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Novel Synthetic Routes Suitable for Constructing Benzopyrone Combinatorial Libraries

Abhijit S. Bhat, Jennifer L. Whetstone, and Robert W. Brueggemeier[1]*

500 W. 12th Avenue, Division of Medicinal Chemistry and Pharmacognosy, College of Pharmacy, The Ohio State University, Columbus, OH 43210

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Abstract

A series of O-(*t*-butylsilyloxy)benzoyl chlorides generated from the corresponding silyl esters were coupled with a range of terminal alkynes to afford the corresponding alkynyl ketones. The alkynyl ketones were converted to enaminoketones and then cyclized to yield the desired benzopyrone ring system. This synthetic protocol utilizes readily available starting materials, mild and high yielding reactions with good functional group tolerance, and is ideal for developing combinatorial libraries centered around the benzopyrone ring system.

Keywords: Benzopyrones; Flavonoids; Combinatorial chemistry; Sonogashira coupling

Synthesis and biological screening of a heterocyclic, small molecule library forms the backbone of most combinatorial chemistry programs today [1,2,3]. Molecular scaffolds that have been shown to interact with different receptor systems whose natural ligands bear no resemblance with each other are termed as "privileged structures" [4]. There is substantial interest in synthesizing libraries of privileged structures, with the hope that screening of such libraries would yield ligands for a diverse collection of pharmacological targets. The driving force behind synthesis and screening of privileged structure libraries is the underlying promise of reducing the synthetic effort required to generate lead structures for a range of biological targets. Benzodiazepines are examples of privileged structures that have been explored using combinatorial methods [1,2,3].

The benzopyrone ring system represents a privileged structure that is yet to be fully exploited by combinatorial chemistry [5,6]. This ring system is present in a number of natural products

[1] e-mail: brueggemeier.1@osu.edu

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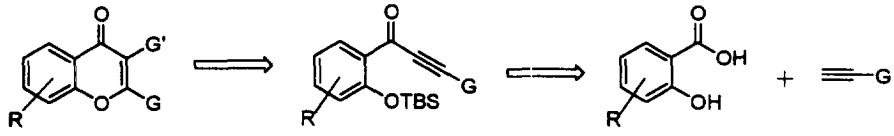
including flavonoids that interact with various enzymes and receptor systems of pharmacological significance.[2]

The benzopyrone ring system presents a fairly rigid molecular framework, resistant to hydrophobic collapse, with multiple sites to introduce potential diversity elements. The prevalent literature methods for constructing benzopyrones are not ideally suited for making libraries as these methods suffer from harsh reaction conditions, poor substituent tolerance and low yields [7].

Figure 1



Heteroannulation reactions of *o*-iodophenols and terminal alkynes in presence of CO are known to produce mixtures of 6-membered benzopyrones and 5-membered aurones [8,9]. In our synthetic planning we proposed to use salicyloyl chlorides as the coupling partner of terminal alkynes in order to obviate high CO pressure conditions required for heteroannulations (**Figure 1**). Also, the phenolic hydroxyl is masked as a TBS ether in order to prevent the oxypalladation reactions leading to mixtures of 5- and 6- membered ring systems. The desired benzopyrone would be then constructed by 6-endo-dig cyclization of the alkynone under controlled conditions that preclude the formation of aurones.

Salicylic acids were treated with 2.2 equiv of TBSCl and Et_3N in CH_2Cl_2 to generate the bisTBS protected salicylic acids ($\mathbf{A_1}$-$\mathbf{A_5}$) in quantitative yield [10]. The bisTBS salicylic acids were reacted with 1.2 equiv of oxalyl chloride in presence of catalytic amounts of DMF to provide the corresponding acid chlorides [11]. The acid chlorides were used for the Sonogashira couplings without any further purification (**Figure 2**). The acid chloride in Et_3N was reacted with a variety of terminal alkynes ($\mathbf{B_1}$-$\mathbf{B_7}$) in the presence of catalytic amount of $Pd(PPh_3)_2Cl_2$ and CuI [12]. It was important to use 3-5 mole excess of terminal alkynes and deoxygenate the reaction mixture in order to reduce the amount of alkyne homocoupled byproducts (Glaser Coupling). Salicylic acids ($\mathbf{A_2}$-$\mathbf{A_5}$) were coupled with phenyl acetylene ($\mathbf{B_1}$) to evaluate the effect of substitutions on the salicylic acid component over the coupling reactions. All of the coupling reactions gave desired alkynones in excellent yields (**Table 1, 2**). The acid sensitive NH-Boc function ($\mathbf{A_5}$) is successfully carried through the acid chlorination step, emphasizing the mild nature of reaction conditions. The one-pot acid chlorination-

[2] Molecules with benzopyrone ring system have shown to be active as tyrosine and protein kinase C inhibitors, antifungal and antiviral agents as well as antitubulin and antihypertensive agents. This nucleus can be exploited to develop novel antiinflammatory agents as well as selective modulators of estrogen receptors α/β, and adenosine receptor antagonists. Synthesis and screening of benzopyrone libraries would allow us to harvest the biological potential of these molecules.

Sonogashira coupling, key for introducing diversity, displays a wide substituent tolerance in both the coupling partners and provides the desired alkynones in excellent yields.

Figure 2

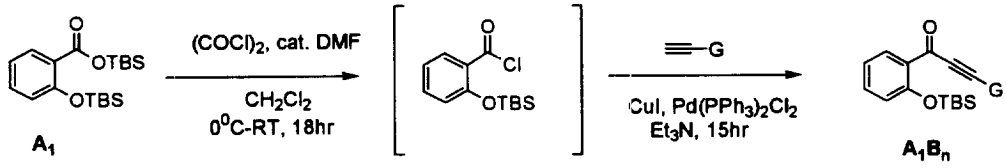


Table 1. Coupling of A_1 with terminal alkynes

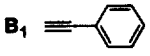
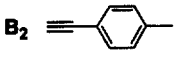
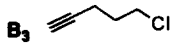
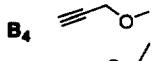
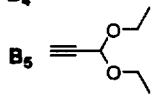
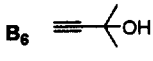
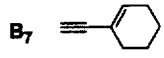
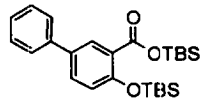
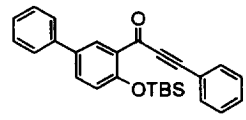
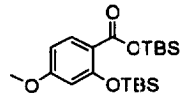
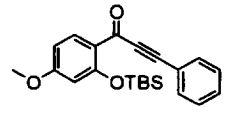
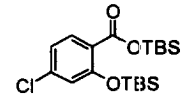
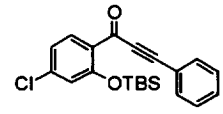
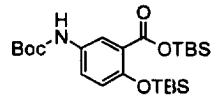
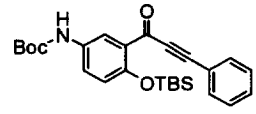
	≡—G	Product A_1B_n (Yield)*
B_1		A_1B_1 (92%)
B_2		A_1B_2 (95%)
B_3		A_1B_3 (85%)
B_4		A_1B_4 (84%)
B_5		A_1B_5 (78%)
B_6		A_1B_6 (74%)
B_7		A_1B_7 (96%)

Table 2. Coupling of B_1 with salicylic acids A_2-A_5

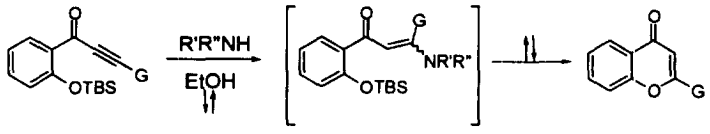
	Salicylic acid	Product	A_nB_1 (Yield)*
A_2			A_2B_1 (90%)
A_3			A_3B_1 (92%)
A_4			A_4B_1 (83%)
A_5			A_5B_1 (78%)

* Isolated yields after workup and flash chromatography

Upon removal of TBS group, the free phenolic hydroxyl can effect 6-endo-dig or 5-exo-dig cyclization to yield either benzopyrones or aurones respectively [13]. We reasoned that, if the alkynones were first converted to enaminoketones and then subjected to TBS deprotection, the system would be prone to undergo Michael addition followed by elimination of secondary amine to exclusively yield the desired benzopyrones. To our surprise, we discovered that conversion of the alkynones to enaminoketones and subsequent cyclization could be effected in a single step. Thus, ethanolic solutions of alkynones refluxed with 10 equiv of diethylamine for 24 hours underwent cyclization to give the benzopyrones via enaminoketone intermediates. TLC revealed that the starting material was consumed within two hours and subsequent NMR analysis of the reaction mixture after 10 hours of reflux revealed a mixture of enaminoketone and benzopyrone. Pure samples of the enaminoketones were prepared by stirring an alcoholic solution of the alkynone with 10 equiv of the secondary amine for two hours. These

enaminoketones when refluxed with excess diethylamine formed benzopyrones. The results of these cyclizations are shown in **Figure 3**. Similar results were obtained by refluxing the alkynones with dimethylamine (2M solution in THF) and N-benzyl-ethylamine. This strategy effectively eliminates the 5-exo-dig cyclization option.

Figure 3. Cyclizations with Diethylamine



Alkynone
A_1B_n

Flavone

Alkynone	% Yield of Flavone*
A_1B_1	96%
A_1B_2	87%
A_1B_3	73%
A_1B_4	68%
A_1B_5	75%
A_1B_6	54%
A_1B_7	82%

*Isolated yield after workup and flash chromatography

In summary, we have disclosed a novel way to construct the benzopyrone nucleus. This method utilizes readily available starting materials, mild reaction conditions and displays a wide substituent tolerance and therefore should prove useful in constructing libraries of benzopyrones not readily accessible by conventional synthetic protocols.

Experimental: Oxalyl chloride (1.1mmol) was added dropwise to a cold (0°C) solution of bisTBS salicylic acid (1mmol) in CH_2Cl_2 containing 3 drops of DMF. The resulting solution was stirred at 0°C for two hours and stirred at room temperature for 16 hours. Solvent was evaporated, Et_3N(3mL) was added to the residue and argon was bubbled through the solution for five minutes. 5mmol of alkyne, 5mg $Pd(PPh_3)_2Cl_2$ and 5mg of CuI were added and the reaction mixture was deoxygenated by bubbling argon gas for 10min and stirred at room temperature for 12 h. MeOH (5mL) was added to the reaction mixture and solvents evaporated, the residue was taken up in diethylether, organics were washed with water, brine, dried (Na_2SO4) and concentrated, the residue was purified by flash chromatography (SiO_2; 18% EtOAc in Hexanes). All the coupling products were characterized by ^1H, ^{13}C NMR, IR and HRMS.

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