



HAL
open science

On Reuben G. Jones synthesis of 2-hydroxypyrazines

Pierre Legrand, Yves Janin

► **To cite this version:**

Pierre Legrand, Yves Janin. On Reuben G. Jones synthesis of 2-hydroxypyrazines. Journées de Chimie Organique 2022, Nov 2022, Palaiseau, France. . hal-03932333

HAL Id: hal-03932333

<https://hal.science/hal-03932333>

Submitted on 10 Jan 2023

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

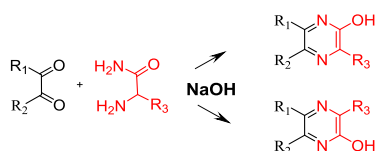


Distributed under a Creative Commons Attribution 4.0 International License

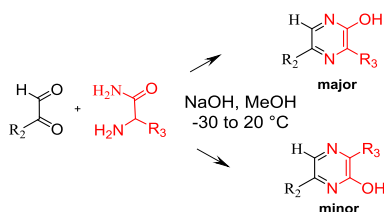
Pierre Legrand, Yves L. Janin

Synchrotron SOLEIL, L'Orme des Merisiers, 91190 Saint-Aubin, France.
Structure et Instabilité des Génomes (StrInG), Muséum National d'Histoire Naturelle, INSERM, CNRS, Alliance Sorbonne Université, 75005 Paris, France.

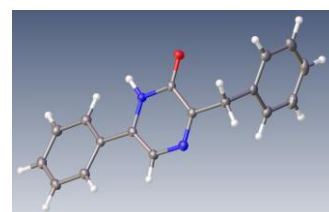
A double condensation between 1,2-dicarbonyls and α -aminoamides upon treatment with sodium hydroxide at low temperature to give hydroxypyrazines, which is "plagued with regioselectivity issues"



Jones, R.G. *J. Am. Chem. Soc.* **1949**, *71*, 78-81
Karmas, G.; Spoerri, P.E. *J. Am. Chem. Soc.* **1952**, *74*, 1580-1584
Konakahara, T.; Takagi, Y. *Heterocycles* **1978**, *9*, 1733-1739

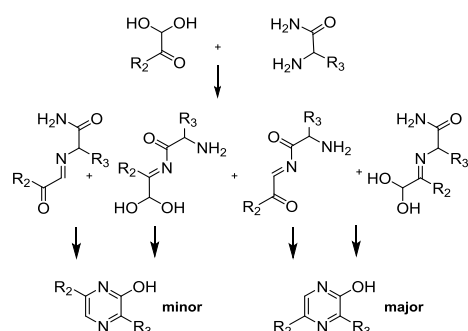


But, from α -ketoaldehyde, there is a degree of selectivity

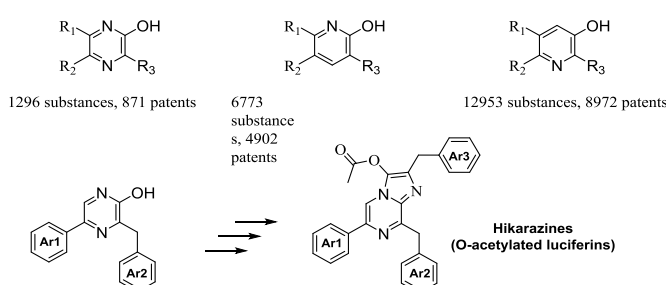


ORTEP of 4{1,2}

A counter-intuitive regioselectivity



Hydroxypyrazines are "under-represented in chemical libraries"



Coutant, E.P.; Gagnot, G.; Hervin, V.O.; Baatallah, R.; Goyard, S.; Jacob, Y.; Rose, T.; Janin, Y.L. *Chem. Eur. J.* **2020**, *26*, 948-958

Optimization and mechanism insights

-> Solvent, base, concentration, addition speed, temperature, reaction time...

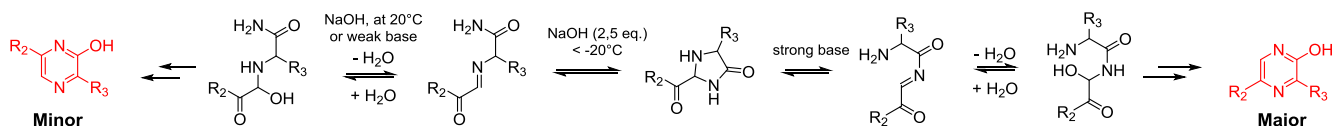
Table 1, condensation between 1{1} and 2{1}

1) Stirring in solvent (S), 2) Addition of base (B) with a (N) concentration, at speed s (mmol/min) and temperature T (°C), 3) Stirring for t h (from T back to 20 °C), 4) Addition of 4 eq. of 37% HCl, 5) Work up (neutralization and extraction) and chromatography. All reactions run at a 13.1 mmol scale in 35 mL of solvent.

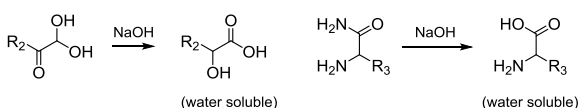
| Entry | T (°C) | eq. | N | B | S | s | t (h) | Comments | %3 | %4 |
|-------|--------|-----|-----|---------------------|------|-----|-------|--------------------------------|----|----|
| 1 | -78 | 2.5 | 6 | NaOH | MeOH | 65 | 2 | | 52 | 4 |
| 2 | -78 | 2.5 | 6 | NaOH | MeOH | 3.6 | 2 | | 68 | 3 |
| 3 | -78 | 2.5 | 2 | NaOH | MeOH | 2.3 | 2 | | 71 | 4 |
| 4 | -78 | 2.5 | 6 | NaOH | MeOH | 4.0 | 1 | | 61 | 2 |
| 5 | -78 | 2.5 | 6 | NaOH | MeOH | 4.6 | 4 | | 70 | 4 |
| 6 | -78 | 2.5 | 6 | NaOH | MeOH | 3.6 | 2 | NH ₄ Cl quench | 60 | 1 |
| 7 | 20 | 2.5 | - | NEt ₃ | MeOH | - | 18 | | 0 | 11 |
| 8 | reflux | 2.5 | - | NEt ₃ | MeOH | - | 22 | | 0 | 8 |
| 9 | -78 | 1.5 | 2 | NaOH | MeOH | 3.6 | 2 | 1.5 eq. of NaOH | 34 | 18 |
| 10 | -78 | 2.5 | 1.4 | NEt ₃ OH | MeOH | 2.2 | 2 | | 76 | 3 |
| 11 | -78 | 2.5 | 2 | NaOH | MeOH | 3.6 | 2 | 1 eq. of 1{1}, 0.5 eq. of 2{1} | 85 | 1 |
| 12 | -78 | 2.5 | 2 | NaOH | MeOH | 3.6 | 2 | 0.5 eq. of 1{1}, 1 eq. of 2{1} | 74 | 3 |

Table 2, condensation between 1{1} and 2{2}

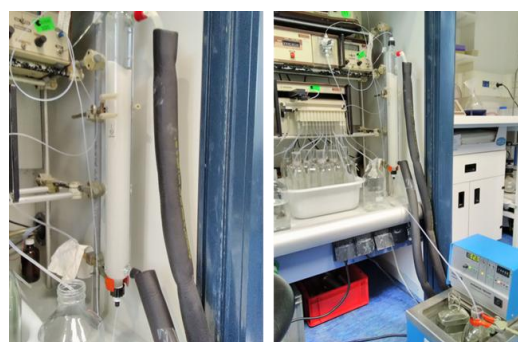
| Entry | T (°C) | eq. | N | B | S | s | t (h) | Comments | %3 | %4 |
|-------|--------|------|------|---------------------|-------|-----|-------|--|----|----|
| 1 | -78 | 2.05 | 6 | NaOH | MeOH | 2.9 | 2 | | 40 | 4 |
| 2 | -78 | 2.5 | 6 | NaOH | MeOH | 3.5 | 2 | | 45 | 3 |
| 3 | -78 | 2.5 | 6 | NaOH | MeOH | 0.5 | 2 | Very slow addition | 45 | 3 |
| 4 | -78 | 2.5 | 6 | NaOH | MeOH | 2.7 | 2 | Addition of water before 37% HCl | 45 | 5 |
| 5 | -78 | 2.5 | 2 | NaOH | MeOH | 3.1 | 2 | | 51 | 7 |
| 6 | -78 | 2.5 | 1 | NaOH | MeOH | 1.7 | 2 | freezing at -78°C | 58 | 3 |
| 7 | -78 | 2.5 | 2 | NaOH | EtOH | 2.7 | 2 | freezing at -78°C | 33 | 2 |
| 8 | -78 | 2.5 | 2 | NaOH | iPrOH | 2.7 | 2 | freezing at -78°C | 21 | 2 |
| 9 | -78 | 2.5 | 2 | LiOH | MeOH | 1.6 | 2 | | 56 | 6 |
| 10 | -78 | 2.5 | 2 | KOH | MeOH | 3.1 | 2 | | 54 | 4 |
| 11 | -78 | 2.5 | 2 | NH ₄ OH | MeOH | 3.0 | 2 | | 0 | 6 |
| 12 | reflux | 2.5 | 2 | NEt ₃ | MeOH | - | 18 | | 0 | 25 |
| 13 | -78 | 2.5 | 2.7 | EtONa/EtOH | MeOH | 2.0 | 2 | 1 mm needle | 38 | 2 |
| 14 | -78 | 2.5 | 0.75 | NBu ₄ OH | MeOH | 0.9 | 2 | Base diluted in water, freezing at -78°C | 67 | 2 |
| 15 | -78 | 2.5 | 0.75 | NBu ₄ OH | MeOH | 0.7 | 2 | Base diluted in methanol | 64 | 2 |
| 16 | 20 | 2.5 | 6 | NaOH | MeOH | 2.7 | 2 | Addition at -78°C | 11 | 8 |
| 17 | 20 | 2.5 | 1.4 | NBu ₄ OH | MeOH | 75 | 2 | Fast addition at 20°C | 55 | 2 |
| 18 | -78 | 2.5 | 2.8 | NEt ₃ OH | MeOH | 1.1 | 2 | | 61 | 2 |
| 19 | -78 | 2.5 | 1.4 | NEt ₃ OH | MeOH | 2.0 | 2 | | 65 | 3 |
| 20 | -78 | 2.5 | 1.4 | NEt ₃ OH | MeOH | 2.0 | 3 | | 66 | 3 |
| 21 | -78 | 2.5 | 1.4 | NEt ₃ OH | MeOH | 2.0 | 2 | 1 eq. of 1{1}, 0.5 eq. of 2{2} | 77 | 2 |
| 22 | -78 | 2.5 | 1.4 | NEt ₃ OH | MeOH | 2.0 | 2 | 0.5 eq. of 1{1}, 1 eq. of 2{2} | 70 | 4 |
| 23 | -20 | 2.5 | 1.4 | NEt ₃ OH | MeOH | 2.0 | 2 | Addition at -20°C | 65 | 3 |



Side reactions (the base counter ion seems important)



Isomers are separable by chromatography, but at 60°C...



Legrand, P.; Janin, Y. L. *Beilstein J. Org. Chem.* **2022**, *18*, 935-943