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Proceeding Paper

One-Pot Synthesis of 3-Tetrazolylmethyl-4*H*-Chromen-4-Ones via Ugi-Azide Reaction †

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Abstract

1,5-disubstituted tetrazoles (1,5-Ds-T) are heterocyclic bioisosteres of the cis-amide bond, commonly found in bioactive compounds, pharmaceuticals, and functional materials. Chromones are privileged scaffolds widely present in natural products and are well known for their diverse biological activities, including anticancer, antimicrobial, antidiabetic, anti-inflammatory, and antioxidant properties. Isocyanide-based multicomponent reactions, such as the Ugi-Azide (UA-4CR), provide a versatile strategy for synthesizing 1,5-Ds-T, which can be incorporated into other privileged heterocyclic or commercially available drugs. Herein, we describe a sonochemical one-pot synthesis of 1,5-Ds-T connected to chromone under mild conditions, highlighting their potential relevance in medicinal chemistry.

Keywords: 1,5-disubstituted tetrazoles; chromone; one-pot; IMCR; Ugi-Azide

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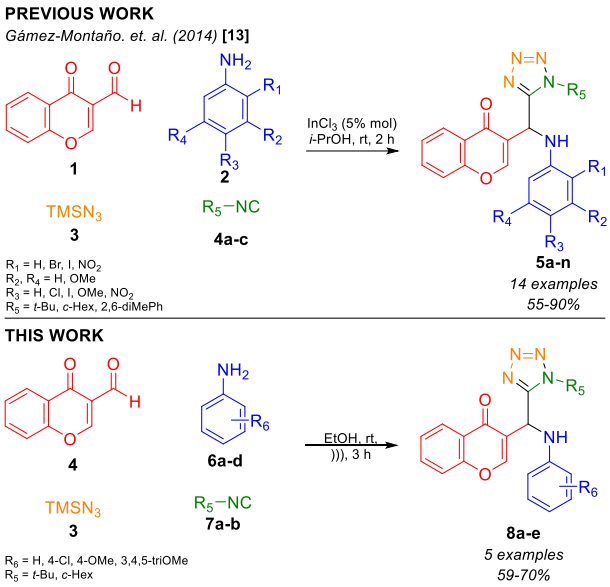
1. Introduction

Heterocyclic compounds containing carbon and at least one heteroatom (nitrogen, oxygen, or sulfur) are fundamental structural motifs in medicinal chemistry [1]. In recent years, bis-heterocycles have attracted considerable attention due to the synergistic enhancement of their physicochemical and biological properties, offering promising applications across various fields [2,3]. However, the synthesis of bis-heterocycles remains challenging, as conventional methods typically involve multiple steps, resulting in non-eco-friendly protocols that require an extensive amount of reagents and excess of solvents involved in purification procedures, as well as reduced overall yields [4].

One-pot synthetic processes are undoubtedly one of the green synthetic tools that have emerged in modern organic synthesis as key strategies in the development of sustainable processes. Among them, isocyanide-based multicomponent reactions (IMCRs) are particularly valuable for the green synthesis of nitrogen-containing heterocycles, including 1,5-Ds-T [5,6]. The UA-4CR is especially noteworthy, as it enables the one-pot synthesis of 1,5-Ds-T derivatives. The reaction proceeds through the condensation of an aldehyde or ketone with a primary amine, followed by the incorporation of an isocyanide and an azide source, commonly trimethylsilyl azide ($TMSN_3$), which produces hydrazoic acid in situ [7–13].

MCRs have been employed for the direct construction of heterocycles. However, heterocyclic moieties can also serve as substituents in MCR inputs, thereby increasing the complexity of the final product [14]. In 2014, Gámez-Montaño et al. reported the use of 3-formylchromone in the UA-4CR, employing indium (III) chloride as a catalyst (Scheme 1) [15]. This strategy highlights the potential of integrating heterocyclic frameworks into multicomponent reaction pathways.



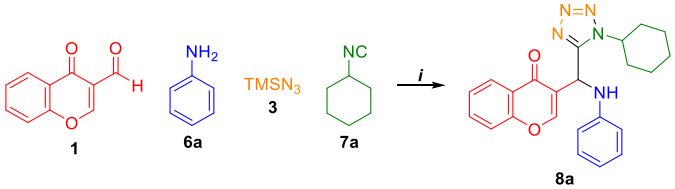
Scheme 1. Previous report of synthesis of 3-tetrazolylmethyl-4*H*-chromen-4-ones.

Herein, we report a sonochemical one-pot synthesis of 3-tetrazolylmethyl-4*H*-chromen-4-ones via the UA-4CR under free catalyst conditions, affording good overall yields (59–70%) (Scheme 1). This strategy approach provides a valuable platform for generating novel tetrazole-chromone analogs with potential application in medicinal chemistry and materials science.

2. Results and Discussion

Initially, the synthesis of 1,5-DS-1*H*-T (**8a**) via a UA-4CR, which involves 3-formylchromone (**1**), aniline (**6a**), trimethylsilylazide (**3**), and cyclohexyl isocyanide (**7a**) under conventional conditions in EtOH at room temperature (Table 1, Entry 1), yielded **8a** in 56%. Recently, we introduced the green USI-assisted UA-4CR under solvent-free conditions [9], however, the model proposed herein yielded unsatisfactory performance. When the reaction was performed using EtOH was afforded in moderate yield (Table 1, entries 1–2).

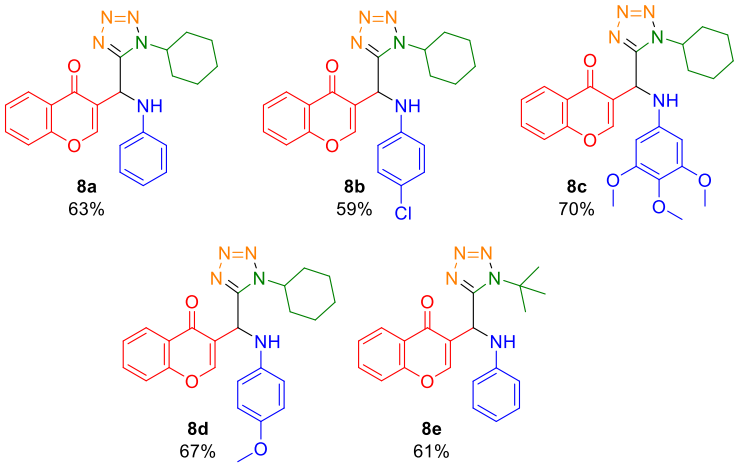
Table 1. Screening conditions for the synthesis of molecule **8a**.



Entry	Solvent	Temperature	Time	Yield (%)
1	EtOH [a]	r.t.	12 h	56
2	--- [b]	r.t.	3 h	Traces
3	**EtOH** [b]	**r.t.**	**3 h**	**63**

(***a***) stirring, (***b***) sonication.

Using the optimized conditions, a series of 3-tetrazolylmethyl-4H-chromen-4-ones (**8a–e**) is depicted (Scheme 2). The effect of the electronic nature of the amine component was evaluated; the methodology doesn't work for aliphatic amines. The final products were obtained with moderate yields (59–70%).



Scheme 2. Synthesis of 3-tetrazolylmethyl-4*H*-chromen-4-ones scope.

3. Experimental Methods

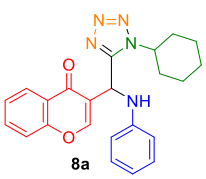
3.1. General Experimental Information

NMR spectra (^{1}H and ^{13}C) were obtained on a Bruker Ascend 400 MHz, with deuterated chloroform ($CDCl_3$). Chemical shifts (δ) are indicated in ppm, tetramethylsilane (TMS) as reference. Coupling constants (J) in Hertz (Hz), and signal multiplicities are described with standard abbreviations: singlet (s), doublet (d), triplet (t), quartet (q), and multiplet (m). MestReNova software (version 14.2.0-26256) was used for spectral analysis. TLC on silica gel F254 aluminum sheets was used for reaction monitoring, which was visualized under UV at 254 nm. The purification was performed by column chromatography using silica gel (230–400 mesh). Elution was performed with hexane and ethyl acetate, also used in TLC and retention factor (R_f) calculations. All reagents from Sigma-Aldrich were used without purification.

3.2. Procedure

In a sealed vial, 3-formylchromone (**1**, 1.0 equiv.), amine (**2a–d**, 1.0 equiv.), trimethylsilylazide (**3**, 1.0 equiv.), and isocyanide (**7a–b**, 1.0 equiv.) were dissolved in EtOH (1.0 M), then the reaction mixture was sonicated at room temperature, affording the corresponding 1,5-Ds-Ts (**8a–e**).

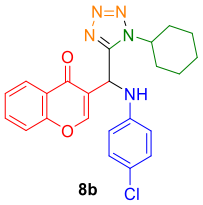
3.3. Spectral Data



3-((1-cyclohexyl-1H-tetrazol-5-yl)(phenylamino)methyl)-4H-chromen-4-one (**8a**)

White solid, R_f = 0.37 (30% ethyl acetate in hexanes), ^{1}H (400 MHz, $CDCl_3$, 25 °C, TMS) δ 8.31 (s, 1H), 8.18 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.68 (ddd, *J* = 8.5, 7.1, 1.7 Hz, 1H), 7.47–7.41 (m,

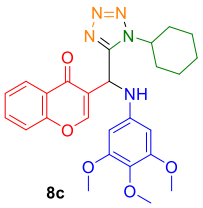
2H), 7.21–7.14 (m, 2H), 6.82–6.75 (m, 1H), 6.72–6.67 (m, 2H), 6.17 (d, *J* = 7.1 Hz, 1H), 4.97 (d, *J* = 7.1 Hz, 1H), 4.74–4.65 (m, 1H), 2.08–1.87 (m, 8H), 1.50–1.37 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.6, 156.5, 155.3, 154.1, 145.1, 134.1, 129.5, 125.5, 123.4, 121.3, 119.3, 118.3, 113.7, 58.3, 44.5, 33.2, 32.6, 29.6, 25.1, 24.8.



8b

3-(((4-chlorophenyl)amino)(1-cyclohexyl-1H-tetrazol-5-yl)methyl)-4H-chromen-4-one (**8b**)

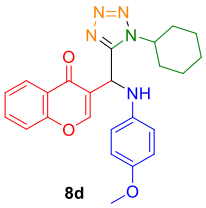
Yellow solid, R_f = 0.37 (30% ethyl acetate in hexanes), ^{1}H (400 MHz, $CDCl_3$, 25 °C, TMS) δ 8.27 (d, *J* = 0.7 Hz, 1H), 8.19 (ddd, *J* = 8.0, 1.9, 0.5 Hz, 1H), 7.70 (ddd, *J* = 8.7, 7.1, 1.7 Hz, 1H), 7.48–7.41 (m, 2H), 7.15–7.09 (m, 2H), 6.66–6.61 (m, 2H), 6.15 (d, *J* = 7.7 Hz, 1H), 5.15 (d, *J* = 7.8 Hz), 4.73–4.61 (m, 1H), 2.02–1.78 (m, 8H), 1.53–1.38 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.6, 156.4, 155.6, 154.0, 143.5, 134.3, 129.5, 125.8, 125.6, 124.2, 123.4, 121.1, 118.4, 114.9, 58.4, 44.5, 33.3, 32.8, 25.2, 24.8



8c

3-((1-cyclohexyl-1H-tetrazol-5-yl)((3,4,5-trimethoxyphenyl)amino)methyl)-4H-chromen-4-one (**8c**)

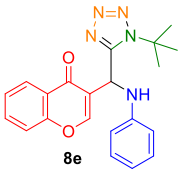
Yellow solid, R_f = 0.14 (30% ethyl acetate in hexanes), ^{1}H (400 MHz, $CDCl_3$, 25 °C, TMS) δ 8.21 (s, 1H), 8.04 (d, *J* = 7.9 Hz, 1H), 7.59–7.54 (m, 1H), 7.35–7.28 (m, 2H), 6.06 (d, *J* = 7.9 Hz), 5.86 (s, 2H), 5.01 (d, *J* = 8.1 Hz, 1H), 4.53–4.45 (m, 1H), 3.61 (s, 6H), 3.59 (s, 3H), 1.87–1.72 (m, 8H), 1.35–1.23 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.2, 155.0, 1545, 153.0, 152.7, 140.3, 133.0, 129.9, 124.5, 124.2, 122.0, 120.5, 117.1, 90.4, 63.0, 59.7, 57.0, 54.7, 43.1, 31.8, 31.5, 24.0, 23.8, 23.5.



8d

3-((1-cyclohexyl-1H-tetrazol-5-yl)((4-methoxyphenyl)amino)methyl)-4H-chromen-4-one (**8d**)

Yellow oil, R_f = 0.25 (30% ethyl acetate in hexanes), ^{1}H (400 MHz, $CDCl_3$, 25 °C, TMS) δ 8.29 (s, 1H), 8.18 (dd, *J* = 8.1, 1.7 Hz, 1H), 7.69 (ddd, *J* = 8.6, 7.1, 1.7 Hz, 1H), 7.47 (dd, *J* = 8.6, 1.2, 1H), 7.42 (ddd, *J* = 8.6, 7.2, 1.7, 1H), 6.77 (d, *J* = 8.9 Hz, 2H), 6.66 (d, *J* = 8.9 Hz, 2H), 6.06 (s, 1H), 4.69–4.59 (m, 1H), 4.47 (s, 1H), 3.72 (s, 3H), 2.11–1.79 (m, 7H), 1.51–1.38 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.9, 155.5, 153.8, 139.0, 134.4, 125.8, 125.8, 123.6, 122.7, 121.8, 118.5, 118.4, 116.1, 115.3, 58.5, 55.8, 46.1, 33.4, 32.9, 25.5, 25.0.



8e

3-((1-(tert-butyl)-1H-tetrazol-5-yl)(phenylamino)methyl)-4H-chromen-4-one (**8e**)

White solid; R_f = 0.32 (30% ethyl acetate in hexanes)), ^{1}H (400 MHz, $CDCl_3$, 25 °C, TMS) δ 8.31 (s, 1H, CH), 8.16 (d, *J* = 8.0 Hz, 1H), 7.70–7.66 (m, 1H), 7.47 (d, *J* = 8.4 Hz, 1H), 7.43–7.39 (m, 1H), 7.19–7.15 (m, 2H), 6.80–6.75 (m, 1H), 6.68 (d, *J* = 7.9 Hz, 2H), 6.46 (d, *J* = 7.6 Hz, 1H), 4.79–4.76 (m, 1H), 1.85 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.9, 156.5, 155.6, 134.1, 129.6, 125.6, 125.5, 123.5, 118.4, 113.3, 62.3, 45.2, 30.0.

4. Conclusions

The main contribution of the present work falls mainly in the multicomponent one-pot synthesis and pharmaceutical fields.

The use of heterocyclic input in UA-4CR increased the complexity of 1,5-disubstituted tetrazoles, thereby enhancing their potential applications.

This protocol offers several advantages, including one-pot synthesis, good overall yields, an alternative green energy source, short reaction times, an eco-friendly solvent, operational simplicity, and the avoidance of toxic catalysts.

Author Contributions: D.G.-G. (methodology, software, investigation, data curation, writing—original draft preparation); K.A.G.-P. and I.A.G.-G. (methodology); R.G.-M. (conceptualization, formal analysis, resources, writing—review and editing, visualization, supervision, validation, project administration, funding acquisition). All authors have read and agreed to the published version of the manuscript.

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