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# N–H Insertion Reactions of Boc-Amino Acid Amides: Solution- and Solid-Phase Synthesis of Pyrazinones and Pyrazines

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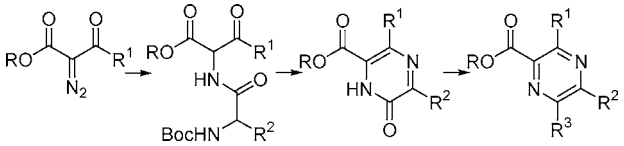
## ABSTRACT



**A series of α-diazo-β-ketoesters were reacted with Boc amino acid amides in the presence of rhodium octanoate catalyst. The resulting N–H insertion products were treated with acid, providing the 1,4-azine intermediates, which were oxidized by air to form the corresponding pyrazine-6-one products. The pyrazine-6-ones were further derivatized by N-alkylation or by conversion to the arylpyrazines using sequential bromination and Suzuki coupling reactions.**

The synthesis of collections of small "druglike" compounds is of great importance to meet the need for high throughput screening programs in the search for new medicines.[1] Accordingly, simple methodologies that employ common reagents and reaction strategies, yet can yield a multitude of chemically and structurally diverse scaffolds are in high demand.[2] In addition, solid-phase strategies that enable the automated synthesis of chemical arrays are of great importance.[3] To these ends, research in our own laboratory has centered upon the utility of polymer-bound α-diazo-β-ketoesters[4] as modular building blocks for the synthesis of a plethora of different heterocycles. By utilizing the high synthetic utility of diazocarbonyl-functionalized molecules,[5] rhodium carbenoid N-H insertion reactions with primary amides, *N*-alkylanilines, and primary ureas have been employed to synthesize arrays of oxazoles,[6] indoles[7] and imidazolones,[8] respectively.

For the synthesis of imidazolones, a series of primary ureas were reacted with the polymer-bound α-diazo-β-ketoesters, and the five-membered ring was formed using an acid-catalyzed imine formation reaction. The efficiency of this methodology led us to speculate as to whether an imine-

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type formation reaction could also be used to prepare heterocyles from N-H insertion products with different ring sizes, as depicted in Figure 1. We were especially interested

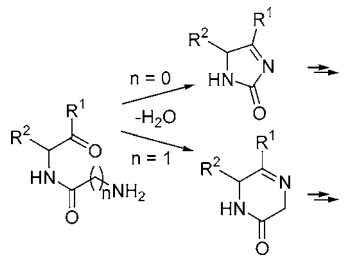
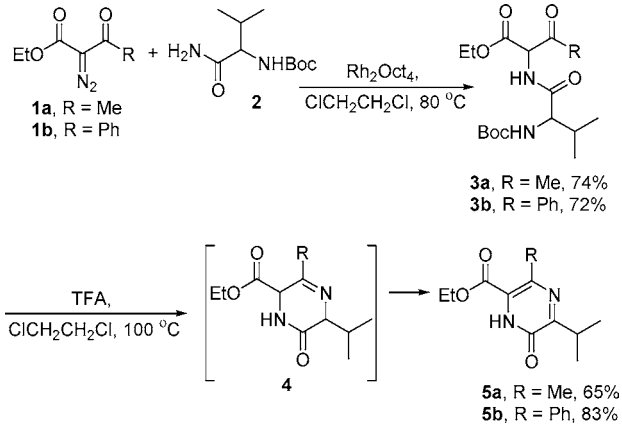



**Figure 1.** Intramolecular imine formation of N-H insertion products.

as to whether this chemistry could be used for the synthesis of pyrazines since this class of heterocylcle exhibits a wide range of biological functions, including the drug pyrazinamide that is used to treat tuberculosis.[9]

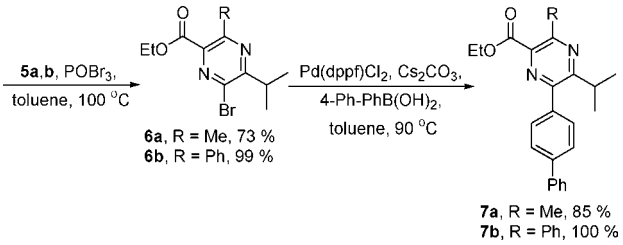
**Scheme 1**




To test this hypothesis, N-H insertion reactions of primary amino acid amides were explored.[10] More specifically, a series of α-diazo-*β*-ketoesters **1** were reacted with Boc-valine amide **2** in the presence of rhodium octanoate catalyst to give the corresponding N−H insertion product, α-acylamino-*β*-ketoester **3**. This set the stage to investigate the conversion of insertion product **3** into the corresponding cyclic products. Treatment of **3** with trifluoroacetic acid swiftly removed the Boc group as estimated by thin-layer chromatography (TLC). After this reaction was warmed, two new spots were observed by TLC; however, after continued heating, the lower $R_f$ product was completely consumed. After isolation of the products from these reactions, the spectroscopic data obtained were consistent with the 6-oxo-1,6-dihydro-pyrazine-2-carboxylic acid ester (pyrazine-6-ones) **5**. We believe that the intermediate product from this reaction was the cyclic imine **4**, which then is oxidized by atmospheric oxygen to form the stable product **5**.

With these results in hand, methodology to convert the pyrazine-6-ones into the fully aromatized pyrazines was investigated. Accordingly, treatment of pyrazine-6-ones **5** with phosphorus oxybromide in 1,2-dichloroethane gave the corresponding 6-bromopyrazines **6** in excellent yield, Scheme 2. Next, the 6-bromopyrazines **6** were subjected to Suzuki[11]

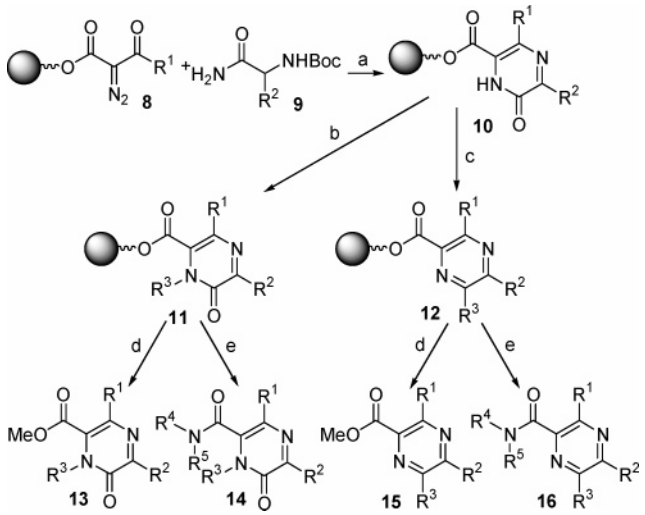
**Scheme 2**




coupling conditions; biphenyl boronic acid in the presence of cesium carbonate base and $Pd(dppf)Cl_2$ catalyst gave the 6-arylpyrazines **7** in excellent yields.

With a successful solution-phase strategy for the synthesis of pyrazine-6-ones and pyrazines developed, attention was turned to the synthesis of these scaffolds using a solid-phase approach, Scheme 3, Table 1. In this approach, the *J*anda*J*el[12] polymer-bound α-diazo-*β*-ketoesters[4] **8** were employed as the key building blocks.

**Scheme 3**[a]




[a] Reagents and conditions: (a) (i) **9** (3 equiv), $Rh_2Oct_4$ (2 mol %), $ClCH_2CH_2Cl$, 80 °C, 1 h; (ii) TFA (10 equiv), $ClCH_2CH_2Cl$, 3 h, then wash; (iii) AcOH (~20 equiv), $ClCH_2CH_2Cl$, 100 °C, 3 h. (b) Li$O^t$Bu (5 equiv), $R^3Br$ or $R^3I$ (10 equiv), DMF/THF 1:1, rt, 24 h. (c) (i) $POBr_3$ (7 equiv), $ClCH_2CH_2Cl$ 100 °C, 4 h; (ii) $ArB(OH)_2$ (7 equiv) $Cs_2CO_3$ (7 equiv), $Pd(dppf)Cl_2$ (3 mol %), toluene, rt, 24 h. (d) NaOMe (2.5 equiv), MeOH/THF 1:5, 60 °C, 2 h. (e) $R,^4R^5NH$ (5 equiv), $AlMe_3$ (2.5 equiv) toluene, 80 °C, 17 h.

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**Table 1.** Solid-Phase Synthesis of Pyrazine-6-ones **13** and **14** and Pyrazines **15** and **16**

| entry | $R^1$ | $R^2$ | $R^3$ | $R^4$ | $R^5$ | $R^6$ | product | purity (%)[a] | yield (%)[b] |
|---|---|---|---|---|---|---|---|---|---|
| 1 | Me | $^i$Pr | H | | | | **13** | *c* | 93 |
| 2 | Me | $^i$Pr | H | | Bu | H | **14** | 63 | 24 |
| 3 | Ph | $^i$Pr | H | | Bu | H | **14** | 88 | 49 |
| 4 | Me | Bn | H | | Bu | H | **14** | 58 | 32 |
| 5 | Me | Bn | H | | Bn | H | **14** | 48 | 26 |
| 6 | Me | $^i$Pr | Me | | | | **13** | *c* | 36 |
| 7 | Me | $^i$Pr | Bn | | | | **13** | *c* | 25 |
| 8 | Ph | $^i$Pr | Me | | | | **13** | *c* | 13 |
| 9 | Ph | Ph | Me | | Bu | H | **14** | *c* | 28 |
| 10 | Ph | Ph | Bn | | Ph | H | **14** | *c* | 59 |
| 11 | Ph | Ph | 4-ClBn | | Bu | H | **14** | *c* | 36 |
| 12 | Ph | Ph | 4-MeOBn | | Bn | H | **14** | *c* | 53 |
| 13 | Me | $^i$Pr | | 4-Ph-$C_6H_4$ | | | **15** | 87 | 60 |
| 14 | Me | $^i$Pr | | 4-Ph-$C_6H_4$ | -$(CH_2)_5$ | | **16** | 34 | 29 |
| 15 | Me | $^i$Pr | | 4-MeO-$C_6H_4$ | Bn | H | **16** | 26 | 23 |
| 16 | Ph | $^i$Pr | | Ph | Bu | H | **16** | 45 | 29 |
| 17 | Ph | $^i$Pr | | Ph | benzothaizole | | **16**[d] | *c* | 16 |
| 18 | Ph | $^i$Pr | | 4-Ph-$C_6H_4$ | | | **15** | 61 | 43 |
| 19 | Ph | $^i$Pr | | 4-Ph-$C_6H_4$ | Et | Et | **16** | 25 | 9 |
| 20 | Ph | $^i$Pr | | 4-Ph-$C_6H_4$ | Bn | H | **16** | 26 | 15 |
| 21 | Ph | $^i$Pr | | 4-MeO-$C_6H_4$ | morpholine | | **16** | 57 | 8 |

[a] Purity of crude product assessed using HPLC (254 nm). [b] Yield of pure product after isolation by preparative TLC. [c] Not determined. [d] Benzothiazole cleavage product prepared according to ref 14c.

Treatment of **8** with a series of Boc amino acid amides[13] **9** in the presence of rhodium catalyst gave the corresponding insertion products that were converted into the pyrazine-6-ones **10**. To devise milder conditions that are more amenable to the use of building blocks that contain diverse functional or protecting groups, the cyclization procedure was modified. After brief treatment with TFA to remove the Boc group, the intermediate was isolated by filtration and the excess TFA was washed away with solvent. Acetic acid was then added to effect the imine/pyrazine-6-one formation reaction to give the polymer-bound products **10**. Pyrazine-6-ones **10** were then subjected to further diversification before cleavage from the resin. N-Alkylation was performed by treating **10** with a mixture of lithium *tert*-butoxide base and either alkyl bromides or iodides in a DMF/THF solvent mixture. Alternatively, polymer-bound pyazine-6-ones **10** were treated with $POBr_3$ to provide the corresponding 6-bromopyrazines, which were reacted with a series of aryl boronic acids under solid-phase Suzuki coupling reactions to give the corresponding 6-arylpyrazines **12**. Finally, both the pyrazine-6-one **11** and 6-arylpyrazine **12** scaffolds were cleaved from the resin either by using transesterification with sodium methoxide or by a diversity-building amide formation/resin-cleavage reaction[14] to give the products **13**, **14**, **15**, and **16**.

The results from this study for the preparation of a small library of pyrazine-6-ones and 6-arylpyrazines are outlined in Table 1. Given the number of steps in the library synthesis, in most cases the purified products were isolated in modest to good yields based upon the loading of starting resin **8**, (8−93%, av 34%) and the purity of the crude products was 25−88% (av 52%) as estimated by HPLC.

In summary, new methodology for the efficient synthesis of pyrazin-6-ones and pyrazines utilizing a rhodium-catalyzed N−H insertion reaction between Boc amino acid amides and α-diazo-β-ketoesters as the key step has been developed. These N-H insertion products are easily converted into the corresponding pyrazin-6-ones by acid-promoted cyclodehydration and can be further decorated by N-alkylation with alkyl halides. Alternatively, the pyrazin-6-ones are converted readily into the corresponding 6-bromopyrazines that can be further elaborated using Suzuki cross coupling reaction with aryl boronic acids. Finally, we have shown that this methodology is amenable to the synthesis of libraries using solid-phase procedures.

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**Supporting Information Available:** Representative procedures, characterization of all products, and $^1$H NMR spectra of compounds **3**−**16**. This material is available free of charge via the Internet at http://pubs.acs.org.

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