Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron Letters
Tetrahedron Letters 47 (2006) 8873–8876

Synthesis of fused imidazole rings by sequential van Leusen/C–H bond activation

Vijaya Gracias,* Alan F. Gasiecki, Thomas G. Pagano and Stevan W. Djuric

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

Received 13 September 2006; revised 9 October 2006; accepted 11 October 2006

Abstract—A concise route to access fused imidazole rings employing the van Leusen three-component reaction followed by a Pd/Cu catalyzed intramolecular C-arylation is reported. The reaction was found to be general and the products were formed in moderate to excellent yields using the two-step reaction sequence.

Multicomponent reactions (MCRs) have been extensively exploited in organic and diversity-oriented synthesis mostly due to their ability to rapidly assemble complex structures in simple one-step transformations from readily available starting materials.[1] Combined with post-modification reactions, MCRs allow access to richly functionalized heterocyclic molecules.[2] As part of our efforts to develop new routes to access novel heterocyclic structures using MCRs coupled with post-modification reactions, we have recently reported the synthesis of imidazoles employing sequential van Leusen/RCM, van Leusen/enyne metathesis, van Leusen/alkyne–azide cycloadditions and van Leusen/Heck reactions.[3] We now present a van Leusen imidazole synthesis[4] followed by an intramolecular C-2 arylation to form fused imidazoles.

The direct C–H activation of heteroaromatics represents an important carbon–carbon bond forming reaction in organic synthesis.[5] There are reports of palladium-catalyzed[6] and rhodium-catalyzed[7] C-arylation of azoles with aryl halides that allow for direct C–C bond formation without the need for prior functionalization of the azole core. More recently, this reaction has been found to proceed even under base-free and ligand-free conditions.[8] Herein, we report an intramolecular variant of this chemistry between a tethered aryl halide and the imidazole ring via a C-arylation reaction to give fused imidazoles (Fig. 1).

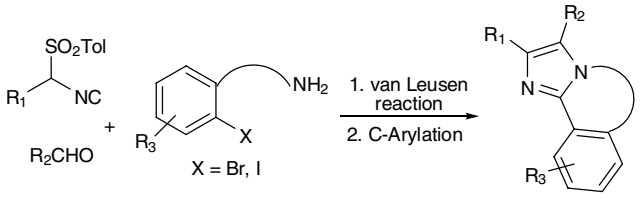


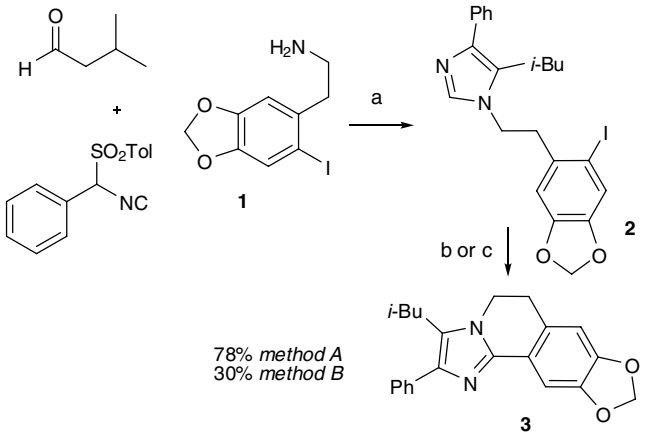
Figure 1. General strategy to fused imidazoles.

This chemistry allows access to 5*H*-imidazo[2,1-*a*]isoindole, 5,6-dihydroimidazo[2,1-*a*]isoquinoline and 6,7-dihydro-5*H*-benzo[*c*]imidazo[1,2-*a*]azepine rings depending on the tether length of the amine used. An alternate route to synthesize the 5,6-dihydroimidazo[2,1-*a*]-isoquinoline system, utilizing radical cyclization reactions of tethered aryl halides onto imidazole rings has been reported.[9] The imidazole precursors in this report were prepared via alkylation chemistry. Our method uses the van Leusen reaction to assemble the imidazoles followed by transition metal catalyzed C–C bond formation.

Isovaleraldehyde was condensed with 2-iodo piperonylamine **1** in DMF to form the imine, followed by the addition of phenyl tosylmethylisocyanide (TOSMIC) and K_2CO_3. The reaction was heated at 60 °C for 14 h to provide imidazole **2** in an 85% yield. Substrate **2** was subsequently converted to imidazole **3** in a 78% yield using Pd-mediated conditions. A combination of $Pd(OAc)_2$ (10 mol %), PPh_3 (0.2 equiv), CuI (2.0 equiv), $CsCO_3$ (1.0 equiv) in DMF at 140 °C for 14 h (method

* Corresponding author. Tel.: +1 847 937 6324; fax: +1 847 935 0310; e-mail: vijaya.gracias@abbott.com

0040-4039/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2006.10.051

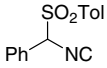
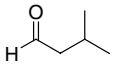
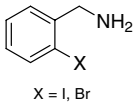
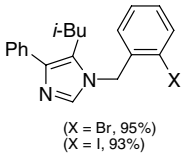
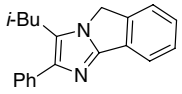
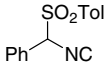
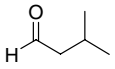
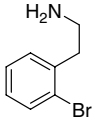
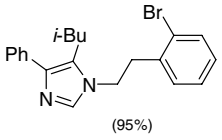
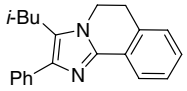
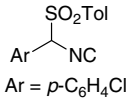
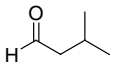
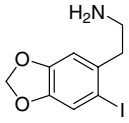
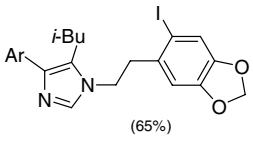
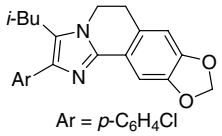
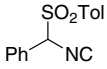
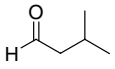
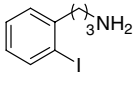
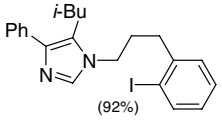
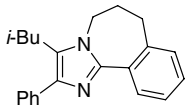
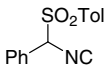
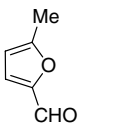
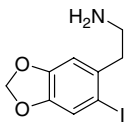
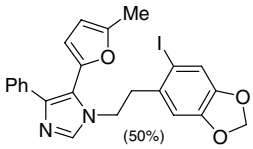
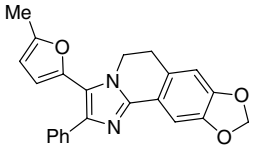
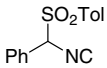
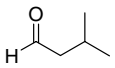
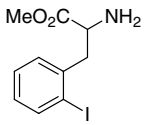
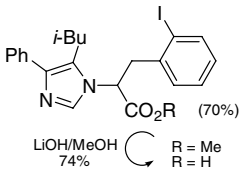
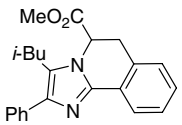


Scheme 1. Reagents and conditions: (a) DMF, K_2CO_3, 85%; (b) $Pd(OAc)_2$, PPh_3, CuI, Cs_2CO_3, DMF 140 °C, 14 h, (method A); (c) $Pd(OAc)_2$, CuI, DMF, 140 °C, 14 h, (method B).

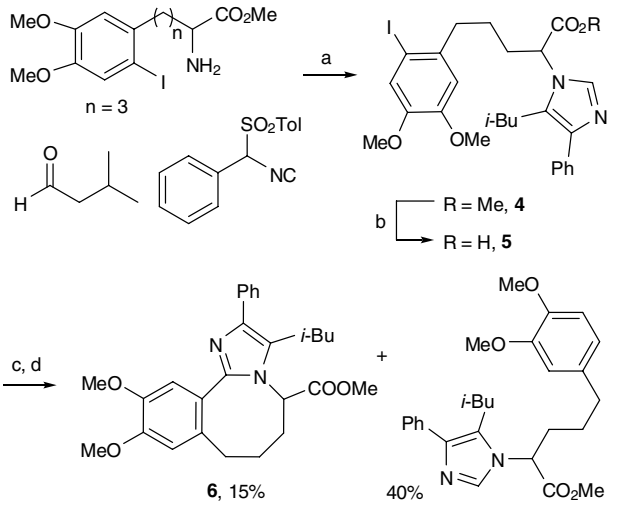
A) was optimal for the cyclization.[10] The base-free and ligand-free conditions reported by Bellina and co-workers were also investigated namely, $Pd(OAc)_2$ (5 mol %), CuI (2.0 equiv) in DMF at 140 °C for 14 h (method B); however, the cyclized product **3** was obtained in a 30% yield (Scheme 1). A series of imidazole precursors were synthesized to evaluate the scope of the C-arylation reaction. The results are outlined in Table 1. The reaction was found to be general for various van Leusen imidazole substrates, substituted phenylTosMIC's and aromatic aldehydes. Finally, in addition to simple primary amines, amino esters could also be used.

The cyclization reaction of the imidazole precursors using the optimized reaction conditions (method A) gave access to a variety of fused bicyclic imidazoles. Arylbromides were found to be comparable to the aryliodides in the C-arylation reaction (Table 1, entries 1 and 2). Five-membered fused rings, 5*H*-imidazo[2,1-*a*]-isoindoles were obtained from the 2-halobenzylamines (Table 1, entry 1). Six-membered and seven-membered rings were accessible when the amine precursors were the 2-iodophenethylamines and 2-iodophenylpropylamines, respectively.[11] In the case of entry 6 (Table 1),

Table 1. van Leusen and C-arylation products

Entry	TOSMIC	R_2–CHO	R_3–NH_2	van Leusen product (yield %)	C-arylation product	Yield (%)
1						R = Br, 29 R = I, 37
2						65
3						68
4						63
5						73
6						72[a]

[a] The crude reaction was treated with $TMSCHN_2$/MeOH to form the ester.



Scheme 2. Reagents and conditions: (a) DMF, K_2CO_3, 62%; (b) LiOH, MeOH, 70%; (c) $Pd(OAc)_2$, PPh_3, CuI, Cs_2CO_3, DMF 140 °C, 14 h, (method A); (d) $TMSCHN_2$, MeOH.

we found that the C-arylation reaction was significantly cleaner with the acid. Thus the ester was hydrolyzed to the acid using LiOH/MeOH prior to the cyclization reaction. The crude reaction mixture was then treated with TMS–diazomethane to reform the ester in order to ease purification of the final product.

Attempts to apply this chemistry to obtain the synthetically more challenging eight-membered rings were successful albeit, in a low yield. Compound **5** was subjected to the reaction conditions employed in method A. In addition to yielding the desired product **6** in a 15% yield,[12] significant deiodination of substrate **5** was observed under the reaction conditions (Scheme 2).

In conclusion, a two-step reaction sequence utilizing the van Leusen imidazole synthesis, followed by the intramolecular C–H activation allowing access to functionalized fused imidazoles, has been developed. This reaction sequence utilizes readily available starting materials to afford products in an efficient and concise manner. Furthermore, the final products obtained are structural chemotypes that could be useful scaffolds for lead generation. Other van Leusen post-modification reactions as well as application of the C-arylation methodology to other multicomponent reactions are currently in progress and will be reported in due course.

Acknowledgements

The authors would like to thank Dr. Rajesh Iyengar for the purification of compound **6** and the Structural Chemistry staff for NMR and MS data.

References and notes

1. For reviews on Ugi 4-CC reaction and other MCRs with isocyanides, see: (a) Dömling, A.; Ugi, I. *Angew. Chem., Int. Ed.* **2000**, *39*, 3168–3210; (b) Hulme, C.; Gore, V. *Curr. Med. Chem.* **2003**, *10*, 51–80; (c) Dömling, A. *Curr. Opin. Chem. Biol.* **2002**, *6*, 306–313; (d) Zhu, J. *Eur. J. Org. Chem.* **2003**, 1133–1144; (e) Gokel, G.; Lüdke, G.; Ugi, I. In *Isonitrile Chemistry*; Ugi, I., Ed.; Academic: New York, 1971; pp 145–199; (f) Dömling, A. *Chem. Rev.* **2006**, *106*, 17–89.
2. Maraccini, S.; Torroba, T. In *Multicomponent Reactions*; Zhu, J., Bienaymé, H., Eds.; Wiley-VCH: Weinheim; 2005, Chapter 2.
3. (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; (c) Gracias, V.; Darczak, D.; Gasiecki, A. F.; Djuric, S. W. *Tetrahedron Lett.* **2005**, *46*, 9053–9056; (d) Beebe, X.; Gracias, V.; Djuric, S. W. *Tetrahedron Lett.* **2006**, *47*, 3225–3228.
4. (a) van Leusen, A. M.; Wildeman, 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 leusen, D.; van Leusen, A. *Org. React.* **2001**, *57*, 419–659; (d) Sisko, J.; Kassick, A. J.; Mellinger, M.; Filan, J. J.; Allen, A.; Olsen, M. A. *J. Org. Chem.* **2000**, *65*, 1516–1524.
5. (a) Arndsten, B. A.; Bergman, R. G.; Mobley, T. A.; Peterson, T. H. *Acc. Chem. Res.* **1995**, *28*, 154–162; (b) Shilov, A. E.; Shul'pin, G. B. *Chem. Rev.* **1997**, *97*, 2879–2932; (c) Dyker, G. *Angew. Chem.* **1999**, *111*, 1808–1822; Dyker, G. *Angew. Chem., Int. Ed.* **1999**, *38*, 1698–1712; (d) Gauri, Y.; Sabo-Etienne, S.; Chaudret, B. *Eur. J. Inorg. Chem.* **1999**, 1047–1055; (e) Kakiuchi, F.; Murai, S. *Top. Curr. Chem.* **1999**, *3*, 47–77; (f) Kakiuchi, F.; Murai, S. In *Topics in Organometallic Chemistry*; Murai, S., Ed.; Springer-Verlag: Berlin-Heidelberg, 1999; Vol. 3; pp 47–49; (g) Crabtree, R. H. *J. Chem. Soc., Dalton Trans.* **2001**, 2437–2450; (h) Ritleng, V.; Sirlin, C.; Pfeffer, M. *Chem. Rev.* **2002**, *102*, 1731–1769; (i) Kakiuchi, F.; Murai, S. *Acc. Chem. Res.* **2002**, *35*, 826–834; (j) Tan, K. L.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2001**, *123*, 2685–2686; (k) Bercaw, J. E.; Labinger, J. A. *Nature* **2002**, *417*, 507–514; (l) Miura, M.; Nomura, M. *Top. Curr. Chem.* **2002**, *219*, 212–237; (m) Tan, K. L.; Vasudevan, A.; Bergman, R. G.; Ellman, J. A.; Souers, A. J. *Org. Lett.* **2003**, *5*, 2131–2134; (n) Lane, B. S.; Brown, M. A.; Sames, D. *J. Am. Chem. Soc.* **2005**, *127*, 8050–8057; (o) Deprez, N. R.; Kalyani, D.; Krause, A.; Sanford, M. S. *J. Am. Chem. Soc.* **2006**, *128*, 4972–4973; (p) Wilson, R. M.; Thalji, R. K.; Bergman, R. G.; Ellman, J. A. *Org. Lett.* **2006**, *8*, 1745–1747.
6. (a) Pivsa-Art, S.; Satoh, T.; Kawamura, Y.; Miura, M.; Nomura, M. *Bull. Chem. Soc. Jpn.* **1998**, *71*, 467–473; (b) Kondo, Y.; Komine, T.; Sakamoto, T. *Org. Lett.* **2000**, *2*, 3111–3113; (c) Wang, L.; Woods, K. W.; Li, Q.; Barr, K. J.; McCroskey, R. W.; Hannick, S. M.; Gherke, L.; Credo, B. R.; Hui, Y.; Marsh, K.; Warner, R.; Lee, J. Y.; Zielinski-Mozng, N.; Frost, D.; Rosenberg, S. H.; Sham, H. L. *J. Med. Chem.* **2002**, *45*, 1697–1711; (d) Yokooji, A.; Okazawa, T.; Satoh, T.; Miura, M.; Nomura, M. *Tetrahedron* **2003**, *59*, 5685–5689; (e) Mori, A.; Sekiguchi, A.; Masui, K.; Shimada, T.; Horie, M.; Osakada, K.; Kawamoto, M.; Ikeda, T. *J. Am. Chem. Soc.* **2003**, *125*, 1700–1701; (f) Zificsak, C. A.; Hlasta, D. J. *Tetrahedron* **2004**, *60*, 8991–9016; (g) Alagille, D.; Baldwin, R. M.; Tamagnan, G. D. *Tetrahedron Lett.* **2005**, *46*, 1349–1351; (h) Bellina, F.; Cauteruccio, S.; Mannina, L.; Rossi, R.; Veil, S. *J. Org. Chem.* **2005**, *70*, 3997–4005.
7. (a) Lewis, J. C.; Wiedemann, S. H.; Bergman, R. G.; Ellman, J. A. *Org. Lett.* **2004**, *6*, 35–38; (b) Lewis, J. C.; Wu, J. Y.; Bergman, R. G.; Ellman, J. A. *Angew. Chem., Int. Ed.* **2006**, *45*, 1589–1591.

8. (a) Bellina, F.; Cauteruccio, S.; Rossi, R. *Eur. J. Org. Chem.* **2006**, 1379–1382; (b) Bellina, F.; Cauteruccio, S.; Mannina, L.; Rossi, R.; Veil, S. *Eur. J. Org. Chem.* **2006**, 693–703.
9. Allin, S.; Bowman, W. R.; Elsegood, M. R. J.; McKee, V.; Karim, R.; Rahman, S. S. *Tetrahedron Lett.* **2005**, *61*, 2689–2696; for other methods to access similar structural chemotypes see: (a) Toja, E.; Omodei-Salé, D.; Favara, D.; Cattaneo, C.; Gallico, L.; Galliani, G. *Arzneim-Forsch* **1983**, *33*, 1222–1226; (b) Möhrle, H.; Grimm, B. *Arch. Pharm.* **1986**, *319*, 774–787; (c) Ek, F.; Wistrand, L.; Frejd, T. *Tetrahedron* **2003**, *59*, 6759–6769.
10. A representative procedure is demonstrated by the preparation of 3-isobutyl-2-phenyl-5,6-dihydro-[1,3]dioxolo[4,5-*g*]-imidazo[2,1-*a*]isoquinoline (**3**). To the isovaleraldehyde (215 mg, 2.5 mmol) in DMF (12 mL) was added 2-iodohomopiperonylamine **1** (1.0 g, 3.44 mmol) and 4 Å sieves (400 mg) and the reaction mixture was heated at 60 °C for 4 h. This was followed by the addition of phenyl TOSMIC (542 mg, 2.0 mmol) and K_2CO_3 (276 mg, 2.0 mmol) and the reaction mixture was allowed to stir for an additional 14 h at 60 °C. The reaction mixture was quenched by the addition of water. The aqueous layer was extracted with EtOAc, dried (anhyd $MgSO_4$) concentrated and purified by flash chromatography (80% EtOAC/hexane) to afford 805 mg (85%) of **2** as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.85 (d, $J = 9.0$ Hz, 6H), 1.86 (m, 1H), 2.66 (d, $J = 6.0$ Hz, 2H), 3.09 (t, $J = 9.0$ Hz, 2H), 4.07 (t, $J = 9.0$ Hz, 2H), 5.95 (s, 2H), 6.55 (s, 1H), 7.21–7.41 (m, 5H), 7.64–7.67 (m, 2H); MS (ESI): *m*/*z* 475 (M+H); To a solution of **2** (238 mg, 0.5 mmol) in DMF (6 mL) was added $Pd(OAc)_2$ (11.2 mg, 0.05 mmol), PPh_3 (26.2 mg, 0.1 mmol), CuI (190 mg, 1.0 mmol) and Cs_2CO_3 (163 mg, 0.50 mmol) and the reaction mixture was heated at 140 °C for 14 h. The reaction was cooled to room temperature diluted with EtOAc (20 mL). A solution of saturated aqueous NH_4Cl was added and the reaction mixture was stirred at room temperature for 30 min. The aqueous layer was separated and extracted with EtOAc (2×50 mL). The combined organic layers were dried (anhyd $MgSO_4$), concentrated and purified by flash chromatography (10% EtOAc/hexane) to afford 135 mg (78%) of **3** as a light brown oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.92 (d, $J = 6.0$ Hz, 6H), 1.91 (m, 1H), 2.70 (d, $J = 9.0$ Hz, 2H), 3.06 (t, $J = 9.0$ Hz, 2H), 4.01 (t, $J = 6.0$ Hz, 2H), 5.98 (s, 2H), 6.71 (s, 1H), 7.23–7.42 (m, 3H), 7.62 (s, 1H), 7.73 (m, 2H); MS (ESI): *m*/*z* 347 (M+H).
11. For the synthesis of the starting materials see: (a) Reimann, E.; Ettmayr, C. *Monatshefte für Chemie* **2004**, *135*, 1143–1155; (b) Tietze, L. F.; Schirok, H. *J. Am. Chem. Soc.* **1999**, *121*, 10264–10269; (c) Javier, R.; Ainhoa, A.; Roberto, I.; Nuria, S.; Esther, L. *Tetrahedron* **2005**, *61*, 3311–3324; (d) Eustache, J.; Van de Weghe, P.; Le Nouen, D.; Uyehara, H.; Kabuto, C.; Yamamoto, Y. *J. Org. Chem.* **2005**, *70*, 4043–4053.
12. Compound **6** was purified by Reverse phase-HPLC on an Agilent Zorbax RX-C18 column using acetonitrile/water as the eluent.