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Synthesis of Medium Ring Heterocycles Using an Intramolecular Heck Reaction

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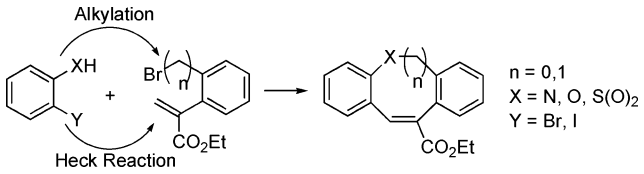
ABSTRACT



Historically, general convergent syntheses of medium ring heterocycles have been difficult to develop. Herein, we describe the synthesis of five classes of heterocycles: dihydrodibenzo[*b*,*f*]azepine, -oxocine, and -thiocine and dibenzo[*b*,*f*]azepine and -oxepine using a strategy of alkylation followed by highly selective intramolecular Heck arylation reaction. The hetero-tricyclic compounds were available in only two steps starting from commercially available starting materials.

Many natural products, drugs, and preclinical leads contain medium-size heterocycles fused to aryl rings. For example carbamazine (Tegretol), a dihydro[*b*,*f*]azepine,[1] is an important antiepileptic drug.[2] A general synthesis for seven- and eight-membered heterotricyclic compounds of these classes is missing. Therefore we developed a novel alkylation−Heck reaction sequence giving access to these important pharmaceutical building blocks.

The intramolecular Heck reaction has been widely used for the synthesis of cyclic natural products[3] and was therefore highly attractive. However, whereas intermolecular coupling between aryl halides and monoaryl-substituted olefins is highly regio- and stereoselective,[4] the intramolecular version proceeds with a wide range of regioselectivity depending on ring size and reaction conditions.[3,5] Low regioselectivity is generally observed for the formation dibenzo[*a*,*e*]annulene-like molecules.[6] In contrast, the intramolecular Heck coupling between aryl halides and α-substituted acrylates proceeds with high regio- and stereoselectivity for seven- and eight-membered rings to give trisubstituted olefins.[7] Herein, we present an intramolecular Heck coupling between α-aryl-substituted acrylates and aryl halides using the general phosphine-free reaction conditions developed by Buchwald and co-workers[8] to synthesize compounds such as dihydrobenzo[*b*,*f*]azocines.

Aniline derivatives (**1** and **2**) and phenols (**3** and **4**) were alkylated in good yield using substituted benzyl bromide **11** to give the products **5**−**8** (Scheme 1).

The Heck reaction was carried out in *N*,*N*-dimethylacetamide using Cy_2NMe as a base, Et_4NCl as a promoter,[9] and

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(3) For a review, see: Link, J. *Org. React.* **2002**, *60*, 157.

(4) For a recent review see: (a) Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed.* **2001**, *41*, 4176. (b) Beletskaya, I. P.; Cheprakov, A. V. *Chem. Rev.* **2000**, *100*, 3009.

(5) For a recent example, see: Geng, X.; Miller, L. M.; Lin S.; Ojima, I. *Org. Lett.* **2003**, *5*, 3733.

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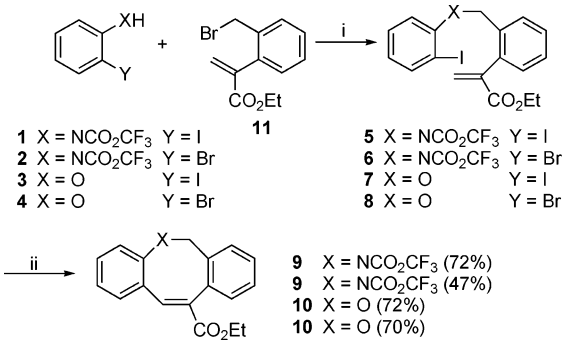
Scheme 1. Synthesis of Dibenzo[*b*,*f*]azocine and Dibenzo[*b*,*f*]oxocine Derivatives[a]

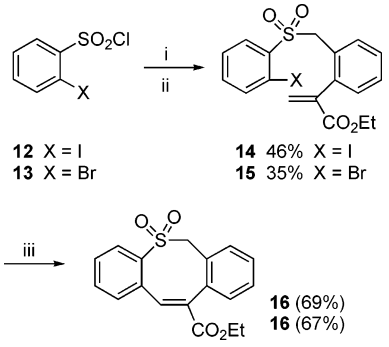


[a] Reagents and conditions: (i) K_2CO_3, acetone, 12 h, 50 °C, yields 72−82%; (ii) $Pd(OAc)_2$ (0.03 equiv), Et_4NCl, Cy_2NMe, *N*,*N*-dimethylacetamide, 4−12 h, 95 °C.

$Pd(OAc)_2$ as precatalyst. All reactions gave the 8-*endo* products **9** and **10** exclusively in up to 72% yield. Bromo analogues **6** and **8** required longer reaction times (12 h) in contrast to the corresponding iodo compounds **5** and **7** (4 h). The Heck reaction with compound **6** gave dibenzo[*b*,*f*]-azocine **9** in only 47% yield as the major product along with the formation of some uncharacterized compounds.

The sequence described could not be applied to the synthesis of 6*H*-dibenzo[*b*,*f*]thiocine because thiols undergo a conjugate addition reaction with the unsaturated esters under basic conditions.[10] Instead, 2-iodobenzenesulfonyl chloride **12**[11] and 2-bromobenzenesulfonyl chloride **13** were alkylated with **11** under reductive conditions[12] to give the products **14** and **15** in 46% and 35% yield, respectively (Scheme 2).

Scheme 2. Synthesis of 5,5-Dioxo-5,6-dihydro-dibenzo[*b*,*f*]thiocine-11-carboxylic Acid Ethyl Ester[a]

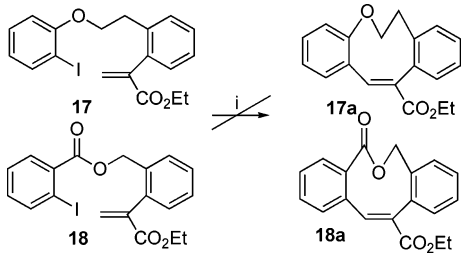


[a] Reagents and conditions: (i) NaH_2PO_4, Na_2SO_3, water, 12 h, 60 °C; (ii) **11**, acetone, 50 °C, 12 h; (iii) $Pd(OAc)_2$ (0.03 equiv), Et_4NCl, Cy_2NMe, *N*,*N*-dimethylacetamide, 12 h, 100 °C.

Both the iodo and bromo derivatives **14** and **15** afforded cyclic products in good yield when exposed to the Heck reaction conditions (67% and 69%), giving a novel cyclic sulfone **16**.

All attempts to apply the new method to the synthesis of nine-membered rings (**17a** and **18a**) failed (Scheme 3).

Scheme 3. Attempted Synthesis of Nine-Membered Rings[a]

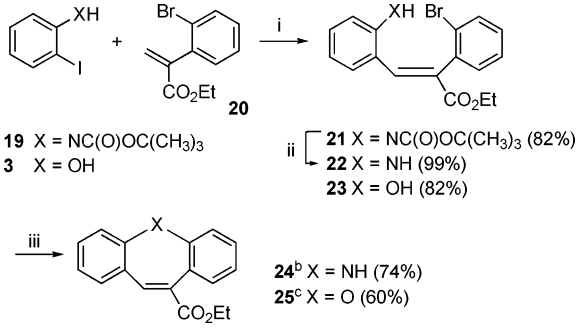


[a] Reagents and conditions: (i) $Pd(OAc)_2$ (0.03 equiv), Et_4NCl, Cy_2NMe, *N*,*N*-dimethylacetamide, 12 h, 100 °C.

The standard Heck reaction conditions gave a complex mixture consisting of intermolecular Heck reaction products, starting material, and various uncharacterized degradation products.

In contrast, the synthesis of dibenzo[*b*,*f*]azepine and dibenzo[*b*,*f*]oxepine derivatives could be achieved by varying the reaction sequence (Scheme 4).

Scheme 4. Synthesis of Dibenzo[*b*,*f*]azepine and Dibenzo[*b*,*f*]oxepine Derivatives[a]



[a] Reagents and conditions: (i) $Pd(OAc)_2$ (0.03 equiv), Et_4NCl, Cy_2NMe, *N*,*N*-dimethylacetamide, 12 h, 100 °C; (ii) TFA, CH_2Cl_2; (iii) (b) K_3PO_4, $Pd(t\text{-}Bu_3P)_2$ (0.03 equiv), toluene, 16 h, 90 °C; (c) K_3PO_4 $Pd(OAc)_2$ (0.03 equiv), 2-(di-*tert*-butylphosphino)biphenyl (0.06 equiv), toluene, 16 h, 90 °C.

The Heck reaction was carried out first, giving a selective reaction with the aryl iodide in the presence of an aryl bromide (**20**). Very good chemoselectivity was observed, giving products **21** and **23** exclusively in 82% yield.

Applying the $Pd(t\text{-}Bu_3P)_2$-catalyzed amination reaction conditions developed by Hartwig and co-workers[13] failed to

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(13) Hartwig, J. F.; Kawatsura, M.; Hauck, S. I.; Shaughnessy, K. H.; Alcazar-Roman, L. *J. Org. Chem.* **1999**, *64*, 5575.

give the seven-membered ring of compound **21**. Therefore, the carbamate **21** was deprotected using TFA to give the free aniline **22**. In contrast to the compound **21**, compound **22** gave the dibenzo[*b*,*f*]azepine **24** in 74% yield. Phenol **23** was obtained in 82% yield using 2-iodophenol and **20**. The cyclization of **23** using the catalytic conditions developed by Buchwald and co-workers[14] gave **25** in 60% yield.

In summary, we have developed a general strategy for the synthesis of dibenzo[*b*,*f*]azepine, -oxocine, -thiocine, -azepine, and -oxepine using transition metal catalysis. The advantages of this strategy are (1) a very direct and convergent synthesis of tricyclic compounds and (2) the tolerance of various functional groups. Application of this strategy to the synthesis of a heterocyclic library is under way and will be reported in due course.

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Supporting Information Available: Complete description of the experimental detail and product characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

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