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AN ECO-SAFE APPROACH: MECHANOCHEMICAL SYNTHESIS OF HETEROCYCLES BASED ON QUINAZOLINONE CORE

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INTRODUCTION

Mechanochemical synthesis represents an eco-safe method for preparing heterocycles through the reactions facilitated by mechanochemical force. It presents a green alternative to traditional organic synthesis by reducing solvent consumption. [1] The quinazolinone core, recognized for its broad spectrum of biological activities, plays an important role in medicinal chemistry. [2] Natural deep eutectic solvents (NADESs) represent promising type of green solvents that can successfully replace volatile organic solvents. They are composed of hydrogen bond acceptors (HBAs) and hydrogen bond donors (HBDs). Based on natural origin, e.g. amines, carboxylic acids, and polyols, NADESs have been explored in various processes due to their favorable properties. [3] To improve the effectiveness of NADESs, they are combined with other green methods such as mechanochemical synthesis.

CHEMISTRY

NADES preparation

The mixture of choline chloride (ChCl)/malonic acid (1: 1) was vigorously stirred and heated at 70 °C until a homogeneous liquid was formed.

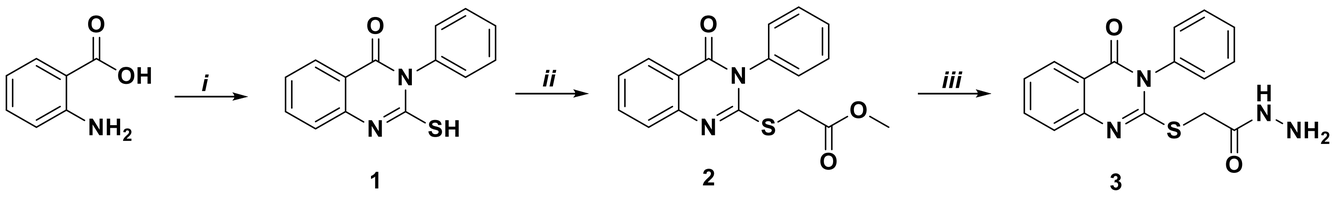
*General procedure for the synthesis of quinazolinone-based Schiff bases **4** – **13***

The reaction mixture of hydrazide **3** (0.5 mmol) and aromatic aldehyde (0.6 mmol) (Scheme 2) in ChCl/malonic acid NADES (0.5 mL) was milled for 10 min at 30 Hz. The reaction mixture was cooled to room temperature and water (15 mL) was added. The crude product was collected by filtration, dried and recrystallized from ethanol.

*General procedure for the synthesis of quinazolinone-based semicarbazides **14** – **23***

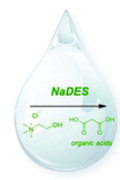
The reaction mixture of hydrazide **3** (0.5 mmol) and isocyanate (0.6 mmol) was milled for 10 min at 30 Hz (Scheme 2). The reaction mixture was cooled to room temperature and water (15 mL) was added. The crude product was collected by filtration, dried and recrystallized from ethanol.

RESULTS



Scheme 1. Synthesis of quinazolinyl hydrazide **3**
Reaction conditions: (*i*) phenyl isothiocyanate, ChCl/urea (1: 2), 80 °C, 2 h
(*ii*) methyl bromoacetate, sodium acetate, ethanol, 2 h
(*iii*) hydrazine hydrate, ethanol, 2 h

Scheme 2. Synthesis of quinazolinone-based Schiff bases **4** – **13** and quinazolinone-based semicarbazides **14** – **23**.
Reaction conditions: (*iv*) aromatic aldehyde, ChCl/malonic acid (1: 1), 30 Hz, 10 min
(*v*) aromatic/aliphatic isocyanate, 30 Hz, 10 min



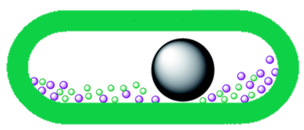


Table 1. Isolated yields obtained with mechanochemical synthesis

Compound	R	Yield	Compound	Isocyanate	Yield
4	2,3-$(OH)_2$	74	**14**	Ethyl	68
5	2,4-$(OH)_2$	78	**15**	Octyl	61
6	2,5-$(OH)_2$	98	**16**	Allyl	59
7	3-Br	91	**17**	Phenyl	80
8	4-Br	94	**18**	1-Naphthyl	76
9	2-Cl	94	**19**	3-Bromophenyl	86
10	3-Cl	92	**20**	*o*-Tolyl	90
11	2-OMe	91	**21**	*m*-Tolyl	64
12	3-OMe	85	**22**	*p*-Tolyl	87
13	4-OMe	88	**23**	3,5-Dimethylphenyl	69

CONCLUSION

In conclusion, we have developed new a approach for preparing quinazolinones **4** – **13** performed in NADES and **14** – **23** by solvent-free mechanochemical synthesis. Mechanochemical synthesis was shown to be the method of choice, especially in a combination with choline chloride/malonic acid (1: 1) NADES, as all compounds were obtained in high yields of up to 98 %.

References

[1] T. Friščić, C. Mottillo, H. M. Titi, Angew. Chem. 59 (2020) 1018.
[2] S. N. Murthy Boddapati et al., Arab. J. Chem. 16 (2023) 105190..
[3] B. B. Hansen et al, *Chem. Rev.* **121** (2020) 1232–1285.

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