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MICROWAVE-ASSISTED THREE-COMPONENT ONE-POT SYNTHESIS OF HIGHLY SUBSTITUTED 2-PYRIDINONES

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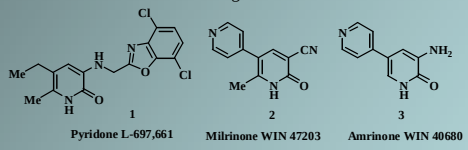
❶ Introduction

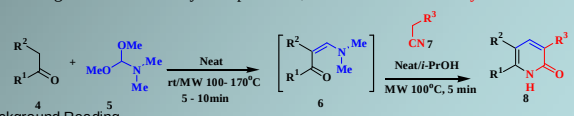
Pyridone and quinolone analogous are known to possess valuable biological activities. Some of them are used as drugs:



1 Pyridone L-697,661 — 2 Milrinone WIN 47203 — 3 Amrinone WIN 40680

Aims

- Development of a one-pot multi-component synthesis of 2-pyridinone libraries.
- Application of controlled ***microwave heating*** to gain rapid access to diverse 2-pyridinones utilizing CH-acidic carbonyl compounds **4**, DMFDMA **5** and methylene active nitriles **7**.

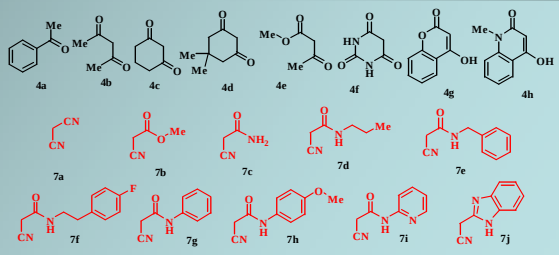


4 5 6 7 8

Background Reading

Junek, H.; Wolfbeis, O. S.; Sprintschnik, H.; Wolny, H. *Monatshefte fuer Chemie* **1977**, *108*, 689-702.
Fossa, P; Boggia, R.; Presti, E.L.; Mosti, L.; Dorigo, P.; Floreani M. *Farmaco* **1997**, *52*, 523-530.
Molteni, V.; Hamilton, M. M.; Mao, L.; Crane, C. M.; Termin, A. P.; Wilson, D. M. *Synthesis* **2002**, 1669-1674.

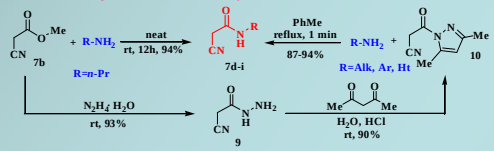
❷ Building Blocks



4a 4b 4c 4d 4e 4f 4g 4h

7a 7b 7c 7d 7e 7f 7g 7h 7i 7j

Synthesis of Methylene Active Compounds



7b 7d-i 10 9

❸ Optimized One-pot Reactions Conditions

Step 1: Enamine Key Intermediate Preparation

Table 1. Time and temperature optimization for adduct **6a-h** formation (neat).

Reagents	Adduct	Time (min)	Temp. (°C)	Conversion (HPLC)
4a + 5	**6a**	10	170	95%
4b + 5	**6b**	5	100	>99%
4c + 5	**6c**	5	rt	>99%
4d + 5	**6d**	5	rt	>99%
4e + 5	**6e**	5	rt	67%
4f + 5	**6f**	5	100	>99%
4g + 5	**6g**	5	150	49%
4h + 5	**6h**	5	150	43%

Step 2: Cyclization (after addition of methylene active nitrile)

① Choose Solvent
The best solvent is *i*-PrOH.
- ➢ effectively couples with microwaves
- ➢ dissolves building blocks under reaction conditions
- ➢ final products are sparingly soluble at rt, allowing easy isolation

② Optimize Temperature and Time (HPLC conversion and isolated yields)

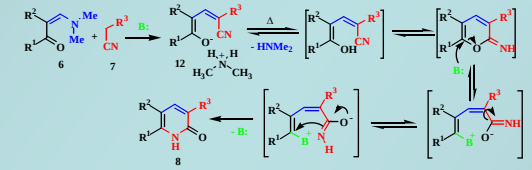
◈ Optimized conditions for the second step are 100°C in 2 mL *i*-PrOH for 5 min, 2 mmol or 4 mmol scale depending on the solubility of final products **8**.

③ Product Isolation
Final 2-pyridone library compounds precipitate and are isolated by simple filtration, and washing with *i*-PrOH and ether

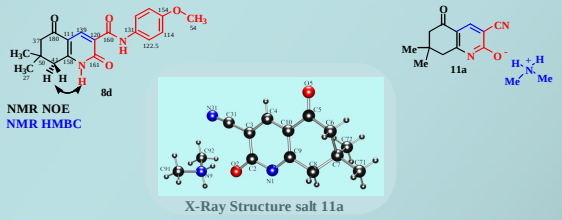
④ Structure Confirmation and Purity Check
RP-HPLC, NMR, MS, elemental analysis

❹ Mechanism and Structure Elucidation

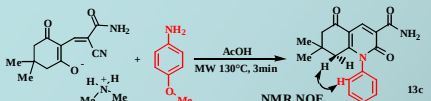
Proposed Mechanism



6 7 12 8

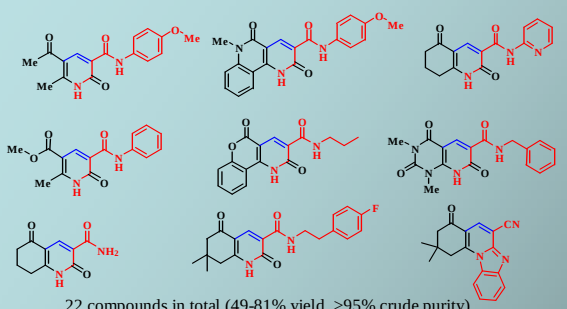


8d 11a



12c 13c

❺ Examples of Library Compounds



22 compounds in total (49-81% yield, >95% crude purity)

❻ Conclusion

- ◈ Reaction times reduced from hours to minutes
- ◈ Reaction optimization within hours
- ◈ High conversion rates
- ◈ Rapid library generation
- ◈ Simple isolation of products

Emrys™ Synthesizer

+ sample robot
+ up to 120 reactions
+ magnetic stirring
+ 12-15 reactions per hour
+ 0-300 W
+ up to 250 °C, 0-20 bar

Acknowledgement

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