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Multicomponent Assembly and Diversification of Novel Heterocyclic Scaffolds Derived from 2-Arylpiperidines

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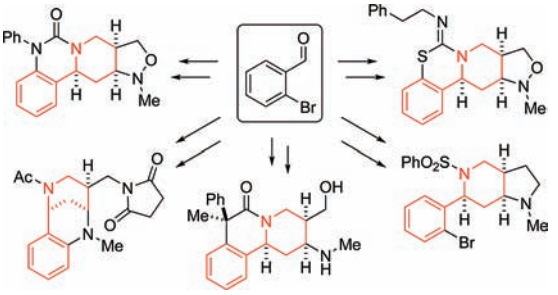
ABSTRACT



A collection of structurally diverse, polyheterocyclic scaffolds comprising a 2-arylpiperidine subunit were synthesized using a Mannich-type multicomponent assembly process, followed by appropriately sequenced ring-forming reactions. An improved procedure for removal of *N*-4-pentenoyl groups was developed; one-pot sequences for tandem urea/thiourea formation and cyclization and tandem enolate arylation/alkylation were discovered. A novel entry to bridged tetrahydroquinoline scaffolds exploiting $A^{1,3}$ strain was also invented. Derivatization of several scaffolds was achieved by cross-coupling and *N*-functionalization.

The continuing demand for small molecules with useful therapeutic properties has necessitated more expedient access to screening libraries containing diverse heterocyclic scaffolds.[1] The identification of so-called privileged substructures, chemotypes that interact with multiple biological targets, and their inclusion in chemical libraries has proven effective toward discovering small molecule probes to study a broad range of known and emerging biological targets.[2] In order to prepare such compounds, there is a continuing need for developing new approaches that enable the rapid generation of functionalized heterocycles that may be easily elaborated and derivatized.

One successful approach toward this end is the build/couple/pair approach that was pioneered in the context of diversity-oriented synthesis (DOS).[3] This strategy involves the construction of molecular frameworks followed by parallel, complexity-generating, ring-forming reactions. We have developed a novel and useful variant of this strategy that features a Mannich-type multicomponent assembly process (MCAP) to generate intermediates that may be quickly elaborated by ring-forming reactions that are preprogrammed by the functionality present in the inputs in the MCAP.[4,5] Ideally, one would be able to access different, functionalized scaffolds having privileged structures from a single intermediate that is generated by the

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(2) (a) Horton, D. A.; Bourne, G. T.; Smythe, M. L. *Chem. Rev.* **2003**, *103*, 893–930. (b) Che, Y.; Brooks, B. R.; Marshall, G. R. *J. Comput.-Aided Mol. Des.* **2006**, *20*, 109–130. (c) Welsch, M. E.; Snyder, S. A.; Stockwell, B. R. *Curr. Opin. Chem. Biol.* **2010**, *14*, 347–361.

(3) (a) Comer, E.; Rohan, E.; Deng, L.; Porco, J. A., Jr. *Org. Lett.* **2007**, *9*, 2123–2126. (b) Nielsen, T. E.; Schreiber, S. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 48–56. (c) Sunderhaus, J. D.; Martin, S. F. *Chem.—Eur. J.* **2009**, *15*, 1300–1308.

(4) For the original application of this approach, see: Martin, S. F.; Benage, B.; Geraci, L. S.; Hunter, J. E.; Mortimore, M. P. *J. Am. Chem. Soc.* **1991**, *113*, 6161–6171.

(5) (a) Sunderhaus, J. D.; Dockendorff, C.; Martin, S. F. *Org. Lett.* **2007**, *9*, 4223–4226. (b) Sunderhaus, J. D.; Dockendorff, C.; Martin, S. F. *Tetrahedron* **2009**, *65*, 6454–6469. (c) Donald, J. R.; Martin, S. F. *Org. Lett.* **2011**, *13*, 852–855. (d) Sahn, J. J.; Su, J. Y.; Martin, S. F. *Org. Lett.* **2011**, *13*, 2590–2593.

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multicomponent assembly process. We now report the successful realization of this goal and its application to the diversity-oriented synthesis of compounds having the fused aryl piperidine substructures **1** and **2** in which the secondary amino group serves as a handle for further skeletal diversification (Figure 1). Significantly, the 2-arylpiperidine subunit is present in NK1 receptor antagonists such as **3**,[6] and the *cis*-fused octahydropyrrolo[3,2-*c*]pyridine core in **2** is found in CCR 5 antagonists as exemplified by **4**.[7]

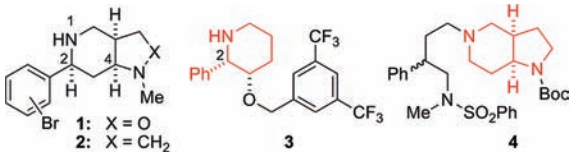

Figure 1. MCAP-derived 2-arylpiperidines **1** and **2** and related bioactive compounds **3** and **4**.

On the basis of previous work, we envisioned that dipolar cycloadditions of unsaturated aldehydes would lead to suitable precursors of **1** and **2**.[5] We had also found that acid chlorides are the preferred electrophilic activators of imines toward addition reactions with π-nucleophiles in Mannich-type, multicomponent assembly processes. Because most tertiary amide derivatives of **1** and **2** would be difficult to hydrolyze to give the secondary amines **1** and **2**, it was necessary to identify a tertiary amide moiety that could be easily removed. It had been shown that *N*-4-pentenamides can be cleaved under mild conditions,[8] so we queried whether the amides **9** and **10** would serve as viable intermediates for preparing **1** and **2**. Accordingly, condensation of bromobenzaldehydes **5** and **6** with allylamine gave intermediate imines that were allowed to react *in situ* with 4-pentenoyl chloride (**7**) and vinyl ether **8** in the presence of catalytic amounts of TMSOTf to furnish **9** and **10** in very good overall yields (Scheme 1). Heating **9** and **10** with *N*-methylhydroxylamine and intramolecular dipolar cycloaddition of the intermediate nitrones gave the isoxazolidines **11** and **12** as single diastereomers. The relative configuration of **11** was confirmed by X-ray crystallography. Treatment of **11** and **12** with iodine in a mixture of THF and aqueous HCl led to facile removal of the *N*-4-pentenoyl group and formation of **13** and **14**, respectively. The presence of HCl in this modified protocol for removing *N*-4-pentenoyl groups was essential to minimize side reactions involving iodohydrin formation that ensued when water alone was used as a cosolvent.

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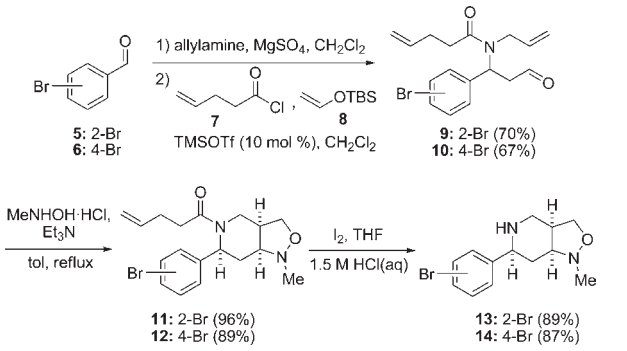
(7) Shah, S. K.; Chen, N.; Guthikonda, R. N.; Mills, S. G.; Malkowitz, L.; Springer, M. S.; Gould, S. L.; DeMartino, J. A.; Carella, A.; Carver, G.; Holmes, K.; Schleif, W. A.; Danzeisen, R.; Hazuda, D.; Kessler, J.; Lineberger, J.; Miller, M.; Emini, E. A.; MacCoss, M. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 977–982.

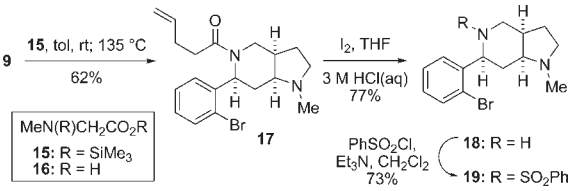
(8) Madsen, R.; Roberts, C.; Fraser-Reid, B. *J. Org. Chem.* **1995**, *60*, 7920–7926.

Scheme 1. Multicomponent Assembly of Amines **13** and **14**



The versatility of the aldehyde **9** as a precursor of other heterocyclic systems was then explored. For example, condensation of **9** with *N*,*O*-bis(trimethylsilyl)sarcosine (**15**) in toluene at room temperature, followed by thermolysis of the putative intermediate oxazolidinone at 135 °C in a sealed tube, afforded **17** in 62% yield (Scheme 2).[9,10] The yield of the corresponding reaction of **9** with sarcosine (**16**) to give **17** was lower-yielding, with β-elimination of the amide moiety from the starting aldehyde **9** being a major side reaction. Reaction of **17** with iodine in a mixture of THF and aqueous HCl gave the desired secondary amine **18**. Optimal selectivity for cleavage of the amide **17** required a higher concentration of HCl than was used for hydrolysis of amide **11**. The amine **18** thus obtained is a versatile substrate for the generation of libraries based on *N*-functionalizations such as sulfonylation to furnish **19**.

Scheme 2. Access to Pyrrolidine-Fused Scaffolds by an Azomethine Ylide Cycloaddition



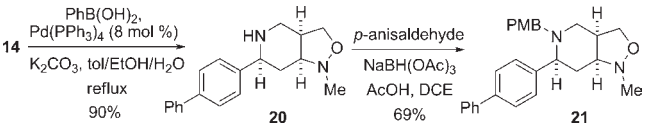
We then explored several tactics for two-dimensional diversification of these scaffolds using the (4-bromophenyl)piperidines **12** and **14**. For example, Suzuki–Miyaura coupling of **14** was readily effected on treatment with various arylboronic acids using $Pd(PPh_3)_4$ as the catalyst to give biphenyls as illustrated by the preparation of **20** (Scheme 3).[11] The secondary amine moiety in **20** is amenable to a variety of *N*-functionalization processes as exemplified by reductive alkylation of **20** to give amine **21**.

(9) Marx, M. A.; Grillot, A.-L.; Louer, C. T.; Beaver, K. A.; Bartlett, P. A. *J. Am. Chem. Soc.* **1997**, *119*, 6153–6167.

(10) Grigg, R.; Idle, J.; McMeekin, P.; Vipond, D. *J. Chem. Soc., Chem. Commun.* **1987**, 49–51.

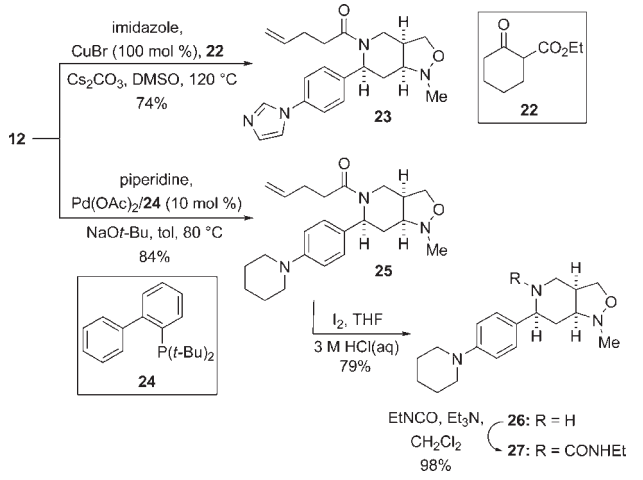
(11) Hadjuk, P. J.; Bures, M.; Praestgaard, J.; Fesik, S. W. *J. Med. Chem.* **2000**, *43*, 3443–3447.

Scheme 3. Biaryl Synthesis via Suzuki Coupling



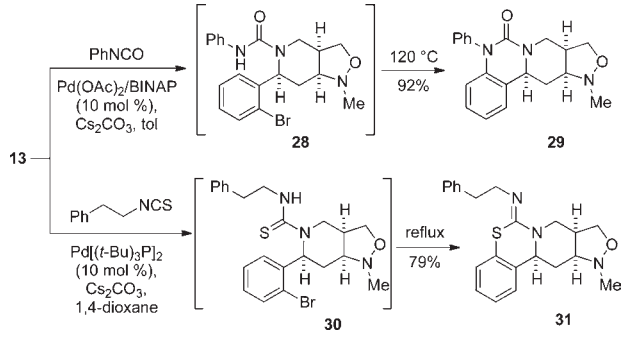
Although the secondary amine **14** can be used as a starting material in carbon−carbon bond-forming cross-couplings, it was necessary to employ the corresponding amide **12** in order to engage the aryl bromide moiety in carbon−heteroatom bond-forming reactions. For example, the amide **12** underwent Ullmann-type coupling with imidazole in the presence of CuBr and the β-ketoester ligand **22** to afford the *N*-arylimidazole **23** (Scheme 4).[12] *N*-Arylimidazoles are structures of biological interest and are found in several compounds with anticonvulsant activity.[13] The analogous Buchwald−Hartwig coupling of **12** with piperidine using $Pd(OAc)_2$ and the phosphine ligand **24** provided the *N*-arylpiperidine **25**.[14] Subsequent removal of the pentenamide group from **25** delivered the amine **26**. That **26** is a useful substrate for diversification by *N*-functionalization is illustrated by formation of the urea **27** on treatment of **26** with ethyl isocyanate.

Scheme 4. Cross-Coupling of **12** with Nitrogen Nucleophiles and *N*-Refunctionalization



In addition to the obvious possibilities for generating libraries from the parent scaffolds **11**, **12**, and **17** and their derived amines, we were intrigued by the opportunity of using these cycloadducts as precursors of more complex heterocycles. For example, a one-pot sequence was developed in which a mixture of **13**, phenyl isocyanate, $Pd(OAc)_2$/BINAP, and Cs_2CO_3 was stirred at room temperature; once urea formation was complete, the mixture was simply heated to provide **29** via a palladium-catalyzed intramolecular *N*-arylation (Scheme 5).[15] It is important to ensure complete formation of the intermediate urea **28** before heating; mixtures of cyclized and uncyclized ureas are otherwise obtained. The dihydroquinazolin-2-one substructure present in **29** is found in Na^+/Ca^{2+} exchange inhibitors and antipsychotic agents.[16,17] In a related transformation, the amine **13** was subjected to a novel one-pot sequence of thiourea formation and palladium-catalyzed cyclization to give the 2-imino-1,3-benzothiazinane **31** via the intermediate thiourea **30**.[18] It is necessary to use Pd[(*t*-Bu_3P)]$_2$ in order to obtain good yields in this latter process.

Scheme 5. Synthesis of the Dihydroquinazolin-2-one **29** and 2-Imino-1,3-benzothiazinane **31**



It occurred to us that we might also form carbon−carbon bonds to form new rings via enolate arylations. In this context, we discovered that reaction of **32**, which was obtained by *N*-acylation of amine **13** with phenylacetyl chloride, with excess LDA in the presence of DMPU effected the desired cyclization, presumably via a benzyne intermediate (Scheme 6).[19] *In situ* methylation of the intermediate enolate **33** resulting from this process proceeded from the sterically more accessible face to give **34** with >95:5 dr (LC−MS).[20,21] Although quenching **33** with 3,5-di-*tert*-butyl-4-hydroxytoluene (BHT) occurred with high diastereoselectivity, the resulting lactam **35** underwent facile epimerization to give mixtures (ca. 2:1) of diastereomers. The biological relevance of compounds such as **34** arises from the observation that 4,4-disubstituted

(12) Lv, X.; Bao, W. *J. Org. Chem.* **2007**, *72*, 3863–3867.

(13) Ohmori, J.; Sakamoto, S.; Kubota, H.; Shimizu-Sasamata, M.; Okada, M.; Kawasaki, S.; Hidaka, K.; Togami, J.; Furuya, T.; Murase, K. *J. Med. Chem.* **1994**, *37*, 467–475.

(14) Zim, D.; Buchwald, S. L. *Org. Lett.* **2003**, *5*, 2413–2415.

(15) Ferraccioli, R.; Carenzi, D. *Synthesis* **2003**, 1383–1386.

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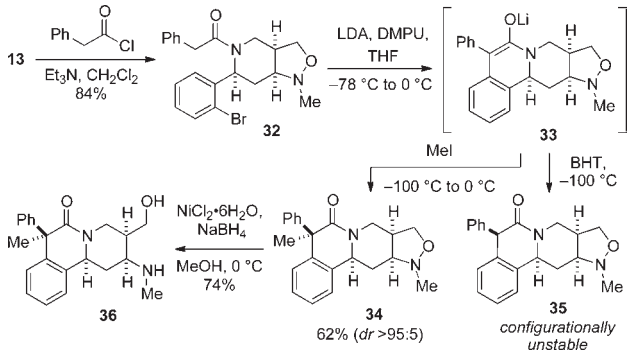
(18) For a related reaction, see: Orain, D.; Blumstein, A.-C.; Tasdelen, E.; Haessig, S. *Synlett* **2008**, 2433–2436.

(19) For examples of base-mediated enolate arylations via benzynes, see: (a) Kessar, S. V.; Singh, P.; Chawla, R.; Kumar, P. *J. Chem. Soc., Chem. Commun.* **1981**, 1074–1075. (b) Flann, C. J.; Overman, L. E.; Sarkar, A. K. *Tetrahedron Lett.* **1991**, *32*, 6993–6996.

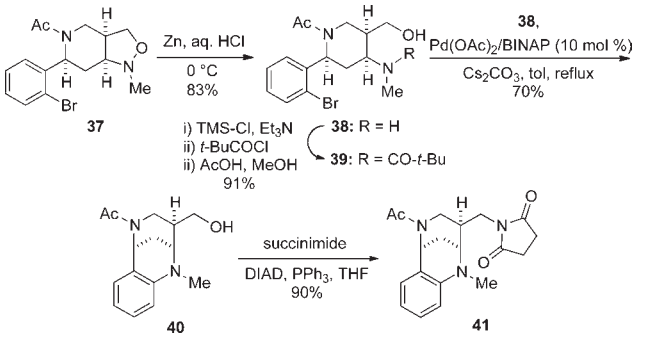
(20) For another example of a tandem enolate arylation/alkylation process, see: Goehring, R. R.; Sachdeva, Y. P.; Pisipati, J. S.; Sleevi, M. C.; Wolfe, J. F. *J. Am. Chem. Soc.* **1985**, *107*, 435–443.

(21) The structure of **34** was established by X-ray crystallographic analysis of its quaternary methiodide salt.

Scheme 6. Dihydroisoquinolin-3-one Synthesis by a Diastereoselective Tandem Enolate Arylation/Alkylation



Scheme 7. Synthesis and Diversification of Amino Alcohol **38** Exploiting $A^{1,3}$ Strain of *N*-Acyl-2-arylpiperidines



dihydroisoquinolin-3-ones have vasorelaxant properties,[22] and several 4-aryltetrahydroisoquinolines exhibit central nervous system activity.[23] Reductive cleavage of the isoxazolidine N−O bond of **34** with nickel boride provided the amino alcohol **36**, which is primed for further diversification by a variety of *N*-functionalizations.

Several strategies for further transforming amino alcohols derived from isoxazolidines may be illustrated beginning with the cycloadduct **37**, which was prepared as previously described.[5] Although reductive cleavage of the N−O bond in **37** with nickel boride was accompanied with extensive dehalogenation, use of zinc in aqueous HCl at 0 °C gave **38** in 83% yield (Scheme 7).[24] *N*-Acylation of **38** proceeded with concomitant *O*-acylation; however, the simple expedient of protecting the primary hydroxyl group in **38** *in situ* as a TMS ether enabled highly efficient amide formation as exemplified by a one-pot synthesis of **39**.

The *cis* relationship between the methylamino group and the 2-bromphenyl substituent in **38** can be exploited by an intramolecular Buchwald−Hartwig coupling, which was achieved by heating **38** in the presence of $Pd(OAc)_2$/BINAP and Cs_2CO_3, to give the bridged tetrahydroquinoline **40** (Scheme 7). The preferred axial orientation of the aryl group in **38** that is enforced by $A^{1,3}$ strain involving the *N*-acetyl group presumably facilitates cyclization.[25] The conformationally constrained bicyclic tetrahydroquinoline framework in **40** is a promising scaffold for DOS as exemplified by using the primary alcohol in **40** as a functional handle in a Mitsunobu reaction to give the succinimide **41**.

In summary, we have significantly expanded the scope of our Mannich-type, multicomponent assembly process followed by dipolar cycloadditions to generate diverse collections of 2-arylpiperidines. New aspects of the process include use of the 4-pentenoyl group as an activating electrophile in the MCAP and as an amine-protecting group that is easily removed using iodine *in the presence of aqueous acid*. This new tactic for deprotecting *N*-4-pentenoyl groups will render it more attractive for future applications. The versatility of the initially formed cycloadducts as precursors of diverse heterocyclic cores that are suitably functionalized for further transformations was established. Indeed, the methods developed for tandem urea or thiourea formation and cyclization as well as enolate arylation and alkylation will be broadly applicable in DOS. The novel entry to bridged tetrahydroquinoline scaffolds exploiting $A^{1,3}$ strain is also expected to be generally useful. The application of these techniques to the synthesis of pilot-scale compound libraries is ongoing, and further results will be reported in due course.

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Supporting Information Available. Experimental procedures, spectral data and copies of ^1H NMR and ^{13}C NMR spectra for all new compounds and **15**, and CIF files for **11** and the methiodide salt of **34**. This material is available free of charge via the Internet at http://pubs.acs.org.

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