Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron Letters
Tetrahedron Letters 48 (2007) 4255–4258

A three-component approach to isoquinoline derivatives by cycloaddition/Heck reaction sequence

Masato Oikawa,[a,*] Yoshiyuki Takeda,[a] Shinya Naito,[a] Daisuke Hashizume,[b] Hiroyuki Koshino[b] and Makoto Sasaki[a]

[a]*Laboratory of Biostructural Chemistry, Graduate School of Life Sciences, Tohoku University, Tsutsumidori-Amamiya, Aoba-ku, Sendai 981-8555, Japan*
[b]*Molecular Characterization Team, Advanced Development and Supporting Center, RIKEN, Hirosawa 2-1, Wako, Saitama 351-0198, Japan*

Received 13 February 2007; revised 10 April 2007; accepted 13 April 2007
Available online 21 April 2007

Abstract—Here, we report a three-component coupling reaction approach between an aldehyde, an allyloxyamine, and a maleimide toward isoquinoline derivatives. At first, an oxime *O*-allylic ether, prepared by dehydrative condensation of the aldehyde and the allyloxyamine, was reacted with the maleimide in the presence of a Pd^{2+} species. The cycloadduct obtained was then subjected to the Heck cyclization employing a Pd^{0} species to give thermodynamically stable diastereomer of isoquinoline derivatives selectively in 25–78% yields.

Not only frequently found in naturally occurring alkaloids, the di- and tetrahydroisoquinoline nuclei are but also an important pharmacophore. Typical examples include papaverine (smooth muscle relaxant),[1] saframycin-B (antitumor agent),[2] indenoisoquinoline (topoisomerase I inhibitor),[3] and narciclasine (antitumor agent).[4] Several methods have been reported to construct the isoquinoline framework, including the Bischler–Napieralski reaction approach on β-phenethylamine derivatives toward dihydroisoquinolines.[5]

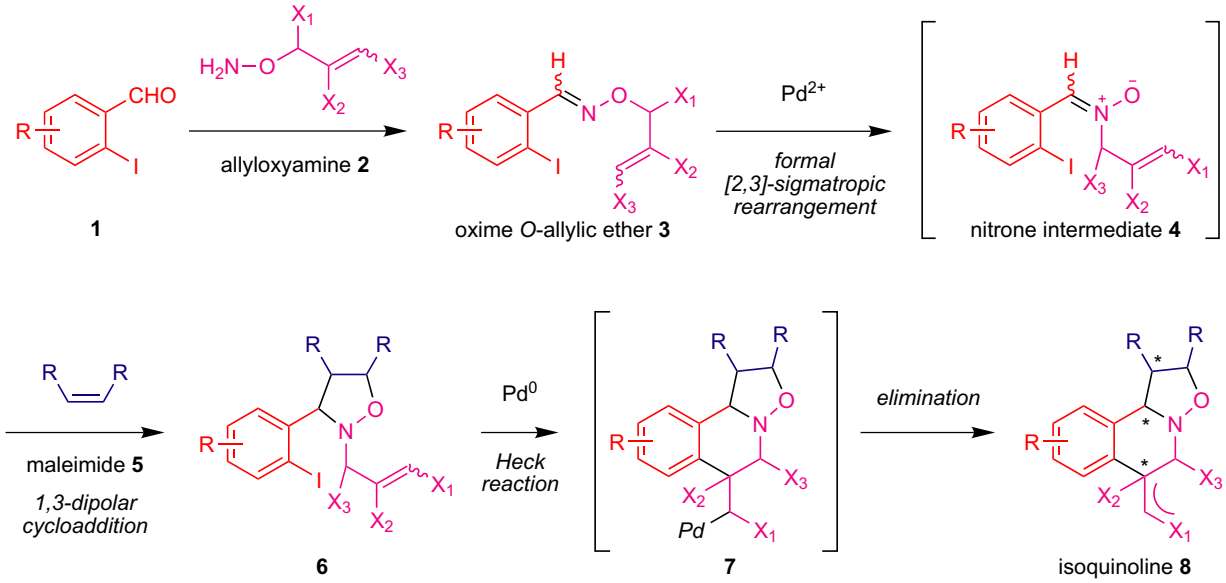
We have been interested in the construction of the isoquinoline scaffold by multicomponent coupling reactions so that a library of diverse isoquinoline derivatives can be accessible by a split-pool synthesis on insoluble polymer beads. Our approach is shown in Scheme 1. The components employed in this study are iodobenzaldehydes **1**, allyloxyamines **2**, and maleimides **5**. These components were coupled sequentially leading to di- or tetrahydroisoquinolines **8** as follows. First, aldehyde **1** and allyloxyamine **2** were dehydratively condensed to the chemically stable oxime *O*-allylic ether **3**, which was then subjected to isomerization to nitrone **4** by the action of Pd^{2+}, followed by 1,3-dipolar cyclization with the dipolarophilic maleimides **5** to give iodoolefin **6**. Upon exposure to Pd^{0}, **6** underwent intramolecular Heck cyclization to the isoquinoline derivative **8**.

Two questions arose in this work: (1) does the isomerization toward nitrone (**3**→**4**) proceed intramolecularly? and (2) is the stereochemistry of the isoquinoline derivative **8** controlled throughout the synthesis? The first question is particularly important if the synthesis is attempted in a split-pool manner, and the second issue arose since stereocontrol of oxime formation and 1,3-dipolar cycloaddition is generally quite poor.

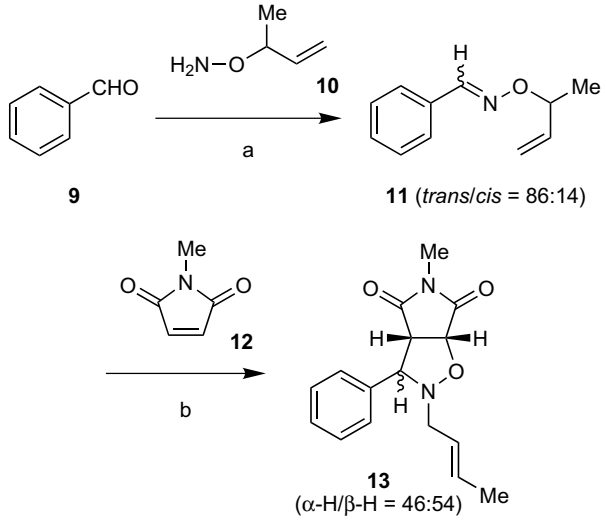
The 1,3-dipolar cycloaddition was performed by the procedure originally reported by Grigg et al.[6] Since they have examined only the oxime *O*-allyl ether and *O*-crotyl ether, we at first synthesized benzoxime *O*-(α-methyl)allyl ether (**11**)[7] by a dehydrative condensation (Na_2SO_4, THF, 60 °C) of benzaldehyde (**9**) with (α-methyl)allyloxyamine (**10**)[8] in 93% isolated yield (trans/cis = 86:14) to investigate the reaction course (Scheme 2). By exposure to 0.15 equiv of $PdCl_2(CH_3CN)_2$ in the presence of *N*-methylmaleimide (**12**), nitrone formation from **11** followed by the cycloaddition took place smoothly to give cycloadduct **13** in 85% yield with no significant stereoselectivity (54:46).[9] However, the α-methylallyl group in **11**

* Corresponding author. Tel./fax: +81 22 7178827; e-mail: mao@bios.tohoku.ac.jp

0040-4039/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2007.04.082



Scheme 1.



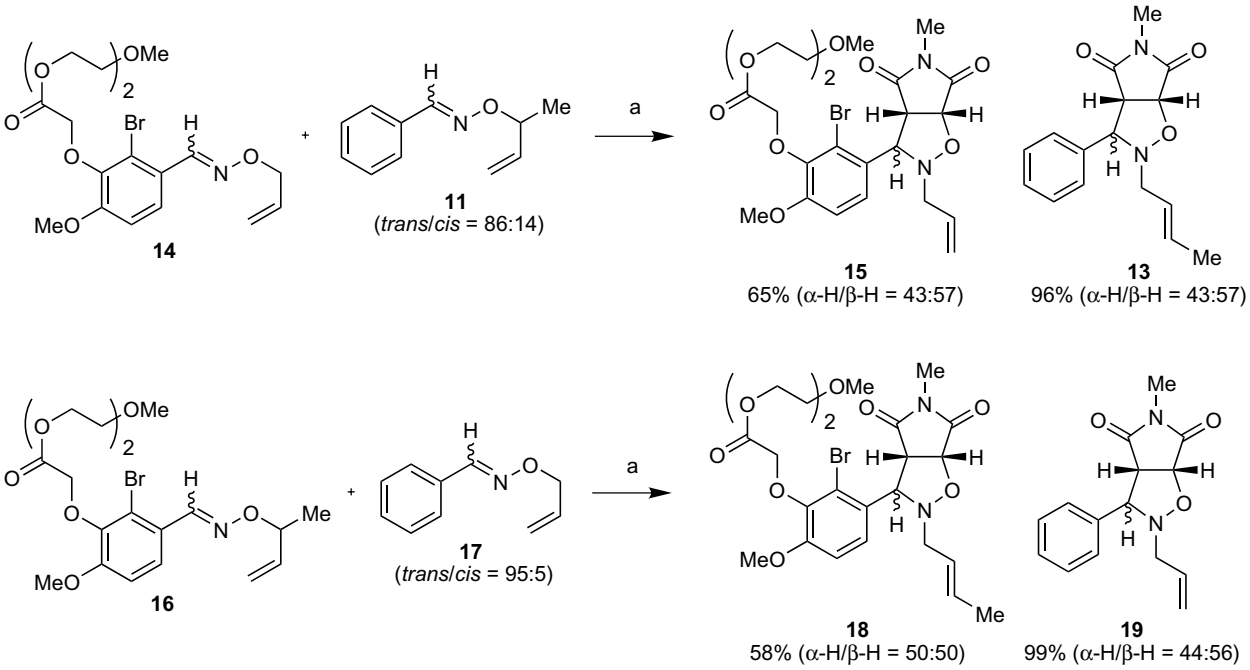
Scheme 2. Reagents and conditions: (a) Na_2SO_4, THF, 60 °C, 24 h, 93%, (b) $PdCl_2(CH_3CN)_2$ (0.15 equiv), $CHCl_3$, 60 °C, 50 h, 85%.

was completely transformed into the crotyl group in **13**, indicating that the nitrone formation proceeds by a formal [2,3]-sigmatropic rearrangement process obviously through addition/elimination of the Pd^{2+} species.

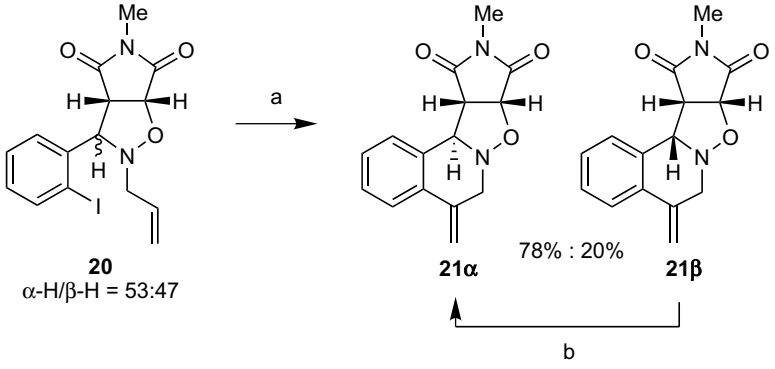
We then synthesized three oxime *O*-allylic ethers **14**, **16**[10] and **17** for crossover experiments to know if the nitrone formation has possibilities to allow scrambling of the partners (Scheme 3). At first, equimolar amounts of **11** and **14** were mixed and subjected to the cycloaddition with *N*-methylmaleimide. After 72 h, two products were chromatographically separated, and the less polar and the polar products were determined to be **13** (96%, α-H/β-H = 57:43) and **15** (65%, α-H/β-H = 57:43), respectively.[11] Another combination (**16** and **17**[6,7]) was next subjected to the reaction, and two products **18** (polar, 58%, α-H/β-H = 50:50)[11] and **19** (less polar, 99%, α-H/β-H = 56:44)[6] were also isolated cleanly. Not even trace amounts of crossover products (**18** and **19** in the former reaction, and **13** and **15** in the latter reaction) were detected, indicating that nitrone formation proceeds completely in an intramolecular fashion.

Efficient conditions for the Heck cyclization of iodoolefin **20**[12] leading to the dihydroisoquinoline scaffold were next investigated. After several experiments with various catalysts, ligands, bases, additives, and solvents, the best result was found to be achieved by employing a simple combination of 0.15 equiv of $Pd(PPh_3)_4$ and 2.0 equiv *i*-Pr_2NEt in *N*,*N*-dimethylacetamide (DMA) at 100 °C for 4 h (Scheme 4). It should be especially noted that triphenylphosphine, frequently used as an additive, causes significant reductive decomposition presumably at the N–O bond to lower the yield to 49%. Another finding in this reaction is that the diastereomeric ratio of the cyclized product **21**, α-H/β-H = 80:20, is inconsistent with that of iodoolefin **20** (α-H/β-H = 53:47) employed. Since thermodynamic equilibrium was suspected from the result, we carried out several experiments, and finally found that β-isomer **21β** completely isomerizes into α-isomer **21α** just upon heating to 100 °C for 5 h in DMA. A prolonged reaction (22 h) for the Heck reaction of **20** gave **21α** with complete stereoselectivity but in lower yield (68%) because of the decomposition. The structure of product **21α** was unambiguously determined by a single crystal X-ray diffraction analysis.[13,14] Although the mechanistic comprehension of this isomerization requires further study, this is reasonably accounted for by the energy difference (3.33 kcal/mol) between **21α** and **21β** calculated at the MMFF94S force field (CONFLEX).[14,15] By this procedure, other dihydroisoquinolines **22α** and **23α**, being different at the imide moiety, were also synthesized in 62% and 61% yields, respectively, also in a diastereoselective manner (Fig. 1).[11]

Finally, iodoolefins with substituents on the allyl moiety were subjected to the Heck cyclization (Scheme 5). As compared to the unsubstituted substrate **20**, these reac-



Scheme 3. Reagents and conditions: (a) *N*-methylmaleimide (**12**), $PdCl_2(CH_3CN)_2$ (0.15 equiv), $CHCl_3$, 60 °C, 72 h.



Scheme 4. Reagents and conditions: (a) $Pd(PPh_3)_4$ (0.15 equiv), *i*-Pr_2NEt (2.0 equiv), *N*,*N*-dimethylacetamide, 100 °C, 4 h, **21α/21β** = 78%:20%, (b) *N*,*N*-dimethylacetamide, 100 °C, 5 h, 92%.

tions on **24**–**26** were found to be sluggish, and the yields for **27**–**29** were apparently lower (33–63%). However, the point that should be much emphasized is that the stereoselectivity is completely controlled in these cases; (1) the stereochemistry of the carbon α to the N–O functionality is α-orientated as in the cases for **21α**–**23α**,[16,17] (2) the double bond takes trans configuration, and (3) another benzylic carbon nearby the allyl group is also controlled to be *R**. These stereochemistries, determined from NMR analysis, are the thermodynamically most stable configurations from the molecular modeling at

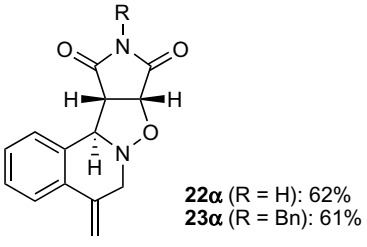
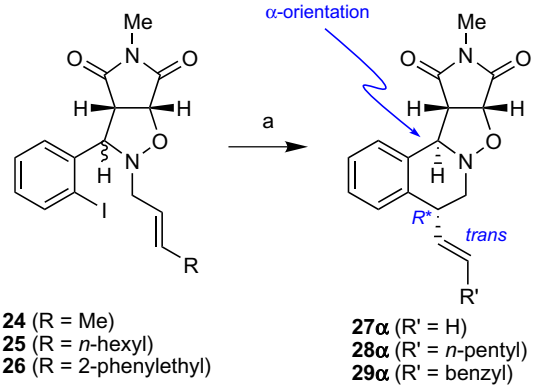


Figure 1. Dihydroisoquinolines **22α** and **23α** synthesized by the cycloaddition/Heck reaction approach.



Scheme 5. Reagents and conditions: (a) $Pd(PPh_3)_4$ (0.15 equiv), *i*-Pr_2NEt (3.0 equiv), *N*,*N*-dimethylacetamide, 100 °C, <48 h, 63% (**27α**), 33% (**28α**), 44% (**29α**).

the MMFF94S force field (CONFLEX).[14,15] In all cases, unreacted iodoolefins were recovered after the reaction.

In summary, we have developed a stereoselective three-component coupling approach to isoquinoline derivatives. Though the intermediary cycloadducts **6** were obtained as a diastereomeric mixture, the finally synthesized isoquinolines **8** were diastereomerically controlled to one isomer under thermodynamic conditions by an as yet unclear mechanism. In addition, we have given clear evidence for the intramolecular, formal [2,3]-sigmatropic rearrangement of the Pd^{2+}-catalyzed nitrone formation. Work is in progress toward realization of a di- and tetrahydroisoquinoline library, and application of the present methodology to biologically important natural products.

References and notes

1. Kaneda, T.; Takeuchi, Y.; Matsui, H.; Shimizu, K.; Urakawa, N.; Nakajyo, S. *J. Pharmacol. Sci.* **2005**, *98*, 275–282.
2. Mikami, Y.; Yokoyama, K.; Tabeta, H.; Nakagaki, K.; Arai, T. *J. Pharm. Dyn.* **1981**, *4*, 282–286.
3. Marchand, C.; Antony, S.; Kohn, K. W.; Cushman, M.; Ioanoviciu, A.; Staker, B. L.; Burgin, A. B.; Stewart, L.; Pommier, Y. *Mol. Cancer Ther.* **2006**, *5*, 287–295.
4. Pettit, G. R.; Gaddamidi, V.; Herald, D. L.; Singh, S. B.; Cragg, G. M.; Schmidt, J. M.; Boettner, F. E.; Williams, M.; Sagawa, Y. *J. Nat. Prod.* **1986**, *49*, 995–1002.
5. Whaley, W. M.; Govindachari, T. R. The Preparation of 3,4-Dihydroisoquinolines and Related Compounds by the Bischler–Napieralski Reaction. In *Organic Reactions*; 1951; Vol. 6, pp 74.
6. Grigg, R.; Markandu, J. *Tetrahedron Lett.* **1991**, *32*, 279–282.
7. Davies, S. G.; Fox, J. F.; Jones, S.; Price, A. J.; Sanz, M. A.; Sellers, T. G. R.; Smith, A. D.; Teixeira, F. C. *J. Chem. Soc., Perkin Trans. 1* **2002**, 1757–1765.
8. Prepared from 2-but-3-enyl chloride and *N*-hydroxyphthalimide over 2 steps (34% yield) by a reported procedure, see: Irie, H.; Katayama, I.; Mizuno, Y.; Koyama, J.; Suzuta, Y. *Heterocycles* **1979**, *12*, 771–773; Koyama, J.; Sugita, T.; Suzuta, Y.; Irie, H. *Chem. Pharm. Bull.* **1983**, *31*, 2601–2606.
9. The change of the diastereomeric ratio in this 1,3-dipolar cycloaddition would be attributed to the isomerization of the intermediary nitrone.[6] The stereochemistries of these products (**13α**, **13β**) were determined by ^{1}H–^{1}H *J*-coupling constants and NOESY experiments, and finally confirmed by X-ray diffraction analysis of **21α**.
10. Oxime *O*-allylic ethers **14** and **16** were prepared from 2-bromo-3-hydroxy-4-methoxybenzaldehyde over 4 and 5 steps for 60% and 46% yields, respectively.
11. The stereochemistries of these products were determined by ^{1}H–^{1}H *J*-coupling constants and NOESY experiments, and finally confirmed by analogy with the synthesis of **21α**.
12. Prepared from 2-iodobenzaldehyde as for **13** shown in Scheme 2 over 2 steps (66% yield).
13. The crystallographic data for **21α** have been deposited at the Cambridge Crystallographic Data Centre and allocated the deposition number, CCDC 620027. Dihydroisoquinoline **21α** has been also recently synthesized by an alternative four-component coupling approach, see: Dondas, H. A.; Fishwick, C. W. G.; Gai, X. J.; Grigg, R.; Kilner, C.; Dumrongchai, N.; Kongkathip, B.; Kongkathip, N.; Polysuk, C.; Sridharan, V. *Angew. Chem., Int. Ed.* **2005**, *44*, 7570–7574.
14. The details will be reported in the full account of this research.
15. Calculated on BARISTA software (BARISTA, version 1.2.2; CONFLEX Co., Yotsuya 4-30, Shinjuku-ku, Tokyo 160-0004, Japan).
16. A considerable amount (30%) of the trisubstituted, olefin isomer of **27α** was also detected in the Heck cyclization of **24**.
17. In the cases for the synthesis of **28α** and **29α**, unreacted β-isomer of **25** (33%) and **26** (33%) were recovered after the reaction, indicating these β-isomers are less reactive than the α-isomer. Because prolonged reaction was found to cause decomposition from the experiment of **20**, we are currently optimizing the other reaction conditions for this transformation.