Regioselective addition of Grignard reagents to N-acylpyrazinium salts: synthesis of substituted 1,2-dihydropyrazines and Δ⁵-2-oxopiperazines

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Abstract

The regioselective addition of Grignard reagents to mono- and disubstituted N-acylpyrazinium salts affording substituted 1,2-dihydropyrazines in modest to excellent yields (45–100%) is described. Under acidic conditions, these 1,2-dihydropyrazines can be converted to substituted Δ⁵-2-oxopiperazines providing a simple and efficient approach towards their preparation.

Introduction

Pyrazine and piperazine ring systems are key structural elements in a large number of biologically active molecules [1-6]. Compounds containing these scaffolds were shown to behave as anticancer agents [2-5], sodium channel blockers [5], and also display antiviral activity [7]. Due to their appearance in an array of biologically active small molecules and natural products, efficient synthetic routes into this class of privileged structures would be very beneficial [7,8]. One approach towards their synthesis involves the addition of nucleophiles to activated pyrazines. We recently showed that 3-alkoxy-substituted N-acylpyrazinium salts can be selectively reduced by tributyltin hydride to afford 1,2-dihydropyrazines in good to excellent yields [9]. There have been other reports involving the addition of TMS-ketene acetalts to pyrazinium salts [10-12]. A double nucleophilic addition of bis(trimethylsilyl)ketene acetalts to pyrazines activated with methyl chloroformate was found to afford polycyclic γ-lactones in moderate yields [3,10,11]. The work by Garduño-Alva and co-workers demonstrated that these
TMS-ketene acetals can be regioselectively added to substituted N-triflate pyrazinium salts to also generate γ-lactones [12].

Grignard reagents have been used as nucleophiles on a variety of N-acyl-activated pyridines in the production of natural products and biologically active small molecules [13-20]. To our surprise, there are no reports on the nucleophilic addition of Grignard reagents to N-acylpriazinium salts. A literature search showed this organometallic reagent reacting with pyrazine N-oxides towards the one-pot synthesis of N-Boc-protected N-hydroxy-substituted piperazines in good yields [6]. Methylmagnesium iodide was observed adding to 2-cyano-6-morpholinylpyrazine [21]. As a part of our continued exploration into the synthetic utility of N-acylpriazinium salts, herein we report the regioselective addition of Grignard reagents to mono- and disubstituted N-acylpriazinium salts towards the synthesis of 1,2-dihydropyrazines and Δ5-2-oxopiperazines.

**Results and Discussion**

Our journey began by first reacting 2-methoxypyrazine with phenyl chloroformate to generate the N-acylpriazinium salt 2 using DCM as the solvent. Next, phenylmagnesium bromide in THF was added at −41 °C. After stirring for 60 min, dihydropyrazine 3a was isolated in a yield of 40% (entry 1, Table 1).

This initial low yield prompted us to switch the Grignard solvent from THF to DCM. Using modified reaction conditions from Andersson and co-workers [22], phenylmagnesium bromide in DCM was added to 2 at −41 °C and after 35 min, dihydropyrazine 3a was only isolated in a 32% yield (entry 2, Table 1). The lower yields appear to be caused by the Grignard attacking the carbonyl of the N-acyl salt 2 causing the formation of phenyl benzoate. When toluene was used as the solvent, both 3a and the ester were obtained in yields of 41% and 39%, respectively (entry 3, Table 1). Changing the solvent to diethyl ether showed no improvement in the yield of 3a but when THF was used, an excellent yield of 87% was produced (entries 4 and 5, Table 1).

Based on our previously developed selective tin hydride reduction of monosubstituted pyrazinium salts [9], we expected the Grignard reagent to add regioselectively to give 1,2-dihydropyrazine 3a. DFT calculations support the observations that the isolated regioisomer we obtained was the result of a thermodynamically favored 1,2-addition over a 1,6-addition [9]. It has also been shown that TMS-ketene acetals add selectively to N-triflate pyrazinium salts [12]. 1H NMR analysis confirmed this by showing a rotameric pair of singlets at 3.89 and 3.84 ppm for the methoxy group at C3, a rotameric pair of singlets at 5.89 and 5.58 ppm for the proton at C2 and a rotameric pair of doublets at 6.17, 6.15 ppm and 6.68, 6.63 ppm for the two vinyl protons at C5 and C6, respectively. This result is in agreement with our observation that nucleophiles favored 1,2-addition over a 1,6-addition [9]. A formation of 1,6-dihydropyrazine was not observed.

With THF identified as the optimal solvent to use, we sought to expand the scope of the Grignard addition to various mono- and disubstituted N-acylpriazinium salts (Figure 1). Phenyl chloroformate was the acylating reagent of choice for this study due to benzyl or methyl chloroformates producing products in very poor yields. A variety of alkyl Grignard reagents were shown to add regioselectively to methoxy-substituted salts to give the dihydropyrazines in yields ranging from 48% to 73% (Figure 1, compounds 3b-g). Aryl Grignard reagents containing an elec-

| entry | solvent | time (min) | yield 3a (%) |
|-------|---------|------------|--------------|
| 1     | DCM     | 60         | 40           |
| 2     | DCM     | 35         | 32           |
| 3     | toluene | 40         | 41<sup>a</sup>|
| 4     | diethyl ether | 60 | 15           |
| 5     | THF     | 30         | 87<sup>b</sup>|

<sup>a</sup>Grignard reagent in THF. <sup>b</sup>Isolated yields. <sup>c</sup>Grignard reagent added as solution in DCM. <sup>d</sup>PhCO<sub>2</sub>Ph (39%) was also isolated. <sup>e</sup>Trace amounts of the ester byproduct PhCO<sub>2</sub>Ph was isolated.
Figure 1: Regioselective addition of Grignard reagents to mono- and disubstituted pyrazinium salts (yields refer to isolated yields).
tron-withdrawing and donating group proceeded to give the desired substituted products in moderate yields (Figure 1, compounds 3b–j). The examination of the Grignard addition to benzyloxy- or p-methoxybenzyloxy (PMB)-substituted pyrazinium salts, resulted in obtaining dihydropyrazines in yields that were comparable to the methoxy salts (Figure 1, compounds 4a,b and 5).

We next subjected disubstituted N-acylpyrazinium salts to this reaction. Based on our results from the monosubstituted substrates, a 1,2-addition of the Grignard was expected to occur. When an aryl group was present on the ring, trisubstituted dihydropyrazines in good yields ranging from 78–100% were produced (Figure 1, compounds 6, 7a,b and 12). An alkyl substitution with either an ethyl or benzyl group on the pyrazinium salts gave an 81% yield for both 10 and 11 (Figure 1). Reacting a Grignard with pyrazinium salts disubstituted with electron-donating alkoxy groups gave us the desired dihydropyrazine in moderate to good yields of 45–88% (Figure 1, compounds 8, 9a,b) while the presence of an electron-withdrawing ester group generated 13 in a yield of 49%.

With the substituted 1,2-dihydropyrazines in hand, we next wanted to demonstrate their usefulness for synthesizing substituted Δ⁵-2-oxopiperazines. Processes into this structural motif would be very useful due to their presence in a variety of biologically active small molecules and natural products [23-30]. We previously reported that 3-methoxy-1,2-dihydropyrazines can be easily converted to Δ⁵-2-oxopiperazines using 1 M HCl(aq) in methanol [9]. When we applied these acidic conditions on the phenyl-substituted 3-methoxy-1,2-dihydropyrazine 3a, only a 5% yield of Δ⁵-2-oxopiperazine 14a was obtained (Table 2, entry 1). This low yield appears to be due to the presence of a ring-opened side product [31]. The yields of the Δ⁵-2-oxopiperazines were improved to 61% and 92%, respectively, when the reaction was repeated on phenyl-substi-

### Table 2: Conversion of dihydropyrazine to Δ⁵-2-oxopiperazines under acidic conditions.

| entry | R  | R¹  | R²  | acid                  | time (min) | product | yield (%)a |
|-------|----|-----|-----|-----------------------|------------|---------|------------|
| 1     | H  | Me  | Ph  | HCl(aq)/MeOH          | 60         | 14a     | 5          |
| 2     | H  | Bn  | Ph  | HCl(aq)/MeOH          | 45         | 14a     | 61         |
| 3     | H  | PMB | Ph  | HCl(aq)/MeOH          | 60         | 14a     | 92         |
| 4b    | H  | Me  | Ph  | HCl/dioxane           | 30         | 14a     | 93         |
| 5b    | H  | Me  | Bn  | HCl/dioxane           | 30         | 14b     | 95         |
| 6b    | H  | Me  | 2-BrBn | HCl/dioxane       | 45         | 14c     | 85         |
Table 2: Conversion of dihydropyrazine to Δ5-2-oxopiperazines under acidic conditions. (continued)

| entry | R        | product | yield (%) |
|-------|----------|---------|-----------|
| 7b    | H        | 14a     | 100       |
| 8b    | H        | 14a     | 100       |
| 9b    | p-MeOPh  | Me      | 73        |

*aIsolated yields. b4 M HCl/dioxane was used.

Table 3: One-pot synthesis of substituted Δ5-2-oxopiperazines.

| entry | R | product | yield (%) |
|-------|---|---------|-----------|
| 1     | H | 14a     | 80        |
| 2     | Et| 15b     | 80        |
1 M HCl$_{aq}$/MeOH was added and the reaction was monitored by TLC. After 1 h, the hydrolysis of 4b was completed to give 14a in a good yield of 80% (Table 3, entry 1). Disubstituted $\Delta^5$-2-oxopiperazines 15b–d can be made similarly with yields ranging from 71–80% (Table 3, entries 2–4). This simple approach towards $\Delta^5$-2-oxopiperazines provides access into compounds that can be reduced into mono- and disubstituted 2-oxopiperazines [33,34]. This structure is a common scaffold found in natural products and biologically active small molecules [23].

**Conclusion**

In conclusion, we have demonstrated that various Grignard reagents can be regioselectively added to mono- and disubstituted N-acylpyrazinium salts to give di- and trisubstituted 1,2-dihydropyrazines in moderate to excellent yields. Under acidic conditions, the dihydropyrazines can be easily converted to substituted $\Delta^5$-2-oxopiperazines. These compounds can potentially serve as templates for making substituted 2-oxopiperazines. The investigation into the synthetic utility of this reaction is currently underway and will be reported in due course.

**Supporting Information**

Supporting Information File 1

Experimental section and NMR spectra. [https://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-15-8-S1.pdf]

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