JOURNAL OF combinatorial CHEMISTRY

Report

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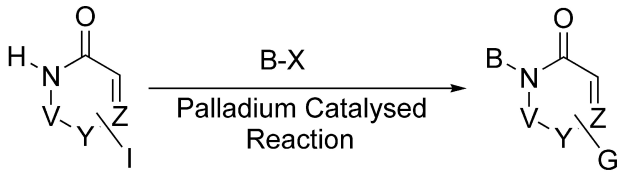
J. Comb. Chem., **2005**, 7 (4), 526-529• DOI: 10.1021/cc050036t • Publication Date (Web): 12 May 2005



V = CH, N, C=O, Y = C, CH, N-R, Z = CH, C, C-Me
B = Me, Et, Bn, CH_2COOR, G = Ar, HetAr, C≡C-K, CH=CH-S

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Expanding the Chemical Diversity of Azinone Libraries by A Consecutive Alkylation/ Palladium-Catalyzed Functionalization Strategy

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Received March 14, 2005

In recent years, tools for the development of new drugs have improved dramatically and now include genomic and proteomic research, biophysical methods, combinatorial chemistry, and high-throughput screening technologies.[1] Although the elucidation of human gene sequences gives rise to immense new opportunities, it simultaneously creates a potential bottleneck regarding the choice of targets and supply of new druglike structures.[1] As a consequence, improvements in the current methods for producing, handling, and screening large numbers of compounds in terms of speed and efficiency are of great interest. Moreover, combinatorial chemistry[2] has not yet achieved its full potential because challenges still exist related to the synthesis, purification, diversity and druglike properties of compound libraries. These issues need to be addressed to successfully fulfill the role assigned to combinatorial chemistry in the post-genomic era. Currently, combinatorial methods that focus on small organic molecules are mainly dominated by two strategies: solid-phase synthesis[3] and, with increasing importance, solution-phase parallel protocols.[4] Because of significant advantages over conventional synthetic procedures, multicomponent reactions[5] and consecutive one-pot functionalizations[6] have demonstrated to be improved synthetic strategies for tailor-made structural scaffolds and combinatorial libraries. These transformations allow the generation of a high level of structural complexity in a few steps from simple starting materials without isolation of intermediates. Additionally, the lack of workup and purification steps but also the less waste, in turn, promotes efficiency in times when a premium is placed on speed during the drug discovery process.

Driven by the widely documented pharmacological activities of azinones[7] (Figure 1), we recently embarked on a program[8] to develop novel high-throughput methodologies to achieve the combinatorial diversification of these privileged scaffolds to satisfy our needs in terms of general purpose screening libraries. The key goal of the project was to develop new strategies that take advantage of the excellent,

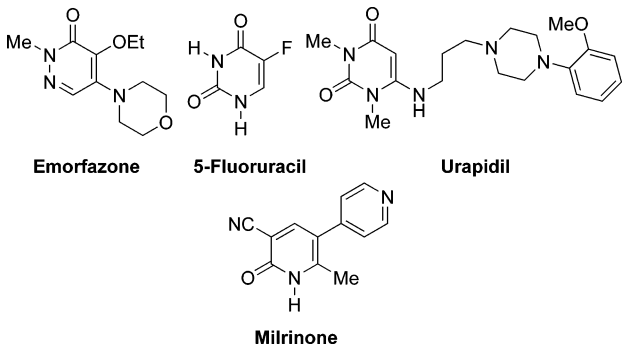

Figure 1. Representative examples of pharmaceutically relevant azinones.[7]

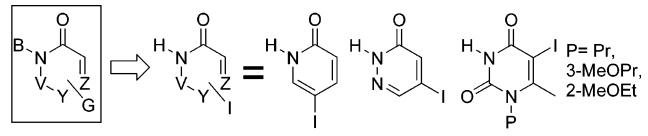

Figure 2. General structure of targeted libraries, retrosynthetic scheme and structure of the starting azinones.

but still rarely exploited,[9] possibilities offered by several well-established palladium-catalyzed reactions (PCR)[10] as a source of diversity in combinatorial chemistry.

The general structure of the targeted libraries is presented in Figure 2. For the sake of brevity, we will only describe in this report the results obtained employing the readily obtainable[11] pyrid-2(1*H*)-one **A1**, pyridazin-3(2*H*)-one **A2**, and pyrimidin-2,4(1*H*,3*H*)-diones **A3**−**A5** as reactive scaffolds (Chart 1). Azinones **A** offer two orthogonal sites for diversification: the lactam NH group and the iodo substituent. Current synthetic approaches to access the target compounds would require the stepwise introduction of the alkyl moieties at the nitrogen, workup, isolation and purification, and then functionalization by PCR; however, this strategy makes it difficult to prepare a large number of analogues rapidly and with variable substitution at the nitrogen. For this reason, our aim was to find a high-throughput synthetic engine that would allow access to these derivatives in a one-pot procedure by a consecutive alkylation−PCR sequence that avoids the workup and purification stages for intermediates (Scheme 1). Several elegant and efficient examples of library synthesis employing a post-coupling modification strategy have been described before;[12] however, to the best of our knowledge, the strategy documented here has not previously been described, probably due to optimization of the experimental conditions, which could be complicated, since usually PCRs require very specific catalysts and ligands to achieve optimal yields and selectivity.

The starting azinones **A** (Chart 1) were selected on the basis of factors such as diversity, availability, and reactivity. A plethora of transition metal-catalyzed reactions[10] have been successfully employed in organic chemistry, and from

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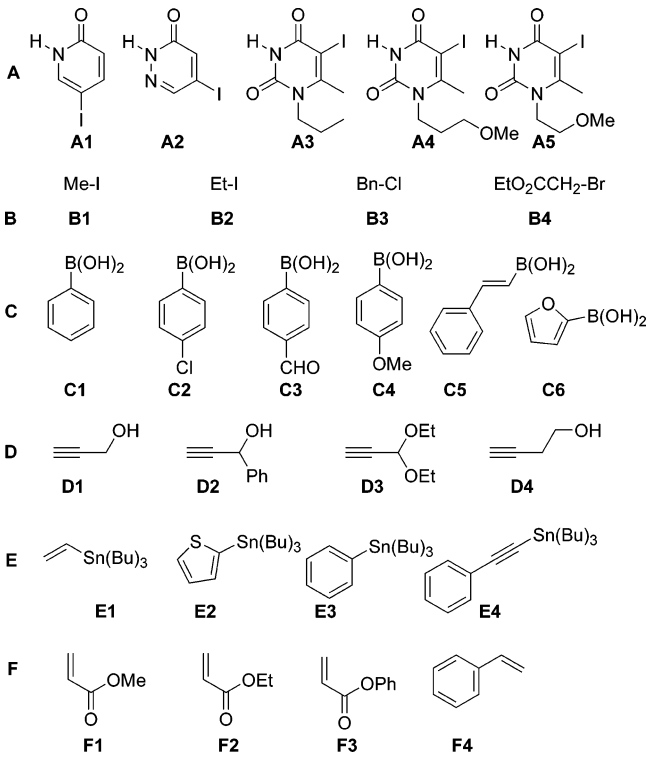
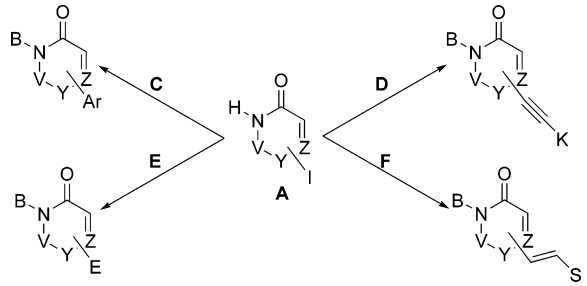
10.1021/cc050036t CCC: $30.25
Published on Web 05/12/2005

Chart 1. Representative Functionality of the Scaffolds (A) and Building Blocks (B−F)



Scheme 1. One-Pot Alkylation/Palladium-Catalyzed Functionalization of Azinones A[a]

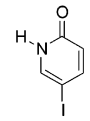
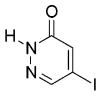
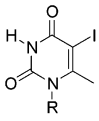


[a] Method C, alkylation−Suzuki sequence; method D, alkylation−Sonogashira sequence; method E, alkylation−Stille sequence; method F: alkylation−Heck sequence.

these, we chose the Suzuki, Sonogashira, Heck, and Stille couplings for this project. The commercial availability of the precursors required for the couplings, mild reaction conditions, and most importantly, their potential contribution to the diversity (covering aromatic, heteroaromatic, alkynyl, and alkenyl groups) of the resulting libraries were key factors in the selection process (Scheme 1, Chart 1).

The first stage of the study involved a comprehensive and judicious screening process to identify mild and selective alkylation conditions that could be optimized for each heterocycle and, most importantly, would be compatible with the subsequent PCR. A small subset of alkyl halides **B** (Chart 1) was employed to evaluate their functional group compatibility and potential utility as a source of diversity. The different parameters evaluated were regiochemistry, yield, solvent and base effect, and the reaction times[13] (Table 1). Relatively weak bases (K_2CO_3 or TEA) were employed in all methods in combination with DME−H_2O,

Table 1. Optimized Experimental Conditions to Perform the One-Pot Alkylation/Palladium-Catalyzed Functionalization of Azinones A[a]

Entry	Scaffold	Suzuki (C)	Sonogashira (D)	Stille (E)	Heck (F)
1		A1C 1) B–X/K_2CO_3, TBAB/DME. 2) ArB(OH)$_2$, Pd(PPh$_3$)$_4$, DME-H_2O	A1D 1) B–X/Et_3N, DMF. 2) HC≡C–K/ CuI $Cl_2Pd(PPh_3)_2$,	A1E 1) B–X/K_2CO_3, TBAB/Toluene. 2) $(R)_3Sn$–E, $Cl_2Pd(PPh_3)_2$	A1F 1) B–X/K_2CO_3, TBAB/MeCN. 2) CH=CH–S, Pd/C
2		A2C 1) B–X/K_2CO_3, TBAB/DME. 2) ArB(OH)$_2$, Pd(PPh$_3$)$_4$, DME-H_2O	A2D 1) B–X/K_2CO_3, TBAB/DME. 2) HC≡C–K/CuI $Cl_2Pd(PPh_3)_2$, DME-H_2O	A2E 1) B–X/K_2CO_3, TBAB/DMF. 2) $(R)_3Sn$–E, $Cl_2Pd(PPh_3)_2$	A2F 1) B–X/K_2CO_3, TBAB/ MeCN. 2) CH=CH-S, Pd/C
3		A3-5C 1) B–X/K_2CO_3, TBAB/ DME. 2) ArB(OH)$_2$, Pd(PPh$_3$)$_4$, DME-H_2O	A3-5D -	A3-5E 1) B–X/K_2CO_3, TBAB/Toluene. 2) $(R)_3Sn$–E, $Cl_2Pd(PPh_3)_2$	A3-5F 1) B–X/K_2CO_3, TBAB/DMF. 2) CH=CH–S, Pd/C

[a] Reactions were performed employing 5 mol % of the required catalyst.

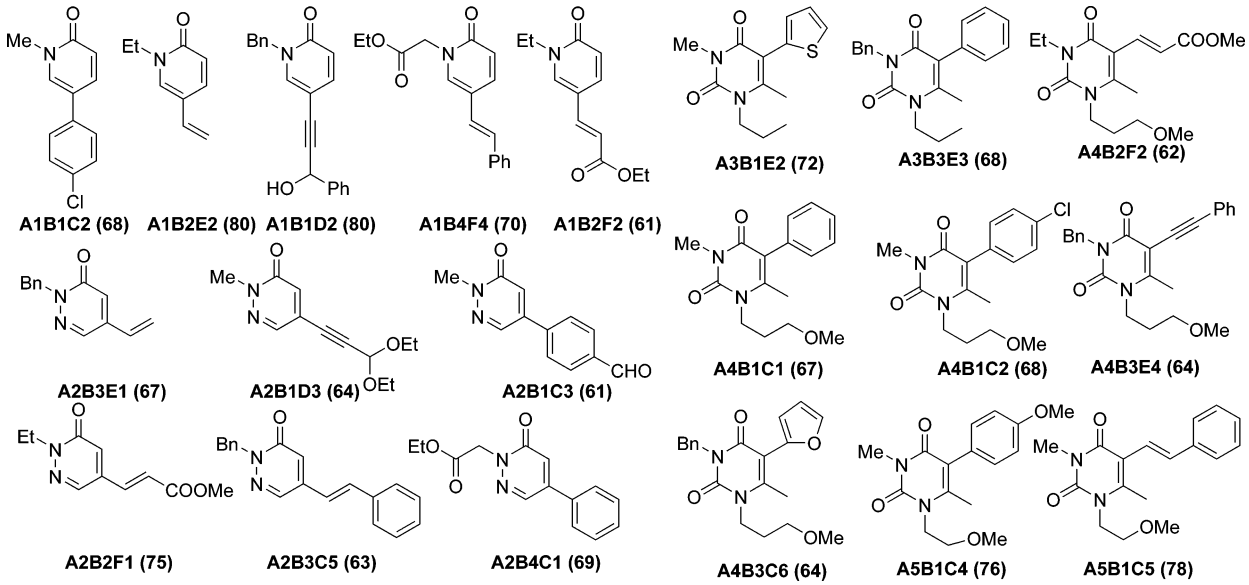
DMF, or acetonitrile as solvents. As expected, K_2CO_3 proved to be a superior base for the alkylation of the NH group of azinones **A**. In all cases, the use of a catalytic amount of TBAB had a positive effect and facilitated the solubility of the reagents, a fast alkylation, and in the case of the Suzuki couplings, activated the boronic acids. Interestingly, these experiments allowed us to identify conditions in which K_2CO_3 (a base usually only employed in Suzuki couplings) can be successfully employed as a base for Sonogashira or Heck couplings on **A**; the one exception being the Sonogashira coupling on iodopyrid-2(1*H*)-one **A1**, which required the use of TEA (Table 1).

Once different alkylation conditions had been optimized, the studies aimed at performing the decoration of the heterocyclic scaffolds **A** (by arylation, alkenylation, or alkynylation) were initiated. A representative selection of the diversity elements incorporated during library production is shown in Chart 1. These were introduced using boronic acids (**C1**−**6**), terminal acetylenes (**D1**−**4**), stannanes (**E1**−**4**), or monosubstituted olefins (**F1**−**4**) as reactive precursors (Chart 1). Optimized conditions are presented in Table 1; all experiments were performed employing 5 mol % of the required palladium catalyst. The standard procedures for each transformation were tested in initial experiments, but these conditions were modified to ensure functional group compatibility and to develop high-throughput syntheses that would enable workup and isolation of products.

Subsequent Suzuki arylation (Table 1, method C) of the in situ N-alkylated building blocks was easily performed under Gronowitz's[14] conditions (Table 1) and afforded the expected derivatives in satisfactory yield and with high purity (Chart 2).

Different bases and solvents were tested to obtain satisfactory yields in the one-pot alkylation−Sonogashira alkynylation sequence on **A** (method D). Optimized conditions for pyridin-2(1*H*)-one **A1** and pyridazin-3(2*H*)-one **A2** are illustrated in Table 1 (method D). Unfortunately, all attempts to perform such a transformation on uracils **A3**−**5** afforded mixtures of compounds in which the desired alkynyl derivatives were present in low yields (27−44%). The

Chart 2. Representative Structure of Diversely Functionalized Azinones Produced[a]



[a] Yields are reported in parentheses.[15]

underrepresented chemical space of alkynyluracils (**A3**−**5BD**) was successfully covered by exploiting the excellent potential offered by the Stille reaction in terms of diversity (Chart 1). Standard conditions were employed to introduce different functional fragments (Chart 1) on **A** using Stille coupling (Table 1, method E).

A systematic evaluation of the optimum combination of reagents to introduce alkenyl fragments into **A** under Heck conditions (method F) was carried out. Optimized conditions are showed in Table 1. It was found that the homogeneous palladium catalysts and complexes usually employed in the Heck reaction[10] {$Pd(AcO)_2$, $Pd(dba)_2$, $Cl_2Pd(PPh_3)_2$} can be successfully replaced by 5% Pd/C and that this change is also compatible with the use of K_2CO_3 as a base (Table 1).

The synthesis, isolation, and purification of compounds were accomplished using equipment routinely available in laboratories for parallel synthesis. A PLS (6 × 4) organic synthesizer was used for compound preparation; isolation of precipitated/triturated products was performed in a 12-channel vacuum manifold from Aldrich, fitted with Aldrich bond-elut reservoirs. Solvent removal was achieved using standard techniques or an evaporation module from Advanced Chemtech. Compounds were purified by column chromatography or by filtration through a plug of silica gel and then characterized by spectroscopic and analytical data.

In summary, a simple, modular consecutive alkylation/palladium catalyzed procedure to prepare libraries of functionalized azinones has been developed. Furthermore, the potential of PCR as a source of diversity in combinatorial chemistry has been demonstrated. These methodologies have addressed our requirements for original and functionalized privileged scaffolds for HTS and the synthesis of new libraries in a cost- and time-effective manner.

Acknowledgment. This work was financially supported by the Comisión Española de Ciencia y Tecnología CICYT and the European Community (EFRD fund Project 1FD 97-2371-C03-03). The authors thank Professor E. Raviña for the use of research facilities.

Supporting Information Available. Detailed experimental procedures, spectroscopic data, analytical data and copies of NMR, IR and mass spectra for representative compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) Methods that required more than 2 h to afford the alkylated products were not considered in the development of the high-throughput synthesis, even when satisfactory yields were obtained.

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(15) Reported yields correspond to purified (recrystallised or chromatographed) compounds.

CC050036T