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Report

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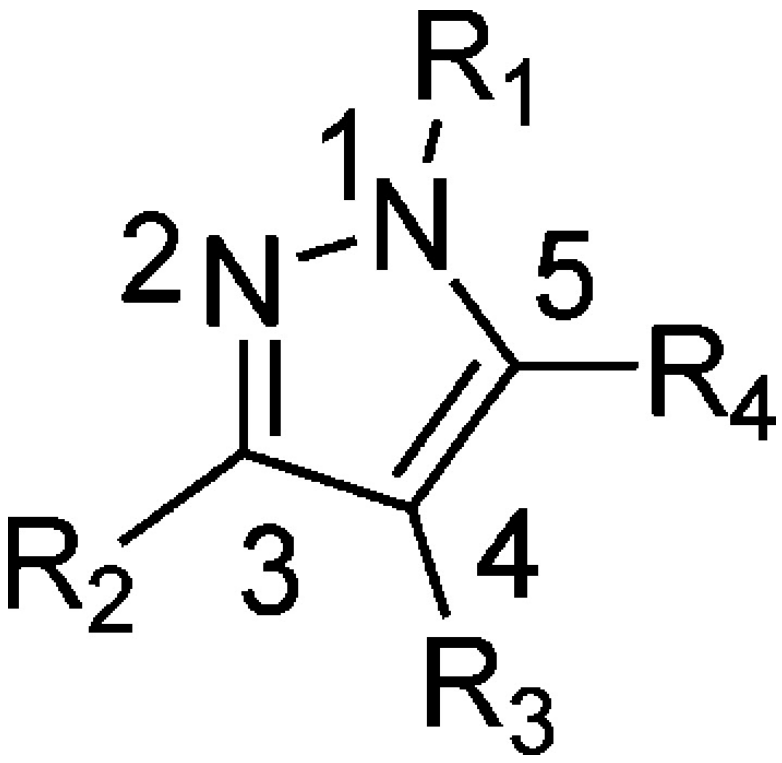

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Three-Component, One-Pot Reaction for the Combinatorial Synthesis of 1,3,4-Substituted Pyrazoles

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Pyrazole (Figure 1) is found widely as a core structure in a large variety of compounds that exhibit important biological activity.[1] It is convenient to synthesize substituted pyrazoles by the intermolecular [3 + 2] cycloaddition of 1,3-dipoles with alkynes or condensation of hydrazine with 1,3-diketones or their equivalents.[2] The use of combinatorial approaches to the high-throughput synthesis of this druglike scaffold would be a powerful advance in helping to speed up drug discovery. Recently, several papers have reported the synthesis of 1,3,5-substituted pyrazoles on solid phase or by using a one-pot process with high efficiency.[3] However, few methods have been explored to generate 1,3,4-substituted pyrazoles. Only Price[4] has reported the high-throughput synthesis of 4-alkoxy pyrazoles by the functionalization of symmetric 1,3-diones using hypervalent iodine with hydrazine, although with low yield. Here, we report a combinatorial synthesis of 1,3,4-substituted pyrazoles using a three-component sequential one-pot reaction.

Chromone as 1,3-diketone equivalent, can be condensed with hydrazine to form *o*-hydroxyphenyl pyrazole.[5] We thus designed a one-pot process to form 1,3,4-substituted pyrazoles or isoxazoles by Suzuki coupling,[6] which is unaffected by the presence of water and air, tolerated a broad range of functional groups, and applies diversified commercial available boronic acids to the chromone core, followed by condensation with a variety of hydrazines or hydroxylamine (Scheme 1).

Treatment of iodochromone, phenylboronic acid, and aqueous hydrazine in the presence of a palladium catalyst, similar to the recently reported Mori's four-component coupling conditions, gave a complicated mixture of products.[3a] When changing aqueous hydrazine to methylhydrazine, *o*-hydroxylphenylpyrazole **3** was achieved by the deiodination of the starting material by palladium(0), followed by condensation with methylhydrazine (Scheme 2).

After screening solvent systems, bases, and ligands for sequential Suzuki coupling and condensation, a mixture of iodochromone and phenylboronic acid in the presence of 2% $Pd(PPh_3)_4$ and 2 equiv of K_2CO_3 in THF−H_2O (4:1) at refluxing overnight succeeded and was completed by adding 1.5 equiv of aqueous hydrazine at room temperature for 2 h to afford the product **4** in 93% yield (Scheme 3).

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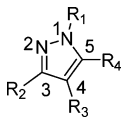
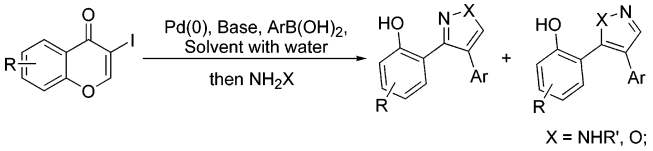
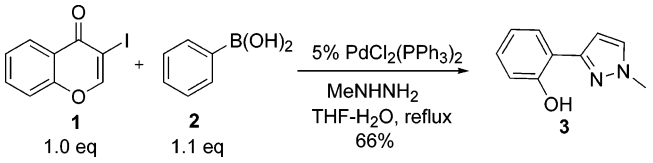


Figure 1.

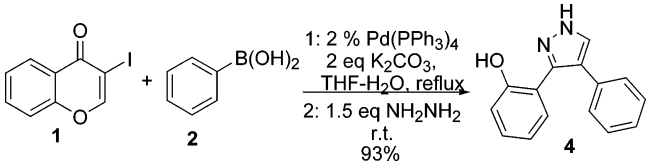
Scheme 1



Scheme 2



Scheme 3



To delineate this approach, particularly in regard to library construction, this methodology was evaluated by using different iodochromones and aryl boronic acids. The results are given in Table 1. The electronic and steric variations on the aryl boronic acid gave the desired product in good to excellent yield. 3-Thiophenylboronic acid gave the desired product **C-7** in excellent yield. Due to electron-withdrawing effects on the chromone ring, the substrate **A-4** afforded the product **C-11** in moderate yield.

The regioselectivity of the one-pot reaction was evaluated with different hydrazines (Scheme 4). The reaction mixture of iodochromone with phenylboronic acid with Suzuki coupling, followed by methylhydrazine and condensation was completed within 2 h and afforded in high selectivity one major product, **5**, in 93% yield. The major product was assigned on the basis of the chemical shift at δ 10.65 ppm of the phenolic proton that forms the intramolecular hydrogen bonding with the pyrazole's nitrogen, as evident in proton NMR. Formation of compound **5** is presumably a result of initial 1,4-conjugate addition of the more nucleophilic methyl-substituted hydrazine nitrogen to the double bond of chromone and then subsequent ring opening, followed by cyclization of the unsubstituted hydrazine nitrogen onto the carbonyl group and dehydration.[5c,2f] After Suzuki coupling, the reaction mixture has to be heated with hydroxylethylhydrazine to obtain two major products, **6** (40% yield) and **7** (42% yield), with poor regioselectivity because the nucleophilic alkyl-substituted hydrazine nitrogen has increased steric hindrance, and the unsubstituted nitrogen can

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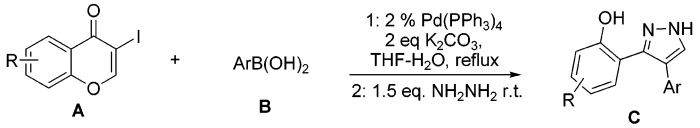
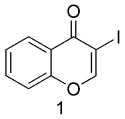
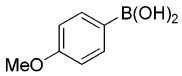
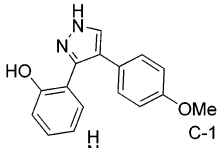
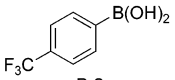
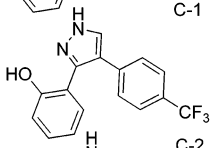
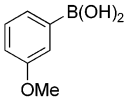
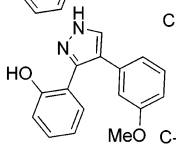
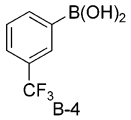
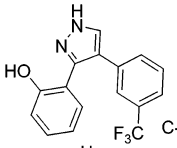
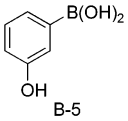
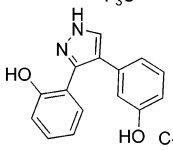
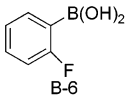
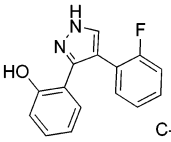
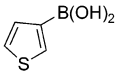
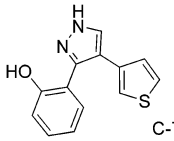
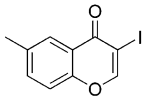
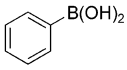
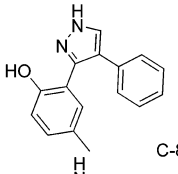
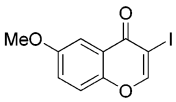
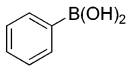
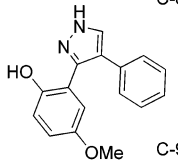
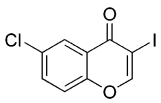
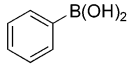
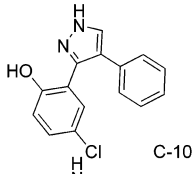
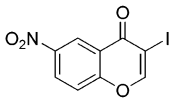
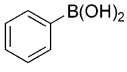
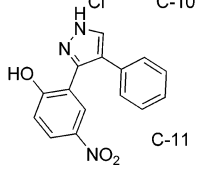
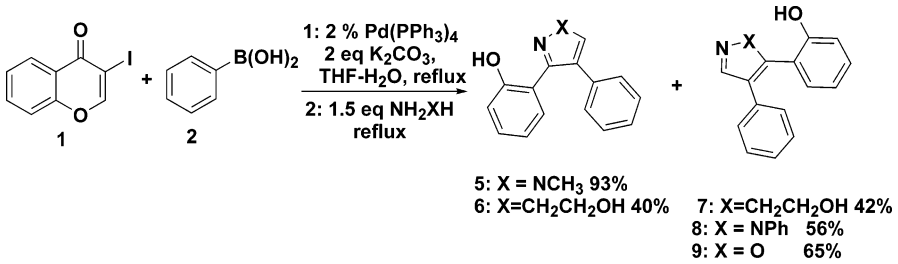
Table 1. Synthesis of Pyrazoles from Diversified Chromone and Aryl Boronic Acid



Entry	Iodochromone	Aryl boronic acid	hydrazine	pyrazole	yield(%)
1	 1	 B-1	NH_2NH_2	 C-1	82
2	1	 B-2	NH_2NH_2	 C-2	73
3	1	 B-3	NH_2NH_2	 C-3	84
4	1	 B-4	NH_2NH_2	 C-4	80
5	1	 B-5	NH_2NH_2	 C-5	88
6	1	 B-6	NH_2NH_2	 C-6	95
7	1	 B-8	NH_2NH_2	 C-7	90
8	 A-1	 2	NH_2NH_2	 C-8	92
9	 A-2	 2	NH_2NH_2	 C-9	95
10	 A-3	 2	NH_2NH_2	 C-10	90
11	 A-4	 2	NH_2NH_2	 C-11	48

Scheme 4



also attack the double bond of the chromone under the refluxing conditions.

As expected, the unsubstituted nitrogen of phenylhydrazine is the more nucleophilic, as compared to the substituted nitrogen of phenyl hydrazine. But its reactivity was much lower than that of methylhydrazine, and it was necessary to reflux overnight under N_2 to obtain the single product **8** in 56% yield with high selectivity. Isoxazole **9** was formed by carrying out the reaction with hydroxylamine.

In conclusion, we developed a method to generate diversified pyrazoles and isoxazoles via a sequential one-pot reaction of iodochromone, arylboronic acid, and hydrazine or hydroxylamine by Suzuki coupling and condensation. This method provides facile construction of these heterocycle libraries that are applicable for biological screening.

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Supporting Information Available. Experimental procedures and spectra of the compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

References and Notes

(1) Elguero, J. In *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R.; Rees, C. W.; Scriven, E. F. V.; Pergamon-Elsevier Science: Oxford, 1996; Vol. 6, pp 1−75. (b) Sutharchanadevi, M.; Murugan, R. In *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R.; Rees, C. W.; Scriven, E. F. V.; Pergamon-Elsevier Science: Oxford, 1996; Vol. 6, pp 221−260. (c) Pevarello, P.; Brasca, M. G.; Orsini, P.; Traquandi, G.; Longo, A.; Nesi, M.; Orzi, F.; Piutti, C.; Sansonna, P.; Varasi, M.; Cameron, A.; Vulpetti, A.; Roletto, F.; Alzani, R.; Cinmei, M.; Albanese, C.; Pastori, W.; Marsiglio, A.; Pesenti, E.; Fiorentini, F.; Bischoff, J. R.; Mercurio, C. *J. Med. Chem.* **2005**, *48*, 2944−2956. (d) Singh, S. K.; Reddy, P. G.; Rao, K. S.; Lohray, B. B.; Misra, P.; Rajjak, S. A.; Rao, Y. K.; Venkatewarlu, A. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 499−504. (e) Sawyer, J. S.; Anderson, B. D.; Beight, D. W.; Campbell, R. M.; Jones, M. L.; Herron, D. K.; Lampe, J. W.; McCowan, J. R.; McMillen, W. T.; Mort, N.; Parsons, S.; Smith, E. C. R.; Vieth, M.; Weir, L. C.; Yan, L.; Zhang, F.; Yingling, J. M. *J. Med. Chem.* **2003**, *46*, 3954−3956. (f) Chimenti, F.; Bolasco, A.; Manna, F.; Secci, D.; Chimenti, P.; Befani, O.; Turini, P.; Giovannini, V.; Mondovi, B.; Cirilli, R.; Torre, F. L. *J. Med. Chem.* **2004**, *47*, 2017−2074. (g) Stauffer, S. R.; Coletta, C. J.; Tedesco, R.; Nishiguchi, G.; Carlson, K.; Sun, J.; Katzenellenbogen, B. S.; Katzenellenbogen, J. A. *J. Med. Chem.* **2000**, *43*, 4934−4947.

(2) For recent publication, see: (a) Katritzky, A. R.; Wang, M.; Zhang, S.; Voronkov, M. V. *J. Org. Chem.* **2001**, *66*, 6787−6791. (b) Peruncheralathan, S.; Khan, T. A.; Ila, H.; Junjappa, H. *J. Org. Chem.* **2005**, *70*, 10030−10035. (c) Peruncheralathan, S.; Yadav, A. K.; Ila, H.; Junjappa, H. *J. Org. Chem.* **2005**, *70*, 9644−9647. (d) Huang, Y. R.; Katzenellenbogen, J. A. *Org. Lett.* **2000**, *2*, 2833−2836. Haddad, N.; Baron, J. *Tetrahedron Lett.* **2002**, *43*, 2171−2173. (e) Wang, X.; Tan, J.; Grozinger, K. *Tetrahedron* Lett. **2000**, *41*, 4713−4716. (f) Bishop, B. C.; Brands, K. M.; Gibb, A. D.; Kennedy, D. *Synthesis* **2004**, *1*, 43−52. (g) Lee, K. Y.; Kim, J. M.; Kim, J. N. *Tetrahedron Lett.* **2003**, *44*, 6737−6740. (h) Lee, K. Y.; Gowrisankar, S.; Kim, J. N. *Tetrahedron Lett.* **2005**, *46*, 5387−5391.

(3) (a) Ahmed, M. S. M.; Kobayashi, K.; Mori, A. *Org. Lett.* **2005**, *7*, 4487−4489. (b) Stauffer, S. R.; Katzenellenbogen, J. A. *J. Comb. Chem.* **2000**, *2*, 318. (c) Chang, K.; Choi, Y. H.; Kim, S.; Yoon, Y.; Lee, W. S. *J. Chem. Soc., Perkin Trans. 1* **2002**, *2*, 207−210. (d) Sen, D.; Shu, M.; Chapman, K. T. *Org. Lett.* **2000**, *2*, 2789−2792. (e) Rossiter, S.; Woo, C. K.; Hartzoulakis, B.; Wishart, G.; Stanyer, L.; Labadie, J. W.; Selwood, D. L. *J. Comb. Chem.* **2004**, *6*, 385−390.

(4) Price, D. A.; Gayton, S.; Stupple, P. A. *Synlett*. **2002**, *7*, 1170−1172.

(5) (a) Dymock, B. W.; Barril, X.; Brough, P. A.; Cansfield, J. E.; Massey, A.; McDonald, E.; Hubbard, R. E.; Surgenor, A.; Roughley, S. D. Webb, P.; Workman, P.; Wright, L.; Drysdale, M. J. *J. Med. Chem.* **2005**, *48*, 4212−4215. (b) Pinto, D.; Silva, A.; Almeida, L.; Cavaleiro, J.; Elguero, J. *Eur. J. Org. Chem.* **2002**, 3807−3815. (c) Pinto, D.; Silva, A.; Cavaleiro, J. J. *Tetrahedron* **1999**, *55*, 10187−10200.

(6) Yokoe, S.; Sugita, Y.; Shirataki, Y. *Chem. Pharm. Bull.* **1989**, *37*, 529−530.

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