RESEARCH LETTER

Greener approach toward one pot route to pyrazine synthesis

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A very simple, cost effective, and environmentally benign method has been reported for the preparation of pyrazine derivatives of pentacyclic triterpenoids. The versatility of the method is determined by synthesizing a large number of pyrazine derivatives of smaller molecules.

Keywords: green synthesis; one pot; triterpenoid; pyrazine; cost effective

Introduction

Compounds containing N-heterocyclic moieties are a class of privileged compounds that have found numerous applications as pharmaceuticals. Pyrazines are important components of aroma fragrances (1), potential pharmacophore of a large number of biologically active substances (2–6), and widely used as agrochemicals (7–9). For example, methoxy pyrazines are relevant components of aromas of many fruits, vegetables, and wines; methyl phenyl derivatives of dihydropyrazines inhibit the growth of *Echerichia coli* by generating hydroxyl and carbenecentered radicals that cause DNA strand breakage; and alklypyrazines have been recognized as flavor components in foods, as pheromones in various insect species (7, 8), and as versatile synthetic intermediates. Pyrazine derivatives are known for use as relaxing cardiovascular and uterine smooth muscle, anti-thrombotic, anti-aggregation, COX-2 inhibiting, and analgesic effects (10). Because of the wide variety of applications associated with the pyrazine moieties, their synthesis has remained the goal of many research groups over the years. Among the various methods developed, pyrazine compounds are synthesized by the reaction of diamines with diols in a vapor phase reaction in presence of granular alumina (11). Catalytic systems such as copper-chromium (12), copper-zinc-chromium (13), zinc-phosphoric acid-manganese (14), and silver (15) are also patented as catalysts for the preparation of 2-methylpyrazine from ethylene-diamine and propylene glycol. Pyrazines are also obtained from condensation reaction of aldehydes and epoxides using copper-chromium catalyst (16), condensation reaction between alkanolamines (17), or cyclodehydrogenation of N-(hydroxyalkyl) alkyldiamine (18) using the same catalysts. In the presence of a palladium catalyst, dehydrogenation of piperazines yields corresponding pyrazines in high yield (19). Recently, synthesis of pyrazines from α-hydroxy ketones and 1,2-diamines via MnO2 catalyzed tandem oxidation process under refluxing conditions has been reported, but the yields are not encouraging and the loading of the catalyst was also high (20). The method of bubbling oxygen under refluxing condition (21) suffers from scientific drawbacks. Strategically, direct condensation reaction of 1,2-diketones with 1,2-diamine (22) is the most straightforward as well as the classical route for the preparation of pyrazines via dihydropyrazines (22). Although, a number of methods are reported in literature for the synthesis of pyrazine, none of them was found to be effective because of poor yield, harsh reaction condition, and tedious work-up procedures (23). Attempts to carry out dehydrogenation under a variety of milder and more convenient laboratory procedures were not successful (24). Although, some of them are apparently useful, most of them are limited by long reaction time, low yields, and use of toxic solvents or heavy metals as the catalyst (24). Therefore, development of mild, efficient, and environmentally benign method for synthesizing pyrazines has been a major challenge in contemporary organic synthesis.

Results and discussion

Triterpenoids are widely distributed in nature, and recent reports have demonstrated the interesting biological activities of this class of natural products. However, triterpenoids possessing a nitrogen containing
heterocycle condensed to an isoprenoid skeleton are rare. Since compounds containing $N$-heterocyclic moieties have found numerous applications as pharmaceuticals as well as in medicines, it is also anticipated that incorporation of a pyrazine ring into the molecule of a pentacyclic triterpenoid may induce or enhance its biological activity. With this view in mind and in continuation of our studies on the transformative reactions of triterpenoids, we report herein the incorporation of pyrazine ring into ring A of the pentacyclic triterpenoids of lupane and friedelan skeleton (Schemes 1 and 2). The protocol comprises a direct condensation between the respective 1,2-diketo compounds with 1,2-diamines in aqueous methanol catalyzed by potassium tert-butoxide ($t$-BuOK) at room temperature. This high yielding process did not require any added expensive catalyst or bubbling of oxygen (21) at higher temperature (Scheme 1). Detection of dihydropyrazine along with pyrazines as well as the starting material at an early stage of the reaction indicated that the developed method involved aromatization following a very simple one pot route via the formation of dihydropyrazine, removing any additional steps as reported in literature.

In order to show the general applicability, we attempted our procedure using a number of both structurally and chemically diversified 1,2-dicarboxyls and 1,2-diamines to synthesize pyrazine derivatives (Table 1) and were able to get identical results in each case. Thus, this cost-effective process may also be considered as an excellent environmentally benign alternative for the preparation of pyrazine derivatives from a host of compounds (Scheme 3).

**General experimental detail**

All the melting points were determined in an open capillary method; UV spectra were recorded in JASCO V-530 UV/VIS spectrophotometer; IR was recorded in Perkin-Elmer FT-IR spectrophotometer; and NMR was recorded in Bruker-Avance 300 MHz FT-NMR instrument using TMS as the internal standard. NMR spectra were recorded in CDCl$_3$. 

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**Scheme 1.** Preparation of diketo derivatives and synthesis of pyrazine derivative.

**Scheme 2.** Preparation of diketofriedelin and synthesis of pyrazine derivative.

**Scheme 3.** Preparation of pyrazines. $R_1$ may be alkyl, aryl or furyl group; $R_2$ may be alkyl, aryl or furyl group or hydrogen; $R_3$ may be hydrogen, alkyl or nitrile group; $R_4$ may be hydrogen or nitrile group.
Table 1. Selective synthesis of pyrazine.

| Entry | 1,2-Diketone | 1,2-Diamine | Time (h) | Pyrazine | % Yield |
|-------|--------------|-------------|----------|----------|---------|
| 1     | ![image](image1.png) | ![image](image2.png) | 8 | ![image](image3.png) | 82 |
| 2     | ![image](image4.png) | ![image](image5.png) | 8 | ![image](image6.png) | 78 |
| 3     | ![image](image7.png) | ![image](image8.png) | 7.5 | ![image](image9.png) | 82 |
| 4     | ![image](image10.png) | ![image](image11.png) | 10 | ![image](image12.png) | 84 |
| 5     | ![image](image13.png) | ![image](image14.png) | 8 | ![image](image15.png) | 76 |
| 6     | ![image](image16.png) | ![image](image17.png) | 8 | ![image](image18.png) | 78 |
| 7     | ![image](image19.png) | ![image](image20.png) | 8.5 | ![image](image21.png) | 78 |
| 8     | ![image](image22.png) | ![image](image23.png) | 8 | ![image](image24.png) | 86 |
| 9     | ![image](image25.png) | ![image](image26.png) | 4 | ![image](image27.png) | 86 |
Table 1 (Continued)

| Entry | 1,2-Diketone     | 1,2-Diamine | Time (h) | Pyrazine     | % Yield |
|-------|------------------|-------------|----------|--------------|---------|
| 10    | ![1,2-Diketone](image) | ![1,2-Diamine](image) | 3.5      | ![Pyrazine](image) | 88      |
| 11    | ![1,2-Diketone](image) | ![1,2-Diamine](image) | 5        | ![Pyrazine](image) | 78      |
| 12    | ![1,2-Diketone](image) | ![1,2-Diamine](image) | 3.5      | ![Pyrazine](image) | 82      |
| 13    | ![1,2-Diketone](image) | ![1,2-Diamine](image) | 4        | ![Pyrazine](image) | 76      |
| 14    | ![1,2-Diketone](image) | ![1,2-Diamine](image) | 4.5      | ![Pyrazine](image) | 74      |
| 15    | ![1,2-Diketone](image) | ![1,2-Diamine](image) | 5        | ![Pyrazine](image) | 76      |
| 16    | ![1,2-Diketone](image) | ![1,2-Diamine](image) | 4.5      | ![Pyrazine](image) | 78      |
| 17    | ![1,2-Diketone](image) | ![1,2-Diamine](image) | 6        | ![Pyrazine](image) | 76      |
| 18    | ![1,2-Diketone](image) | ![1,2-Diamine](image) | 7        | ![Pyrazine](image) | 82      |

Note: % Yield refers to the isolated yield of all the compounds.
The entire chemicals were purchased from Merck, Fluka, SRL, and S.D. fine chemicals companies. The reagents from Merck and Fluka were used as received and others were purified following the standard methodology prior to their use. Betulinic acid, lupeol, and friedelin were isolated from their natural sources (see supporting information).

**Preparation of 1,4-pyrazine derivatives**

In a typical reaction procedure, in a 50 ml round bottom flask, 2 mmol of recrystallized benzil was dissolved in 3 ml of aqueous methanol and was made homogeneous by stirring with a magnetic spinning bar. To this 2 mmol of ethylene diamine and catalytic amount of t-BuOK (10 mg or 0.08 mmol) were added. Stirring was continued until the reaction is completed (checked by TLC). Methanol was evaporated under reduced pressure, and the crude product was purified by chromatography using silica gel. Varied proportion of petroleum ether and ethyl acetate was used as eluent.

**Conclusion**

A mild, efficient, and environmentally benign method has been developed for the synthesis of pyrazines that is superior in every respect than the already reported methods. Introduction of the pyrazine nucleus is expected to induce potent biological activity into the triterpenoids that will be tested with the help of a sister institution having these facilities. The data obtained in the process may be helpful to study the SAR (structure–activity relationship) among this particular class of compounds, especially the triterpenoids of above skeletons.

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**SUPPORTING INFORMATION**

**General experimental detail**

All the melting points were determined in an open capillary method, UV spectra were recorded in JASCO V-530 UV/VIS spectrophotometer; IR spectra was recorded in Perkin-Elmer FT-IR spectrophotometer; NMR was recorded in Bruker-Avance 300 MHz FT-NMR instrument using TMS as the internal standard. NMR spectra were recorded in CDCl₃. The chemicals/reagents purchased from Merck, Fluka, SRL, S d fine chemicals companies and were used either as received (Merck, Fluka) or after purification prior to use. Triterpenoids, Betulinic acid, lupeol and friedelin were isolated from their natural sources (Please see the supporting information) and were used as starting materials in the present investigation.

**Isolation of triterpenoids**

Betulinic acid, lupeol and friedelin were isolated from Biscofia javanica, Xanthozylum budrungs and quercus suber respectively in a soxhlet extractor using petroleum ether (60-80°C) as the solvent. All the triterpenoids were purified by column chromatography followed by crystallization.

**Preparation of diketo derivatives**

Betulinic acid and lupeol were hydrogenated and oxidized to get the corresponding 3-keto compound. The corresponding diketo compounds were prepared by auto-oxidation of each of them following the method as reported elsewhere (Gangully, A. K.; Govindachari, T. R.; Mohamed, P. A. Tetrahedron, 1966, 22, 3597-3599.). Diketo derivative of friedelin was prepared by SeO₂ oxidation of friedelin in aq. Dioxin.

**Preparation of 1, 4-pyrazine derivatives**

In a typical reaction procedure, in a 50 ml round bottom flask 2 mmol of recrystallized benzil was dissolved in 3 ml of wet methanol and was made homogeneous by stirring with a magnetic spinning bar. To this 2 mmol of ethylene diamine and small amount of tBuOK were added. Stirring was continued until the reaction was complete (checked by tlc). Methanol was evaporated under reduced pressure and the crude product was purified by chromatography using silica gel. Varied proportion of petroleum ether and ethyl acetate was used as eluent.

**CHARACTERIZATION OF SOME REPRESENTATIVE COMPOUNDS:**

2, 3-diphenyl pyrazine

![2, 3-diphenyl pyrazine](image)

$^1$H NMR (CDCl₃, 300MHz): $\delta$ 7.14-7.25 (m, 5H, five aromatic hydrogen); 7.37-7.44 (m, 5H, five aromatic hydrogen); 8.52 (s, 2H, 2 aromatic hydrogen of the heterocyclic moiety). $^{13}$C NMR (CDCl₃, 75MHz): $\delta$ 128.1, 128.2, 128.5, 129.5, 138.5, 141.9 and 152.6.

2, 3-di $p$-tolyl pyrazine

![2, 3-di $p$-tolyl pyrazine](image)

$^1$H NMR (CDCl₃, 300MHz): $\delta$ 2.31 (s, 6H, 2-CH₃); 7.04-7.12 (m, 3H, aromatic hydrogen); 7.27-7.46 (m, 5H, five aromatic hydrogen); 8.51 (s, 2H, two aromatic hydrogen of the heterocyclic moiety). $^{13}$C NMR (CDCl₃, 75MHz): $\delta$ 21.3, 129.0, 129.4, 135.8, 138.5, 141.7 and 152.6.

2, 3-bis (4-methoxy phenyl) pyrazine

![2, 3-bis (4-methoxy phenyl) pyrazine](image)

$^1$H NMR (CDCl₃, 300MHz): $\delta$ 3.77 (s, 6H, 2-OCH₃); 6.75-6.85 (m, 4H, four aromatic hydrogen); 7.33-7.43 (m, 4H, four aromatic hydrogen); 8.45 (s, 2H, two aromatic hydrogen of the heterocyclic moiety). $^{13}$C NMR (CDCl₃, 75MHz): $\delta$ 55.2, 113.7, 130. 9, 131.2, 141.4, 152.1 and 159.9.

2-methyl-3-phenyl pyrazine

![2-methyl-3-phenyl pyrazine](image)
$^1$H NMR (CDCl$_3$, 300MHz): δ 2.54 (s, 3H, -CH$_3$); 7.46-7.59 (m, 5H, five aromatic hydrogen); 8.44 (d, 2H, J = 2.4Hz). $^{13}$C NMR (CDCl$_3$, 75MHz): δ 23.1, 128.4, 128.7, 128.9, 138.5, 141.5, 142.1, 151.8 and 154.4.

2, 3-diphenyl-5-methyl pyrazine

$^1$H NMR (CDCl$_3$, 300MHz): δ 1.86 (s, 3H, -CH$_3$); 6.63 (d, 10H, J = 5.1Hz, ten aromatic hydrogen); 7.68 (s, 1H, one aromatic hydrogen of the heterocyclic moiety). $^{13}$C NMR (CDCl$_3$, 75MHz): δ 20.5, 127.4, 127.6, 128.7, 128.8, 137.8, 141.0, 148.8, 150.3, 150.7.

2, 3-bis (4-methoxy phenyl)-5-methyl pyrazine

$^1$H NMR (CDCl$_3$, 300MHz): δ 2.62 (s, 3H, -CH$_3$); 3.80 (s, 6H, 2-OCH$_3$); 6.82 (dd, 4H, J = 1.8 Hz, four aromatic hydrogen); 7.38 (dd, 4H, J = 1.8 Hz, four aromatic hydrogen); 8.39 (s, 1H, one aromatic hydrogen of the heterocyclic moiety). $^{13}$C NMR (CDCl$_3$, 75MHz): δ 21.2, 53.4, 55.2, 130.8, 130.9, 131.2, 131.4, 141.1, 149.0, 150.5, 150.9, 159.8, 159.6.

5, 6-diphenyl pyrazine-2, 3-dicarbonitrile

$^1$H NMR (CDCl$_3$, 300MHz): δ 7.16-7.30 (m, 5H, five aromatic hydrogen); 7.45 (t, 2H, J = 7.3 Hz, two aromatic hydrogen); 7.57 (t, 1H, J = 7.3 Hz, aromatic hydrogen); 7.78 (d, 2H, J = 7.2 Hz, aromatic hydrogen). $^{13}$C NMR (CDCl$_3$, 75MHz): δ 126.5, 127.5, 128.2, 128.4, 130.0, 132.4, 137.5, 143.8, 196.8 (carbon of nitrile group).

5, 6-di$p$-tolylpyrazine-2, 3-dicarbonitrile

$^1$H NMR (CDCl$_3$, 300MHz): δ 2.32 (m, 6H, 2-CH$_3$); 6.99 (m, 4H, aromatic protons); 7.43 (m, 1H, aromatic proton); 7.94, (m, 3H, aromatic protons). $^{13}$C NMR (CDCl$_3$, 75MHz): δ 21.6, 126.8, 128.6, 129.3, 130.0, 139.2, 144.0, 144.3, 193.3.

2, 3 di-(furan-2-yl)-5-methyl pyrazine

$^1$H NMR (CDCl$_3$, 300MHz): δ 2.59 (s, 3H, -CH$_3$); 6.56 (m, 4H, aromatic protons); 7.52 (m, 2H, aromatic protons), 8.37 (s, 1H, aromatic proton). $^{13}$C NMR (CDCl$_3$, 75MHz): δ 21.3, 112.1, 112.7, 139.2, 140.8, 141.7, 143.4, 150.5, 150.6, 151.2.

5-phenylpyrazine 2, 3-dicarbonitrile

$^1$H NMR (CDCl$_3$, 300MHz): δ 7.61 (d, 3H, J = 7.5 Hz); 8.13 (d, 2H, J = 6.6Hz); 8.51 (s, 1H). $^{13}$C NMR (CDCl$_3$, 75MHz): δ 128.0, 129.8, 130.8, 132.5, 133.0, 144.1, 154.8.

5, 6-dieethylpyrazine-2, 3-dicarbonitrile

$^1$H NMR (CDCl$_3$, 300MHz): δ 1.39 (m, 6H); 1.97(m, 2H); 2.97 (m, 2H); $^{13}$C NMR (CDCl$_3$, 75MHz): δ 11.2, 19.8 (2-CH$_3$); 25.1, 27.8 (2-CH$_2$); 113.4, 130.2 (aromatic carbon); 161.3 (-CN).

Pyrazine-2, 3-dicarbonitrile
1H NMR (CDCl₃, 300MHz): δ 9.00 (s, 2H, aromatic protons). 13C NMR (CDCl₃, 75MHz): δ 113.1, 133.84 (aromatic carbons); 147.5 (-CN).

5-methyl-6-propioptyrazine-2, 3-dicarbonitrile

1H NMR (CDCl₃, 300MHz): δ 1.06 (t, 3H, J/C₃₀/7 Hz); 1.78-1.88 (m, 2H); 2.75 (s, 2H, -CH₃); 2.94 (t, 2H, J = 7.5 Hz). 13C NMR (CDCl₃, 75MHz): δ 13.8, 20.4, 22.3, 36.9, 113.3, 113.4, 129.9, 130.4, 157.7, 161.2.

2-methyl-3-propylpyrazine

1H NMR (CDCl₃, 300MHz): δ 0.96-1.04 (m, 3H, -CH₃); 1.70-1.82 (m, 2H); 2.57 (s, 3H, -CH₃); 2.79 (t, 2H, J = 7.5Hz). 13C NMR (CDCl₃, 75MHz): δ 14.0, 21.5, 21.7, 36.9, 141.1, 141.4, 152.3, 156.0.

1, 4-pyrazine derivative of 1, 2-diketo lupane

Crystallization afforded white needle shaped crystals, C₃₂H₅₀N₂, m.p. 220 °C, IR at 1650, 1430 and 1120 cm⁻¹. UV absorption maxima at 272nm (ε = 5831) and 278nm (ε = 5792). Anal. Calc.: 83.12% C, 10.82% H; found 83.10% C, 10.81% H. Mass spectrum showed molecular ion peak at m/z 462. 1H NMR (CDCl₃, δ ppm⁻¹ relative to TMS): 0.78, 0.83, 0.98, 1.11, 1.29, 1.31 (6s, 18H, 6t-CH₃); 0.77, 0.86 (2d, 6H, CH (CH₃)₂, J = 7 Hz); 2.47, 3.04 ppm (2d, J = 16 Hz); 8.27(d, J = 3 Hz); 8.41(dd, J = 3 Hz).

1, 4-pyrazine derivative of 1, 2-diketone of methyl dihydrobetulonate

Crystallization from CHCl₃-MeOH mixture, C₃₃H₅₀O₂N₂, m.p. 220 °C. IR spectrum showed peaks at 1710 cm⁻¹ (CO₂Me); 1665, 1430 and 1120 cm⁻¹. UV spectrum showed absorption maximum at 272nm (ε = 5712) and 278 nm (ε = 5603). Anal. Calc.: 78.26% C, 9.88% H, 5.53% N; found 78.25% C, 9.73% H, 5.50% N. Mass spectrum showed molecular ion peak at m/z 506 as base peak. 1H NMR (CDCl₃, δ ppm⁻¹ relative to TMS): 0.82, 0.985, 0.99, 1.28, 1.305, 0.76 and 0.88 ppm (2d, 6H, j = 7 Hz); 2.48, 3.04 ppm (2d J = 16 Hz); 8.27, 8.41 ppm (2d, J = 3 Hz); 3.66 (s, 3H, ester methyl).