Synthesis of bioactive molecules from 5-hydroxymethylfurfural vía Passerini multicomponent reaction

ACS GCI Summer School on Green Chemistry and Sustainable Energy

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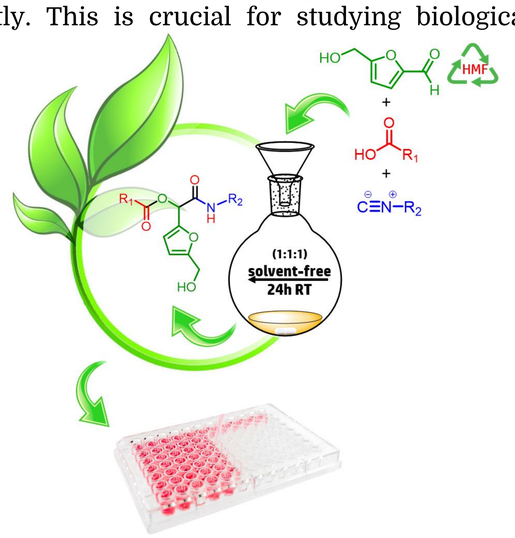
ABSTRACT

One of the greatest challenges for organic and medicinal chemists is obtaining new structurally diverse organic compounds fast, safely, and efficiently. This is crucial for studying biological systems and accelerating drug discovery. In this work, we employ the Passerini multicomponent reaction (P-3CR) under greener conditions to generate a collection of small molecules. This approach allows us to obtain new compounds, structurally diverse, in a single reaction step, minimizing synthetic effort and time. We explored the reactivity of 5-hydroxymethylfurfural (HMF), a biomass-derived chemical platform, to obtain new potentially bioactive molecules. By optimizing the reaction conditions and varying components, we generated a chemolibrary. Acceptable yields of α-acyloxy carboxamides were achieved by performing P-3CR under solvent-free conditions at room temperature for 24 hours. Selected synthesized compounds were evaluated for their antiproliferative activity against human bladder cancer cells (T24, 253J).



INTRODUCTION

Chemistry today faces significant challenges such as reducing the environmental impact of industrial waste and managing natural resources properly. The Principles of Green Chemistry guide the environmentally friendly design of new materials and sustainable processes.

In this line, four key aspects that we apply in our research and development of new compounds and chemical processes, are 1) using green solvents or avoiding the use of traditional organic solvents in our reactions; 2) conducting reactions at room temperature or using efficient energy sources; 3) designing and generating molecular diversity with high atomic efficiency through the application of multicomponent reactions; 4) employing renewable raw materials.

Herein we utilized the P-3CR as part of a valuable strategy for diversity-oriented synthesis (DOS, Figure 2). The P-3CR involves three components: a carbonyl compound, an isonitrile, and a carboxylic acid, which lead to the one-step synthesis of an α-acyloxy carboxamide (Figure 1).

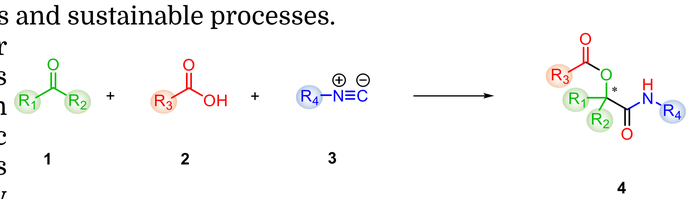


Figure. 1. General Passerini multicomponent reaction

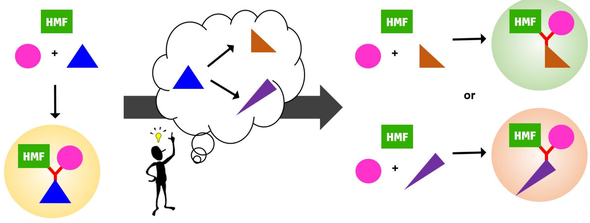


Figure. 2. Diversity oriented synthesis (DOS)

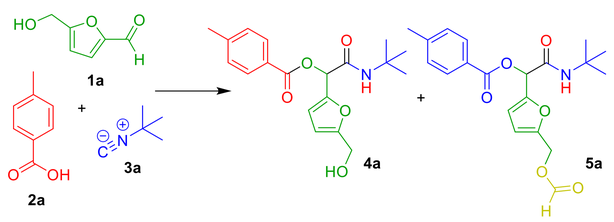
RESULTS AND DISCUSSION

To optimize the reaction conditions, the P-3CR components: HMF, *p*-toluic acid and *tert*-butylisocyanide were used (Scheme 1). First, the reactivity of the P-3CR model was tested on a small scale, both in solvent and in the absence of solvent, the yield of the products was quantify by ^{1}H-RMN using trichloroethylene (TCE) as a standard (Table 1).

Based on the results, we proceeded to work under solvent-free conditions and evaluated other experimental variables such as temperature, time and reagent equivalents (Table 2). A Monowave-50 efficient heating synthesis reactor (Anton Paar) and an ultrasonic bath (Elmesonic) were used as alternative methods to supply energy.

According to our results, carrying out the reaction solvent-free, at room temperature for 24 h, and under an equimolar ratio of reagents favors the formation of the expected product, the α-acyloxy carboxamide 4a.Unexpectedly, the formation of the formylated product on the hydroxymethyl side chain of the furan system 5a was also observed and characterized (Scheme 1).

The study demonstrated that modifying the building blocks in the reaction enables the generation of a diverse chemical library with varying yields, using HMF and its derivatives as key components. This underscores HMF's potential as a versatile building block for synthesizing novel molecules



Scheme 1. P-3CR reactivity model

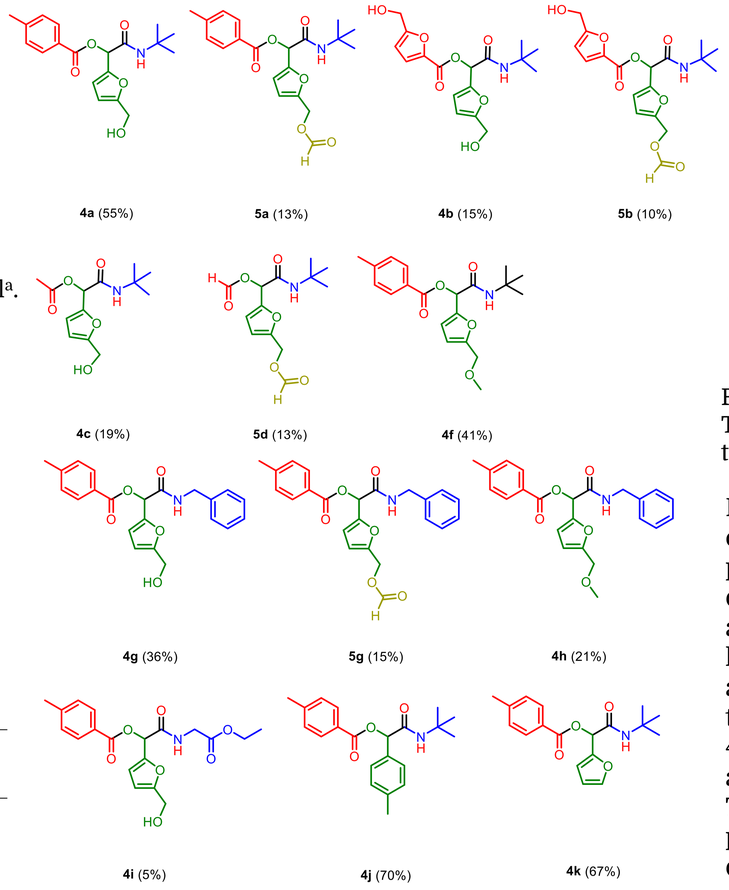
Table 1. Solvent screening for Passerini's reaction reactivity model[a].

Entry	Solvent	Yield: Time (h)	Main Product 4a	Minority producto 5a
1	Solvent free	24	63%	3%
2	Solvent free	48	65%	5%
3	H_2O	24	28%	5%
4	H_2O	48	43%	9%
5	Me-THF	24	16%	-
6	Me-THF	48	18%	-
7	EtOH	24	28%	-
8	EtOH	48	35%	-
9	MeOH	24	-	
10	MeOH	48	26%	-
11	CH_2Cl_2	24	22%	11%
12	CH_2Cl_2	48	25%	19%

[a]Parallel synthesis and products quantified by 1H-NMR with TCE standard. The reactions were carried out at room temperature and in equimolar ratio.

Table 2. Optimization of reaction conditions.

Entry	T (°C)	t (h)	Molar ratio of reagents 1a	2a	3a	Yield 4a	5a	Observations
1	30	5	1	2	1	58 %	13 %	mw-50
2	RT	24	1	2	1	25 %	9 %	-
3	RT	24	1	2	1	22 %	6 %	-
4	RT	48	1	2	1	41%	15 %	-
5	30	6	1	1	1	45 %	5 %	mw-50
6	40	1.5	1	1	1	28 %	9 %	mw-50
7	60	1.5	1	1	1	25 %	36 %	mw-50
8	60	3	1	1	1	12 %	18 %	mw-50
9	120	0.25	1	1	1	-	-	mw-50
10	RT	8	1	1	1	45 %	6%	-
11	RT	24	1	1	1	55 %	13 %	-
12	RT	48	1	1	1	66 %	9 %	-
13	RT	72	1	1	1	65 %	6 %	-
14	35	3	1	1	1	35 %	7 %	US
15	35	6	1	1	1	43 %	8 %	US



Scheme 2. α-acyloxy carboxamides obtained by varying the P-3CR components.

Importantly, this study adheres to seven Principles of Green Chemistry while directly supporting the United Nations 2030 Agenda for Sustainable Development by addressing:
(i) SDG 3 (Good Health and Well-being) via the design of novel anticancer agents, and (ii) SDG 12 (Responsible Consumption and Production) through biomass-derived synthesis routes that minimize petrochemical dependence, exemplifying green chemistry in drug development.

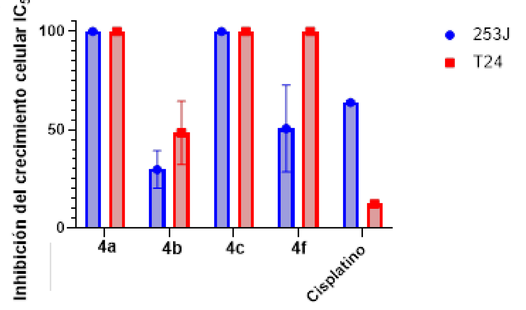


Figure 3. Antiproliferative effect on 253J and T24 cell lines. Expressed as the IC50 value +/- the standard deviation.

Regarding biological evaluation, compound 4b emerged as the most promising candidate in the series. It demonstrated moderate antiproliferative activity against both T24 and 253J cell lines, with notably greater potency against 253J (IC50 values surpassing those of cisplatin). In contrast, compound 4f showed moderate yet selective activity against 253J, as it was inactive against T24. These results underscore 4b potential as a lead compound for developing novel molecules with enhanced antitumor efficacy.

CONCLUSIONS AND PERSPECTIVES

Ongoing research shows the feasibility of developing a green synthesis process for obtaining bioactive α-acyloxy carboxamides from HMF with acceptable yields using multicomponent reactions, renewable raw materials, eliminating the use of solvents and minimizing energy consumption. Antiproliferative activity studies will be completed for the rest of the compounds obtained and their GI_{50} will be determined.

REFERENCES

-Ingold, M; de la Sovera, V; Dapueto, R; Hernández, P; Porcal, W; López, G.V. Greener Synthesis of Antiproliferative Furoxans via Multicomponent Reactions. *Molecules*. 2022. 27, 1756.

ACKNOWLEDGEMENTS

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