH, 93%.

Synthesis of isoquinoline **7** should be achieved from **3f**, which would be obtained from **1f** by our novel synthesis of heterocycles via nickel-mediated carboxylation. For the synthesis of **1f**, commercially available **8** was chosen as a starting material.

Reaction of **8** with trimethylsilylacetylene in the presence of a palladium catalyst afforded alkyne **9**,[7] which was condensed with nitromethane to give **10**. Treatment of **10** with $LiAlH_4$ followed by protection with the ^{t}butyloxycarbonyl group gave alkyne **1f** (Scheme 4).

Carboxylation into alkyne **1f** using a nickel complex proceeded smoothly, and then alkynylzinc reagent **5** was added. After hydrolysis of the reaction mixture and then treatment with diazomethane, ester **2f** was obtained in 69% yield (Scheme 5). Deprotection of the ^{t}butyloxycarbonyl group followed by Michael addition and then deprotection of the silyl group afforded **3f** in high yield. Allylation of secondary amine followed by Swern oxidation and then addition of vinylmagnesium bromide afforded a diastereomeric mixture of alcohol **12**, whose hydroxyl group was protected with the acetyl group to give **13**. For the dienyne metathesis, **13** was treated with HCl in Et_2O because the nitrogen would coordinate to ruthenium metal.[8]

When a CH_2Cl_2 solution of dienyne hydrochloride **13**·HCl was stirred in the presence of 10 mol % of first-generation ruthenium carbene complex **16**[9] at room temperature for 18 h, the reaction proceeded smoothly, and we were very pleased to find that tetracyclic compounds **14a** and **14b** were obtained in quantitative yields in a ratio of 1 to 1. After separation of them, the NOE experiments were carried out. The results of the NOE experiment between the protons of C3 and C14 of each compound **14a** or **14b** indicate that the C3 proton of the less polar product **14a** on TLC is placed at the β-position. Treatment of **14a** with K_2CO_3 in MeOH gave alcohol, whose spectral data agreed with those of erythrocarine (**6b**) reported in the literature.[6d,10] Thus, the total synthesis of erythrocarine was achieved from commercially available 6-bromopiperonal **8** via 15 steps using our novel isoquinoline synthesis and ruthenium-catalyzed dienyne metathesis as the key steps.

The remarkable features of our synthetic method of heterocycles having a highly functionalized carbon center are as follows. An atmospheric pressure of carbon dioxide can be used. Carboxylation proceeds at 0 °C. Various substituents could be introduced on the heterocycles using a zinc reagent. Cyclization using Michael addition smoothly proceeded to give various heterocycles in high yields. Further studies are in progress.

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Supporting Information Available: Experimental details and the spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(7) Grotjahn, D. B.; Vollhardt, K. P. C. *Synthesis* **1993**, 579.

(8) Fu, G. C.; Nguyen, S. T.; Grubbs, R. H. *J. Am. Chem. Soc.* **1993**, *115*, 9856.

(9) Kim, S.-H.; Bowden, N.; Grubbs, R. H. *J. Am. Chem. Soc.* **1994**, *116*, 10801.

(10) The protons of the lower field (the vinyl, aromatic ring and methylene dioxy protons) agree with those of erythrocarine reported in the literature, but those of higher field do not agree.