

Supporting information for:

Tandem Driven Dynamic Combinatorial Resolution via Henry – Iminolactone Rearrangement

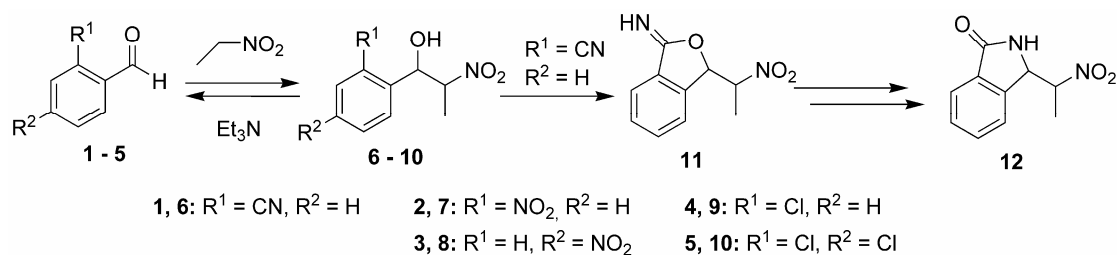
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General methods

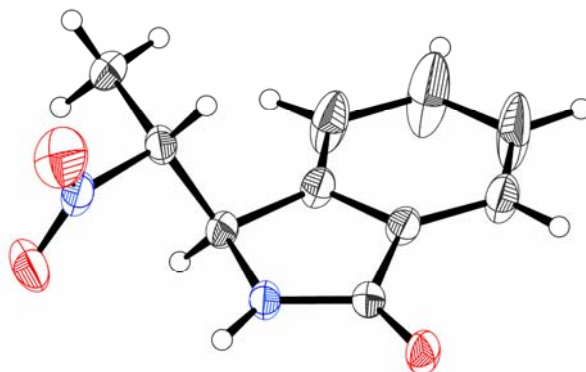
All commercially available starting materials and solvents were of reagent grade and used as received. ^1H and ^{13}C spectra were recorded with a Bruker Avance 400 instrument or a Bruker DMX 500 instrument at 298K in CD_3CN or DMSO, using the residual signals: ^1H : $\delta = 1.94$ ppm; ^{13}C : $\delta = 1.32$ ppm and ^1H : $\delta = 2.50$ ppm; ^{13}C : $\delta = 39.52$ ppm respectively. ^1H peak assignments were made by first order analysis of the spectra, supported by standard ^1H - ^1H correlation spectroscopy (COSY). High resolution mass spectra (HRMS) were performed by Instrumentstationen, Kemiteknik, Lund Institute of Technology, Lund, Sweden.

General procedure for library generation and resolution



The various aldehydes **1-5** (0.15 mmol each) were dissolved in an NMR tube using 750 μL CD_3CN . Subsequently, nitroethane (0.15 mmol) and triethylamine (0.45 mmol) were added and the mixture was left at room temperature. The reaction was followed by ^1H -NMR analysis.

Analytical data for compound 12



^1H NMR (500 MHz, DMSO) δ 1.16 (d, $J = 6.94$ Hz), 1.56 (d, $J = 6.94$ Hz), 5.11 (d, $J = 2.84$ Hz), 5.29-5.38 (m), 7.50-7.57 (m), 7.62-7.67 (m), 7.70 (d, $J = 7.57$) 8.86 (s), 9.02 (s); ^{13}C NMR (125 MHz, DMSO) δ 11.9, 15.2, 57.5, 58.4, 83.0, 83.4, 122.9, 123.1, 123.4, 123.8, 128.8, 129.0, 131.8, 132.1, 132.4, 142.9, 143.0, 169.4, 169.8; HRMS (CI) calcd for $[\text{C}_{10}\text{H}_{11}\text{N}_2\text{O}_3]^+$: 207.0770, found: 207.0763

Kinetic analysis of tandem reaction

Kinetic analysis of the tandem reaction with aldehyde **1** was performed using time-dependent ^1H -NMR-studies. Each starting material (0.2 mmol) and triethylamine (0.1 mmol) were dissolved in CD_3CN (600 μL), and the reaction followed until completion. The chemical kinetics software package Copasi 4.2 was adopted for fitting the resulting NMR-data to the kinetic model,¹ using the Levenberg-Marquardt method at a tolerance of 1×10^{-6} for parameter fitting. Estimated kinetic parameters: k_1 : $7.2 \times 10^{-2} \text{ M}^{-1} \text{ min}^{-1}$ (SD: $1.4 \times 10^{-3} \text{ M}^{-1} \text{ min}^{-1}$), k_{-1} : $5.6 \times 10^{-3} \text{ min}^{-1}$ (SD: $3.3 \times 10^{-4} \text{ min}^{-1}$), k_2 : $1.4 \times 10^{-2} \text{ min}^{-1}$ (SD: $1.2 \times 10^{-4} \text{ min}^{-1}$), where k_1 and k_{-1} are the rate constants of the forward and reverse Henry reaction, respectively, and k_2 is the rate constant for the consecutive cyclization step.

¹ S. Hoops, S. Sahle, R. Gauges, C. Lee, J. Pahle, N. Simus, M. Singhal, L. Xu, P. Mendes and U. Kummer, *Bioinformatics* 2006, **22**, 3067-3074.