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Preparation of Aryloxetanes and Arylazetidines by Use of an Alkyl−Aryl Suzuki Coupling

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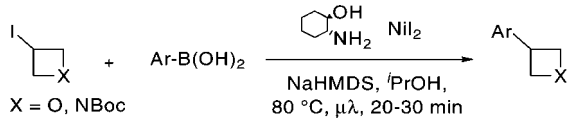
ABSTRACT



The oxetan-3-yl and azetidin-3-yl substituents have previously been identified as privileged motifs within medicinal chemistry. An efficient approach to installing these two modules into aromatic systems, using a nickel-mediated alkyl−aryl Suzuki coupling, is presented.

The introduction of privileged modules with low molecular weight and hydrophilic character into compounds with biological activity is an ongoing challenge within modern medicinal chemistry. The oxetan-3-yl substituent was recently disclosed as one such privileged motif, with demonstrated benefits for property-guided drug discovery and a remarkable ability to alter the pharmacological character of biologically active molecules.[1] For instance, oxetanes can act as a metabolically stable bioisostere of the *tert*-butyl group. Additionally, oxetanes possess an exquisite ability to reduce the octanol/water partition or distribution coefficient of final compounds (log P and log D), which can be useful for reducing biological side effects (e.g., phospholipidosis, i-hERG potassium channel activity).[1] Since an increase in log P, as estimated by calculated methods (clog P), has also been correlated to a number of detrimental events within the drug discovery process,[2] a module that can reduce this parameter is potentially attractive for the medicinal chemist. As part of a study aimed at examining drug-like pharmacophores, we initiated synthetic investigations for the introduction of oxetanes into aromatic and heteroaromatic systems.[3] Our aim was to find a robust process that would complement the existing protocols for oxetane incorporation. Particularly, our attention turned to inclusion of the oxetan-3-yl unit itself into aromatic systems (Figure 1).

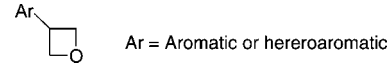


Figure 1. Oxetan-3-yl substituted with an aryl group.

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(2) Leeson, P. D.; Springthorpe, B. *Nat. Rev. Drug Disc.* **2007**, *6*, 881, and references cited therein.

(3) For examples of medicinally active oxetan-3-yl derivatives published prior to 2006, see: (a) Gibson, K. H.; Walter, E. R. H. GB 1976-51196. (b) Edwards, P. N.; Girodeau, J. M. M. M. EP 1989-313384. (c) Kuramoto, Y.; Okuhira, M.; Yatsunami, T. EP 1990-106007. (d) Belley, M. L.; Leger, S.; Roy, P.; Xiang, Y. B.; Labelle, M.; Guay, D. EP 1991-309306. (e) Crawley, G. C.; Dowell, R. I.; Edwards, P. N.; Foster, S. J.; McMillan, R. M.; Walker, E. R. H.; Waterson, D. *J. Med. Chem.* **1992**, *35*, 2600. (f) Vaillancourt, V. A.; Larsen, S. D.; Nair, S. K. WO 2001070706. (g) Homa, F. L.; Wathen, M. W.; Hopkins, T. A.; Thomsen, D. R. WO 2002006513. (h) Wathen, M. W.; Wathen, L. K. WO 2004019933. (i) Wathen, M. W.; Wathen, L. K. WO 2004019940. (j) Allen, D. G.; Coe, D. M.; Cook, C. M.; Cooper, A. W. J.; Dowle, M. D.; Edlin, C. D.; Hamblin, J. N.; Johnson, M. R.; Jones, P. S.; Lindvall, M. K.; Mitchell, C. J.; Redgrave, A. J. WO 2004056823. (k) Watanuki, S.; Koga, Y.; Moritomo, H.; Tsukamoto, I.; Kaga, D.; Okuda, T.; Hirayama, F.; Moritani, Y.; Takasaki, J. WO 2005009971.

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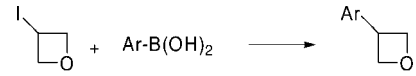
Methods to prepare aryloxetanes include the addition of aryllithium reagents to oxetan-3-one, followed by reductive-deoxygenation,[1] and the cyclization of 2-aryl-1,3 diols.[4,5] We sought a more general alternative to existing techniques and were drawn to the possibility of an alkyl−aryl Suzuki coupling,[6] since it presented a convergent substitute to previous methodology. The development of such reactions has received considerable attention in contemporary organic synthesis, and among the most accomplished methods for undertaking this transformation is a series of nickel-mediated reactions developed by Fu.[7] In this paper we show that a Fu-variant of the Suzuki coupling can be used to introduce both oxetan-3-yl and azetidin-3-yl substiuents into aromatic and heteroaromatic systems. Additionally, we show that the majority of isolated oxetan-3-yl products do not conjugate glutathione when examined in an in vitro screen for reactive metabolites.

Our initial experiments at introducing the oxetan-3-yl group examined reactions between 3-iodooxetane[8] and an appropriate arylboronic acid using a catalyst derived from nickel(II) iodide and *trans*-2-aminocyclohexanol (Table 1). These conditions were employed since González-Bobes and Fu had demonstrated that the reactants required no special handling and that microwave irradiation could be used to accelerate the coupling process, giving rise to the Suzuki products rapidly.[7b] The use of such a method would therefore have obvious attractions for those working in an industrial environment, where ease of synthesis can be a major influence on the desirability to pursue a given transformation. To our delight, we found that the Suzuki coupling proceeded smoothly when 2 equiv of the boronic acid was used,[9] giving rise to 3-aryloxetanes in moderate-to-good yield. In some cases a major byproduct was also produced (vide infra). Additionally, a small quantity of biaryl, arising from homo-coupling of the boronic acid starting material, was also obtained in most examples. As can be seen from Table 1, the reaction tolerated a number of common functional groups such as alkyl, trifluoromethyl, ether, thioether, ester, nitrile, tertiary amine, ketone, chloro, and fluoro. Additionally, *ortho*-, *meta*-, and *para*-substituted boronic acids could be coupled efficiently (entries 1−12). We also used the reaction to prepare 3-(3-bromophenyl)oxetane (entry 13). The preparation of this compound is significant, as it demonstrates that selectivity in coupling can be accomplished between iodoalkane- and arylbromide-containing starting materials. Previously, only selectivity between bromo- and chloro-alkanes had been illustrated, although the increased reactivity of iodides over bromides had been noted.[7b,c] Additionally, 3-(3-bromophenyl)oxetane contains a handle for further manipulation via palladium-, nickel-, and copper-mediated processes and is thus a valuable building block.

Next, we turned our attention to the introduction of the oxetan-3-yl motif into heteroaromatic and bicyclic systems. As can be seen from Table 2, mixed results were obtained.

Table 1. Alkyl−Aryl Suzuki Coupling To Install the Oxetan-3-yl Substituent into Aryl Systems



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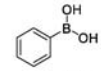
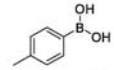
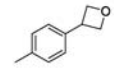
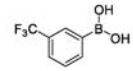
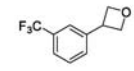
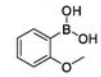
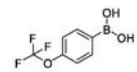
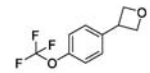
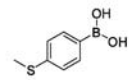
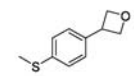
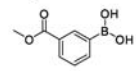
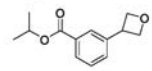
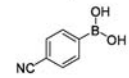
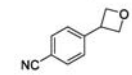
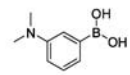
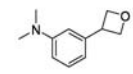
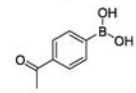
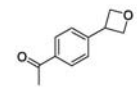
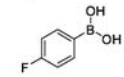
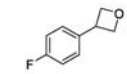
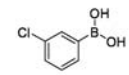
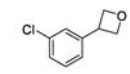
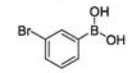
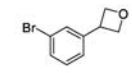
1			54
2			60
3			50
4			67
5			61
6			39
7			35 (53)[b]
8			53
9			56
10			49[c]
11			49
12			65
13			36

[a] Isolated yield from reaction with $ArB(OH)_2$ (2.0 equiv), NiI_2 (0.06 equiv), *trans*-2-aminocyclohexanol hydrochloride (0.06 equiv), 3-iodooxetane (1.0 equiv), NaHMDS (2.0 equiv), and ^{i}PrOH; 80 °C, μwave, 20 min. [b] Desired oxetane product as methyl ester (18% yield) also isolated. [c] Acetophenone (22%) also isolated.

(4) (a) Searles, S.; Hummel, D. G.; Nukina, S.; Throckmorton, P. E. *J. Am. Chem. Soc.* **1960**, *82*, 2928. (b) Castro, B.; Selve, C. *Tetrahedron Lett.* **1973**, *45*, 4459. (c) Picard, P.; Leclercq, D.; Bats, J. P.; Moulines, J. *Synthesis* **1981**, 550. (d) Robinson, P. L.; Barry, C. N.; Kelly, J. W.; Evans, S. A. *J. Am. Chem. Soc.* **1985**, *107*, 5210. (e) Katritzky, A. R.; Fan, W.; Li, Q. *Youji Huaxue* **1988**, *8*, 53.

(5) For alternative synthesis of 3-aryloxetanes, see: (a) Yates, P.; Szabo, A. G. *Tetrahedron Lett.* **1965**, *37*, 485. (b) Nerdel, F.; Kaminski, H.; Frank, D. *Tetrahedron Lett.* **1967**, *39*, 4973. (c) Delmond, B.; Pommier, J. C.; Valade, J. *Tetrahedron Lett.* **1969**, *41*, 2089. (d) Lewis, F. D.; Turro, N. J. *J. Am. Chem. Soc.* **1970**, *92*, 311. (e) Delmond, B.; Pommier, J. C.; Valade, J. *J. Organomet. Chem.* **1973**, *47*, 337.

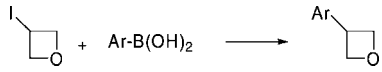
(6) For a review see: Netherton, M. R.; Fu, G. C. In *Topics in Organometallic Chemistry: Palladium in Organic Synthesis*; Tsuji, J., Ed.; Springer: New York, 2005; pp 85−108.

(7) (a) Zhou, J.; Fu, G. C. *J. Am. Chem. Soc.* **2004**, *126*, 1340. (b) González-Bobes, F.; Fu, G. C. *J. Am. Chem. Soc.* **2006**, *128*, 5360. (c) Saito, B.; Fu, G. C. *J. Am. Chem. Soc.* **2007**, *129*, 9602.

(8) Clark, S. L.; Polak, R. J.; Wojtowicz, J. A. US 1966-557376.

(9) Other conditions were not investigated.

Table 2. Alkyl−Aryl Suzuki Coupling To Install the Oxetan-3-yl Substituent into Heteroaryl and Bicyclic Systems



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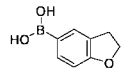
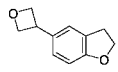
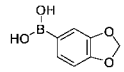
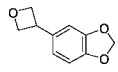
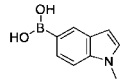
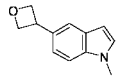
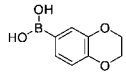
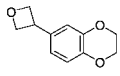
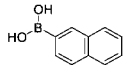
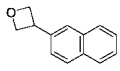
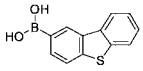
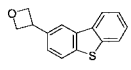
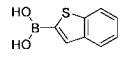
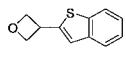
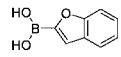
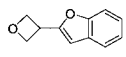
1			36[b]
2			69
3			62
4			45
5			41
6			33
7			9
8			20
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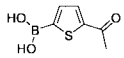
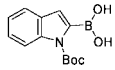
11			60
12			75

[a] Isolated yield from reaction with $ArB(OH)_2$ (2.0 equiv), NiI_2 (0.06 equiv), *trans*-2-aminocyclohexanol hydrochloride (0.06 equiv), 3-iodooxetane (1.0 equiv), NaHMDS (2.0 equiv), and ^{i}PrOH; 80 °C, μwave, 20 min. [b] Unidentified byproduct also obtained.

Although the oxetane group could generally be coupled efficiently to heteroaromatic or bicyclic systems, whose boronic acid resided on a benzenoid substructure (entries 1−6), the use of boronic acids connected to a heteroaromatic ring were rarely successful (entries 7−12). Indeed, benzothiophene, benzofuran, and pyrimidine examples seemed to be the only cases where the oxetane product could be obtained (entries 7−9). Almost all other reactions provided a "deborylated" product in which the starting boronic acid had been cleaved. At present, we do not have an explanation as to why boronic acids directly linked to a heteroaromatic nucleus seem reluctant to participate in the coupling process. A number of reports have indicated that nickel-mediated alkyl−heteroaryl Suzuki couplings are possible,[7a,10] although reduced efficiencies and higher catalyst loadings are sometimes a feature of such reactions.[10a,b] Additionally, all reports to date have utilized a catalyst derived from $Ni(COD)_2$ and bathophenanthroline, rather than NiI_2 and *trans*-2-aminocyclohexanol.[7a,10]

As mentioned previously, for reactions that were successful, two byproducts could usually be observed. First, a small quantity of biaryl arising from homocoupling could be isolated. In other examples, a further byproduct, tentatively identified as the boroxine, was also obtained (Figure 2).

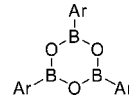


Figure 2. Proposed boroxine byproduct for selected reactions.

While the extent of biaryl coupling was small (<5%), the boroxine byproduct could become quite substantial in a number of cases (e.g., Table 1, entries 2 and 5; Table 3, entry 1).

We also used the general principle of alkyl−aryl Suzuki coupling to install a protected azetidine into numerous aromatic nuclei (Table 3).[11] The reactions proceeded uneventfully, with no significant cleavage of the *N-tert*-butoxycarbonyl (Boc) protecting group.

Finally, a number of aryloxetane products were evaluated in an in vitro screen for reactive metabolites by incubating with human liver microsomes in the presence of glutathione and nicotinamide adenine dinucleotide phosphate (NADPH) cofactor. In just over half of the cases investigated, no glutathione conjugates were observed (Figure 3). As such experiments are commonly used as a qualitative filter for the ability to form covalent adducts upon bioactivation,[12] our results provide additional evidence that the oxetan-3-yl chemotype is attractive from a medicinal chemistry perspective.[13]

In summary, our studies outline a new approach for incorporating the oxetan-3-yl and azetidin-3-yl groups into aromatic systems by use of a nickel-catalyzed alkyl−aryl

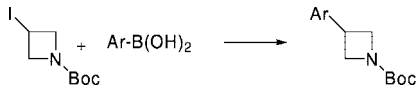
(10) (a) Malpass, J. R.; Handa, S.; White, R. *Org. Lett.* **2005**, *7*, 2759. (b) White, R.; Malpass, J. R.; Handa, S.; Baker, R. S.; Broad, L. M.; Folly, L.; Mogg, A. *Bioorg. Med. Chem.* **2006**, *16*, 5493. (c) Armstrong, A.; Bhonoah, Y.; Shanahan, S. E. *J. Org. Chem.* **2007**, *72*, 8019.

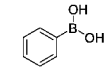
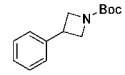
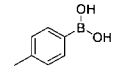
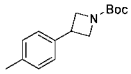
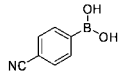
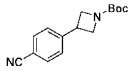
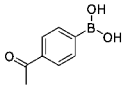
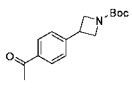
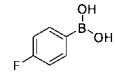
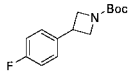
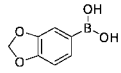
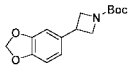
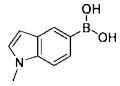
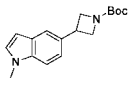
(11) For a previous synthesis of protected arylazetidines using a palladium-mediated (Negishi) coupling of aryl halides with (1-(*tert*-butoxycarbonyl)azetidin-3-yl)zinc(II) iodide, see: (a) Billotte, S. *Synlett* **1998**, 379.

(12) Kumar, S.; Kassahun, K.; Tschirret-Guth, R. A.; Mitra, K.; Baillie, T. A. *Curr. Opin. Drug Discovery* **2008**, *11*, 43.

(13) It should be noted that the glutathione incubation experiment did not ascertain the degree to which compounds undergo phase I metabolism or the site of conjugation to glutathione. Although we cannot rule out that compounds prepared in this paper undergo metabolism at the oxetane group, Rogers-Evans and Carreira have previously demonstrated that model compounds containing an oxetan-3-yl moiety exhibit good metabolic stability.[1] Efforts to determine the position and extent of metabolism for compounds in this paper are under investigation and should yield further information as to any potential metabolic liability associated with the oxetan-3-yl group.

Table 3. Alkyl−Aryl Suzuki Coupling To Install the Azetidin-3-yl Substituent

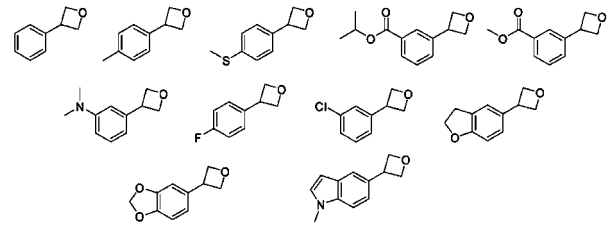


entry	boronic acid	product	yield (%)[a]
1			51
2			24
3			50
4			50
5			57
6			45
7			25

[a] Isolated yield from reaction with $ArB(OH)_2$ (2.0 equiv), NiI_2 (0.06 equiv), *trans*-2-aminocyclohexanol hydrochloride (0.06 equiv), 1-Boc-3-iodoazetidine (1.0 equiv), NaHMDS (2.0 equiv), and ^{i}PrOH; 80 °C, μwave, 30 min.

Suzuki coupling. We show that this technique can be used on starting materials that would be of interest to practicing medicinal chemists. Although our reaction conditions do have limitations when used with certain heteroaromatic systems, the reaction offers an attractive alternative to current methodology for oxetane synthesis in particular.

No conjugates observed when incubated with glutathione



Conjugates observed when incubated with glutathione

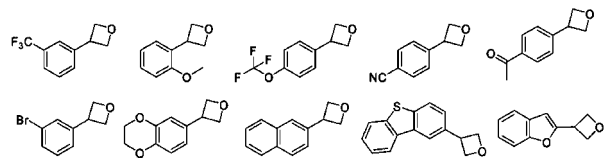


Figure 3. Screen for reactive metabolites by incubation with glutathione in the presence of human liver microsomes and NADPH cofactor. Observation of conjugates is used by many medicinal chemists as a qualitative filter for reactive metabolites.[12,13]

We also demonstrate that a majority of model compounds containing an oxetan-3-yl substituent do not conjugate glutathione when incubated with human liver microsomes in vitro. This result provides additional support for the continued development of oxetanes within medicinal chemistry.

Acknowledgment. We thank Andrew Calabrese and Thomas Ryckmans of Pfizer, Sandwich (United Kingdom) for insightful discussions around the oxetane motif and clog P.

Supporting Information Available: Detailed experimental procedures and copies of analytical data.This material is available free of charge via the Internet at http://pubs.acs.org.

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