Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron Letters
Tetrahedron Letters 47 (2006) 3225–3228

Synthesis of fused imidazo-pyridine and -azepine derivatives by sequential van Leusen/Heck reactions

Xenia Beebe,* Vijaya Gracias and Stevan W. Djuric

Scaffold-Oriented Synthesis, Medicinal Chemistry Technologies, Abbott Laboratories, R4CP, AP10, 100 Abbott Park Road, Abbott Park, IL 60064-6099, USA

Received 13 December 2005; accepted 9 March 2006
Available online 29 March 2006

Abstract—Fused imidazo-pyridine and -azepine derivatives were synthesized using a sequential van Leusen/intramolecular Heck protocol. The combination of a multicomponent reaction followed by an intramolecular carbon–carbon bond forming reaction generates heterocycles of significant molecular complexity from readily available starting materials in just two steps.

With the advent of high throughput organic synthesis, the utility of multicomponent reactions (MCRs) has been exploited due to the ability to rapidly assemble complex structures from readily available starting materials.[1] Coupled with post-modification reactions, MCRs are powerful tools to synthesize compounds of biological interest.[2] In an effort to synthesize novel scaffolds of medicinal importance, our group has employed post-modifications of the Ugi reaction including the sequential Ugi/Heck, Ugi/INOC, Ugi/alkyne–azide cyclization, and Ugi/carbonylation–amidation.[3]

The intramolecular Heck is a powerful carbon–carbon bond forming cyclization reaction.[4] It has recently been used in a sequential manner for the synthesis of multiple natural products and heterocycles including a sequential Heck-iminium ion cyclization,[5] an amide-aldehyde-dienophile MCR/Heck for the synthesis of phenanthridones,[6] an alkenyl amination/Heck for the synthesis of indoles,[7] and an Ugi–Heck for the synthesis of isoquinolines.[8]

Recently, we reported the use of the van Leusen synthesis of imidazoles[9] in sequential van Leusen/RCM, van Leusen/enyne metathesis, and van Leusen/alkyne–azide cylcloaddition reactions.[10] Herein, we report an extension of our previous work wherein we utilize the van Leusen imidazole synthesis followed by an intramolecular Heck reaction to form imidazo[1,5-*a*]pyridines and imidazo[1,5-*a*]azepines as outlined in Figure 1. The imidazoles were synthesized using an appropriate aldehyde containing a vinylogous bromide and condensing it with an amine containing a double bond. Following pre-formation of the imine, the desired tosylmethylisocyanide (TosMIC) reagent and base were added and the cyclization allowed to proceed at room temperature. The imidazole was then isolated and submitted to the palladium-catalyzed Heck reaction to form the desired imidazo-[1,5-*a*]pyridine or imidazo[1,5-*a*]azepine depending on the chain length of the amine containing moiety.

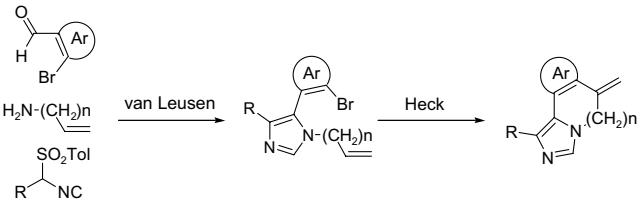


Figure 1. General strategy.

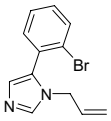
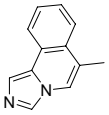
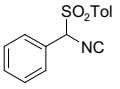
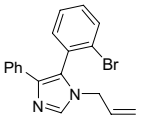
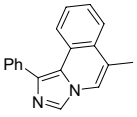
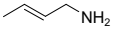
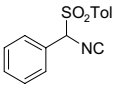
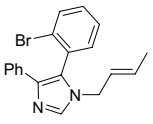
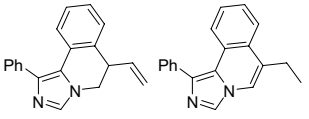
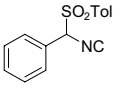
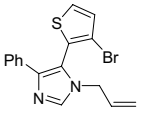
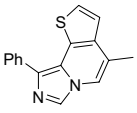
Imidazo[1,5-*a*]pyridines are synthetically challenging scaffolds and have previously been synthesized starting with pyridines and cyclizing to form the imidazole moiety.[11] Our method represents a concise two-step synthesis using milder conditions to form the desired imidazo[1,5-*a*]pyridines in good yields. Furthermore, imidazo[1,5-*a*]azepines are novel heterocycles.

Table 1 shows examples of the types of imidazo[1,5-*a*]-pyridines that can be synthesized using the methodology described above. In entry 1, *o*-bromobenzaldehyde was

* Corresponding author. E-mail: xenia.b.searle@abbott.com

0040-4039/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2006.03.056

Table 1. Imidazole and imidazo[1,5-*a*]pyridine products obtained from the van Leusen/Heck reaction sequence[14]

Entry	Aldehyde	Amine	TosMIC	van Leusen product	Yield (%)	Heck product	Yield (%)
1					7		57
2					55		42
3		 cis/trans 2:3		 cis/trans 2:3	93		96 (2.4:1)
4					24		64

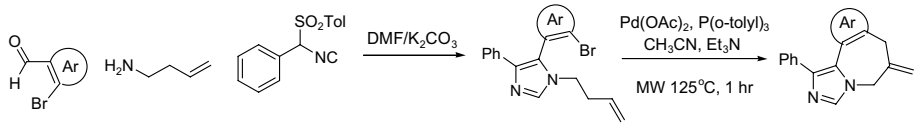
condensed with allylamine to form the imine and then treated with the unsubstituted TosMIC in the presence of base to give imidazole 1 in low yield. TosMIC itself is generally unreactive in the cyclization with imines.[9d] The yields of the imidazoles were then greatly improved by using phenylTosMIC as shown in entries 2–4. Several conditions were surveyed for the intramolecular Heck reactions, and an optimized procedure, which used $Pd(OAc)_2$ (0.1 equiv), $(o\text{-tol})_3P$ (0.4 equiv), Et_3N (2.5 equiv) in acetonitrile was discovered. The reactions were degassed and subjected to microwave heating at 125 °C for 1 h. In entries 1, 2, and 4 the external double bond migrated to give the fully aromatic products as shown in Table 1.

In entry 3, a 2:3 mixture of cis/trans double bonds in the 3-butenamine resulted in a 2:3 mixture of olefins in the imidazole product. The intramolecular Heck cyclization resulted in a migration of the double bond to the terminal position as the major product, with migration of the double bond to give the fully aromatic compound as the minor product. The Heck reaction has been used in the synthesis of indazoles[12] but this is the first instance we know of where the intramolecular Heck reaction is used for the synthesis of a substituted imidazo ring system.

The synthesis of imidazo[1,5-*a*]azepines was carried out using 4-butenamine[13] and phenylTosMIC as shown in Scheme 1. Again, aldehydes containing a vinylogous bromide were condensed with 4-butenamine and then treated with phenylTosMIC and potassium carbonate to give the corresponding imidazoles. The imidazoles were then subjected to the Heck reaction as described previously to give the desired imidazo[1,5-*a*]azepines. As mentioned above, the synthesis of this particular chemotype has not been previously reported in the literature.

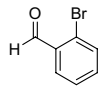
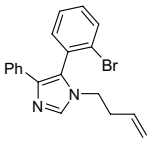
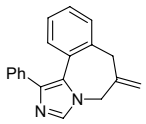
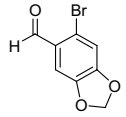
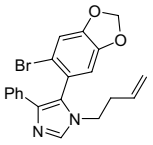
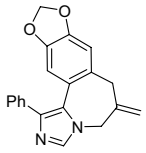
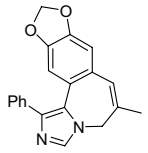
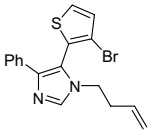
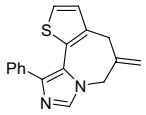
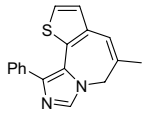
Representative examples of the methodology are shown in Table 2. In entry 5, *o*-bromobenzaldehyde was condensed with 4-butenamine and treated with phenylTosMIC to give the desired imidazole in good yield. The imidazole was then subjected to the Heck conditions and the cyclization to the azepine proceeded smoothly to afford a single product. In entries 6 and 7, the use of heterocyclic aldehydes resulted in the production of novel functionalized azepines. The Heck products represented a mixture of the minor product containing the exocyclic double bond and the major product wherein the double bond had migrated to a conjugated position in the heterocycle. Many different catalyst systems were tried but double bond migration could not be prevented.

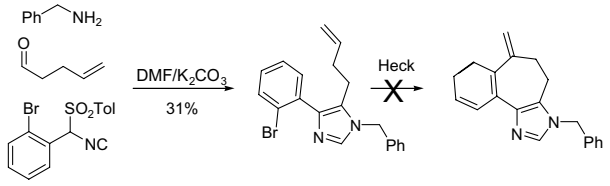
The scope of the reaction sequence merits some comment. Other combinations of reagents were tried including the reaction of *o*-bromophenylTosMIC with benzylamine and 4-pentenal to give the corresponding imidazole as shown in Scheme 2. The resulting aryl bromide could not be induced to undergo the Heck cyclization to the imidazo azepine. The typical Heck conditions resulted in the recovered starting material, and forcing conditions gave debrominated material without cycliza-



Scheme 1. General synthesis of imidazo[1,5-*a*]azepines.

Table 2. Imidazole and imidazo[1,5-*a*]azepine products obtained from the van Leusen/Heck reaction sequence[14]

Entry	Aldehyde	van Leusen product	Yield (%)	Heck product(s)	Yield (%)
5			60		66
6			84	 	74 (1:2)
7			30	 	66 (1:2)



Scheme 2. Attempted synthesis of imidazo-benzazulene.

tion. This may be due to the palladacycle[15] coordinating with the imidazole nitrogen and then locking the aryl bromide away from the terminal double bond.

In addition, the van Leusen MCR with 2-amino-4-pentenoic acid methyl ester, *o*-bromobenzaldehyde and phenylTosMIC gave none of the desired imidazole product. This could be due to steric congestion of the reaction centers in the cyclization. The van Leusen cyclization also did not work with *o*-bromoaniline and 4-pentenal, probably due to the steric hindrance and lack of reactivity of the aniline component.

In conclusion, we have developed a two-step synthetic sequence utilizing the van Leusen imidazole synthesis followed by the Heck cyclization to give imidazo pyridines and imidazo azepines in an efficient manner. This methodology demonstrates a unique multicomponent reaction/post-modification reaction sequence that allows access to both difficultly accessible and unique structural chemotypes.

Acknowledgments

The authors thank J. T. Link for insightful comments and critical reading of the manuscript, and the Structural Chemistry group for NMR and MS data.

References and notes

1. For recent reviews see: (a) Hulme, C.; Gore, V. *Curr. Med. Chem.* **2003**, *10*, 51–80; (b) Hulme, C.; Nixey, T. *Curr. Opin. Drug Discovery Today* **2003**, *6*, 921–929; For a recent synthesis of imidazo[1,2-*a*]pyridines see: Schwerkoske, J.; Masquelin, T.; Perun, T.; Hulme, C. *Tetrahedron Lett.* **2005**, *48*, 8355–8357.
2. Marcaccini, S.; Torroba, T. In *Multicomponent Reactions*; Zhu, J., Bienayme, H., Eds.; Wiley-VCH: Weinheim, 2005, Chapter 2.
3. (a) Gracias, V.; Moore, J. D.; Djuric, S. W. *Tetrahedron Lett.* **2004**, *45*, 417–420; (b) Akritopoulou-Zanze, I.; Gracias, V.; Moore, J. D.; Djuric, S. W. *Tetrahedron Lett.* **2004**, *45*, 3421–3423; (c) Akritopoulou-Zanze, I.; Gracias, V.; Djuric, S. *Tetrahedron Lett.* **2004**, *45*, 8439–8441; (d) Vasudevan, A.; Verzal, M. K. *Tetrahedron Lett.* **2005**, *46*, 1697–1701.
4. (a) Link, J. T. In *Organic Reactions*; Wiley: Hoboken, NJ, 2002; Vol. 60, Chapter 2; (b) Dounay, A. B.; Overman, L E. *Chem. Rev.* **2003**, *103*, 2945–2963.
5. Dounay, A. B.; Overman, L. E.; Wrobleski, A. D. *J. Am. Chem. Soc.* **2005**, *127*, 10186–10187.
6. von Wangelin, A. J.; Neumann, H.; Gordes, D.; Hubner, S.; Wendler, C.; Klaus, S.; Strubing, D.; Spannenberg, A.; Jiao, H.; El Firdoussi, L.; Thurow, K.; Stoll, N.; Beller, M. *Synthesis* **2005**, *12*, 2029–2038.
7. Barluenga, J.; Fernandez, M. A.; Aznar, F.; Valdes, C. *Chem. Eur. J.* **2005**, *11*, 2276–2283.
8. Xiang, Z.; Luo, T.; Lu, K.; Cui, J.; Shi, X.; Fathi, R.; Chen, J.; Yang, Z. *Org. Lett.* **2004**, *6*, 3155–3158.
9. (a) van Leusen, A. M.; Wilderman, J.; Oldenzeil, O. H. *J. Org. Chem.* **1977**, *42*, 1153–1159; (b) van Leusen, A. M. *Lect. Heterocycl. Chem.* **1980**, *5*, S-111; (c) van Nispen, S. P. J. M.; Mensink, C.; van Leusen, A. M. *Tetrahedron Lett.* **1980**, *21*, 3723–3726; (d) Sisko, J.; Kassick, A. J.; Mellinger, M.; Filan, J. J.; Allen, A.; Olsen, M. A. *J. Org. Chem.* **2000**, *65*, 1516–1524; (e) Almansa, C.; Alton, J.; de Arriba, A. F.; Cavalcanti, F. L.; Escamilla, I.; Gomez, L. A.; Miralles, A.; Soliva, R.; Bartroli, J.; Carceller, E.; Merlos, M.; Garcia-Rafanell, J. *J. Med. Chem.* **2003**, *46*, 3463–3475.
10. (a) Gracias, V.; Gasiecki, A. F.; Djuric, S. W. *Org. Lett.* **2005**, *7*, 3183–3186; (b) Gracias, V.; Gasiecki, A. F.; Djuric, S. W. *Tetrahedron Lett.* **2005**, *46*, 9049–9052; Gracias, V.; Darczak, D.; Gasiecki, A. F.; Djuric, S. W. *Tetrahedron Lett.* **2005**, *46*, 9053–9056.
11. (a) Bluhm, M. E.; Ciesielski, M.; Gorls, H.; Doring, M. *Angew. Chem., Int. Ed.* **2002**, *41*, 2962–2965; (b) Langry, K. C. *J. Org. Chem.* **1991**, *56*, 2400–2404; (c) Murashima, T.; Nishi, K.; Nakamoto, K.; Kato, A.; Tamai, R.; Uno, H.; Ono, N. *Heterocycles* **2002**, *58*, 301–310.

12. (a) Kalinin, A. V.; Chauder, B. A.; Rakhit, S.; Snieckus, V. *Org. Lett.* **2003**, *5*, 3519–3521; (b) Lee, K. L.; Goh, J. B.; Martin, S. F. *Tetrahedron Lett.* **2001**, *42*, 1635–1638; (c) Harayama, T.; Sato, T.; Hori, A.; Abe, H.; Takeuchi, Y. *Synlett* **2003**, 1141–1145.
13. Jacobson, M. A.; Williard, P. G. *J. Org. Chem.* **2002**, *67*, 3915–3918.
14. All compounds shown were isolated and characterized by ^{1}H NMR and MS. Representative example for the two-step reaction sequence from entry 2 (Table 1): A solution of *o*-bromobenzaldehyde (62 μL, 0.53 mmol) and allylamine (40 μL, 0.53 mmol) was stirred in 0.5 mL methanol for 30 min, then phenylTosMIC (145 mg, 0.53 mmol) and K_2CO_3 (110 mg, 0.80 mmol) followed by 0.5 mL of DME were added and the solution stirred at rt overnight. Aqueous workup and extraction with dichloromethane, followed by removal of solvent in vacuo and purification of the crude material using silica gel chromatography with ethyl acetate/hexanes gave 99 mg (55%) of the desired imidazole: ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 4.29 (dd, $J = 15.80$, 5.98 Hz, 1H), 4.47 (dd, $J = 15.65$, 5.83 Hz, 1H), 5.07 (d, $J = 17.18$ Hz, 1H), 5.19 (d, $J = 10.13$ Hz, 1H), 5.71–5.94 (m, 1H), 7.13–7.27 (m, 3H), 7.29–7.43 (m, 3H), 7.43–7.49 (m, 2H), 7.75 (dd, $J = 7.52$, 1.69 Hz, 1H), 8.02 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ ppm 48.2, 119.3, 126.2, 126.3, 127.1, 127.3, 128.0, 128.4, 128.5, 131.1, 131.2, 132.0, 132.6, 133.3, 133.6, 136.3; MS (ESI M+H) 339, 341 (d, Br). To a degassed solution of the imidazole (53 mg, 0.16 mmol) and Et_3N (54 μL, 0.39 mmol) was added $Pd(OAc)_2$ (3.5 mg, 0.02 mmol) and of $(o\text{-tol})_3P$ (19 mg, 0.06 mmol) and the reaction degassed again. The reaction was then heated under microwave conditions in a CEM synthesizer at 125 °C for 60 min. The reaction was cooled and purified using silica gel chromatography and ethyl acetate/hexanes to give 17 mg (42%) of a white solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 2.43 (s, 3H), 7.28–7.36 (m, 1H), 7.38–7.54 (m, 4H), 7.63–7.70 (m, 2H), 7.71–7.76 (m, 2H), 8.10–8.17 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ ppm 16.4, 118.9, 120.2, 122.6, 122.8, 124.0, 125.2, 126.9, 127.6, 127.7, 128.3, 128.5, 128.7, 128.8, 129.5, 134.5, 135.8; MS (ESI M+H) 259.
15. Herrmann, W. A.; Brossmer, C.; Ofele, K.; Reisinger, C.; Priermeier, M. B.; Beller, M.; Fischer, H. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1844–1848.