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TCS/$ZnCl_2$ AS A CONTROLLED REAGENT FOR THE MICHAEL ADDITION AND HETEROCYCLIC CYCLIZATION BASED ON THE PHENYL PYRAZOLONE SCAFFOLD WITH DOCKING VALIDATION AS A COVID-19 PROTEASE INHIBITOR

Abdulrahman A. Almehizia[1*], Ahmad M. Naglah[1], Amer A. Zen[2], Tamer K. Khatab[3,4] and Ashraf S. Hassan[4*]

[1]Department of Pharmaceutical Chemistry, College of Pharmacy, King Saud University, P.O. Box 2457, Riyadh 11451, Saudi Arabia
[2]Chemistry & Forensics Department, Clifton Campus, Nottingham Trent University, Nottingham Ng11 8NS, UK
[3]Chemistry Department, Faculty of Science, Mansoura University, 35516 Mansoura, Egypt
[4]Organometallic and Organometalloid Chemistry Department, National Research Centre, Dokki 12622, Cairo, Egypt

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ABSTRACT. TCS/$ZnCl_2$ is presented as a new catalyst for achieving the Michael addition adduct **5a-g** by the reaction of phenyl pyrazolone **4** as the Michael donor and arylidene derivatives **3a-g** as the Michael acceptor. The one-pot multi-component reaction of the same fragments' scaffolds as aldehydes **1a-g**, malononitrile (**2**), and phenyl pyrazolone **4** with the same catalyst gives pyrano[2,3-*c*]pyrazole derivatives **6a-g** as final products. The prepared compounds undergo docking validation as COVID-19 protease inhibitors and are compared with hydroxychloroquine as a reference drug.

KEY WORDS: Pyranopyrazole, multi-component reactions, TCS/$ZnCl_2$ catalyst, COVID-19, the energy score, hydroxychloroquine

INTRODUCTION

Recently, heterocyclic compounds have been a major focus of research in organic chemistry. These compounds also play a crucial role in medicinal chemistry, where they are important templates for developing and discovering drugs and therapeutic agents [1-3]. Both pyrazole and pyran derivatives have demonstrated a broad range of pharmacological applications, including anticancer, antibacterial, antimalarial, antiviral, and anti-inflammatory properties [4-9].

In the last two decades, fused pyranopyrazole derivatives (fused pyrazole with pyran) have been prepared by a growing interest because of possess various pharmaceutical properties [10-14]. Accordingly, organic chemists have prepared this scaffold using numerous procedures. There are various methods for synthesizing pyranopyrazole derivatives, including direct reaction condensation or multi-component reactions in the presence of various catalysts. Examples of these catalysts include Fe_2O_3@SiO_2@VB1 NPs [15], SiO_2@Pr@SO_3H [16], Na_2SeO_4 [17], $(NH_4)_2HPO_4$ [18], and Fe_3O_4@RB@LDH [19].

Tetrachlorosilane (TCS) is becoming increasingly important due to its many positive characteristics. TCS is used in industry on a large scale and is a highly safe, inexpensive, and easily available material with a favorable toxicological profile. It is used as a dehydrator for the formation of amides, hydrazides, dipeptides, carboxamides, and heterocycles, as well as silylating agents and defluorinating agents. More importantly, TCS is a weak Lewis acid, and several successful transformations have been developed using it. TCS has played an important role in our

*Corresponding authors. E-mail: mehizia@ksu.edu.sa (A.A. Almehizia); ashraf_salmoon@yahoo.com (A.S. Hassan)

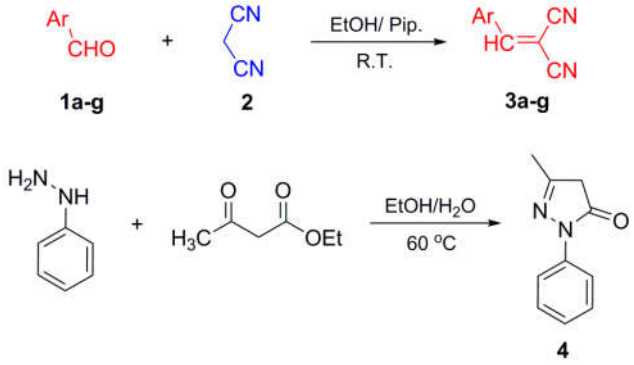
research and will continue to do so [20-23]. Research on the development of new methods for the synthesis of heterocyclic compounds and the design of novel multicomponent reactions using TCS as an *in situ* transformation reagent has led to the development of an efficient protocol for this purpose.

After evaluating the above reports as well as our targets [24-29], this data prompted us to use TCS/$ZnCl_2$ catalyst as a control reagent in the Michael addition and heterocyclic cyclization-based on the phenyl pyrazolone scaffold. Additionally, a molecular docking study of some selected Michael addition adducts and pyranopyrazole derivatives will be performed as potential inhibitors of the COVID-19 main protease (M^{pro}) and compared with hydroxychloroquine as a reference drug.

RESULTS AND DISCUSSION

Tetrachlorosilane (TCS) has recently sparked a lot of interest, particularly in our research group. As a result, we have developed a simple protocol for synthesizing phenyl pyrazolone through a Michael addition and heterocyclic cyclization. This was achieved at room temperature using a binary catalytic system of TCS/$ZnCl_2$. This is part of our ongoing investigations into new methods for synthesizing heterocyclic compounds and designing effective multi-component reactions using TCS and other types of catalysis for in situ mediated transformations in one-pot synthesis [30-36].

The starting materials used in this work were prepared according to the reported method [37, 38], as illustrated in Scheme 1.



Scheme 1. The starting materials **1a-g**, **2**, **3a-g**, and **4**.

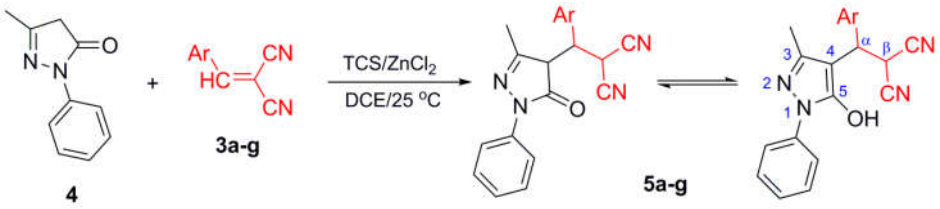
The presented one-pot reaction undergoes an optimization step targeting to choose the best chemical conditions. Table 1 shows a model example in which pyrazolone **4**, malononitrile (**2**), and benzaldehyde (**1a**) are reacted under different chemical conditions. The data obtained indicates that the best condition is to carry out the reaction in DCM as a solvent and stirring at room temperature.

Table 1. Reaction optimization.

Entry	Solvent	Temp.	Time (h)	Yield (%)
1	Ethanol	reflux	5	63
2	CH_3CN	reflux	5	45
3	DCM	reflux	5	87
4	DCM	R.T.	5	88
5	Solvent free	R.T.	5	77

After the reaction optimization step, the reaction was explored by different aromatic aldehydes, as explained in Schemes 2 and 3, and Tables 2 and 3.

The prepared arylidene malononitrile **3a-g** reacts with 3-methyl-1-phenyl-1*H*-pyrazol-5(4*H*)-one (**4**) in dichloromethane as a solvent in the presence of TCS/$ZnCl_2$ and stirring at room temperature (25 °C). After the appropriate time, the Michael addition adducts **5a-g** were obtained (Scheme 2, Table 2). The Michael addition adducts **5a-g** were confirmed by its melting points and different spectroscopic analysis ^{1}H-NMR.



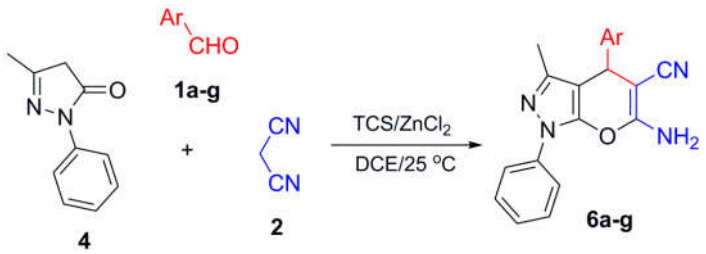
Scheme 2. Michael addition reaction.

Table 2. Two component reaction of different prepared arylidenes and pyrazolone.

Entry	Ar	Products	Time (h)	Yield %	Melting point (°C)
1	C_6H_5-	**5a**	4	86	190 (173-174 [39])
2	4-CH_3-C_6H_4-	**5b**	4.5	82	182
3	4-CH_3O-C_6H_4-	**5c**	4	84	165 (161-162 [39])
4	4-Cl-C_6H_4-	**5d**	3	94	210 (192-193 [39])
5	4-Br-C_6H_4-	**5e**	3.5	91	190 (187-188 [39])
6	2-Furyl	**5f**	5	89	215
7	2-Thienyl	**5g**	4.5	85	162

The ^{1}H-NMR spectra of the Michael addition adducts **5a-g** exhibited the two proton positions of the >(**α**)CH-(**β**)CH< group around 4.22-5.61 ppm (proton at α-carbon) and 5.38-6.69 ppm (proton at β-carbon), which proves their structure.

We modified the reaction method to a one-pot mixing under the same conditions for aldehydes **1a-g**, malononitrile (**2**), and phenyl pyrazolone **4** with the same catalyst TCS/$ZnCl_2$ and solvent DCM at room temperature. This procedure directed the reaction product to cyclization, and the pyrano[2,3-*c*]pyrazole derivatives **6a-g** were separated as final products (Scheme 3, Table 3).



Scheme 3. Pyrano[2,3-*c*]pyrazole derivatives synthesis.

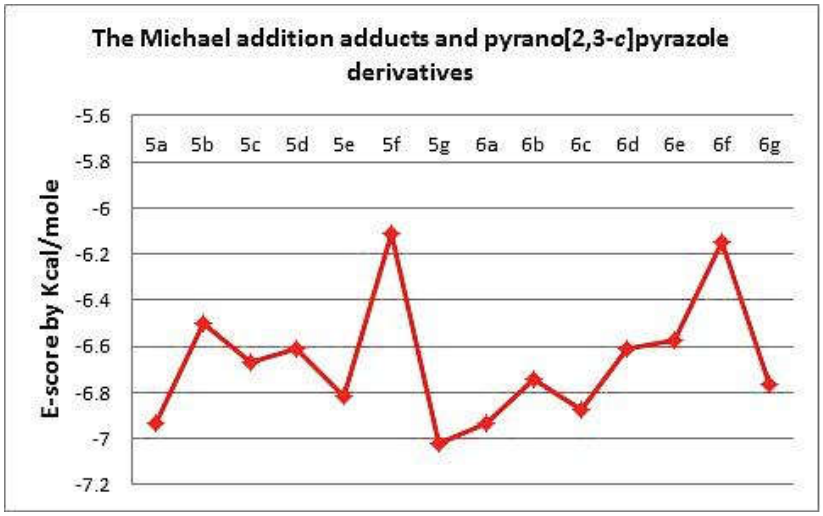
Table 3. One-pot reaction between pyrazolone, malononitrile and different aldehydes.

Entry	Ar	Products	Time (h)	Yield %	Melting point (ºC)
1	C_6H_5-	**6a**	5	88	171-172 (170-173 [40])
2	4-CH_3-C_6H_4-	**6b**	6.5	82	175-176 (175-175 [40])
3	4-CH_3O-C_6H_4-	**6c**	6	83	178-180 (177-180 [40])
4	4-Cl-C_6H_4-	**6d**	3.5	93	180-182 (178-181 [40])
5	4-Br-C_6H_4-	**6e**	4.5	92	189-191 (190-193 [40])
6	2-Furyl	**6f**	5	80	229-231 (225-228 [41])
7	2-Thienyl	**6g**	5	86	169-171 (172-174 [41])

Molecular docking studies

The data presented were designed and calculated using MOE 2014.0901 software (Molecular Operating Environment). The synthesized Michael addition adducts **5a-g** and pyrano[2,3-*c*]pyrazole derivatives **6a-g** were validated as COVID-19 protease (M^{pro}) inhibitors compared with the reference ligand hydroxychloroquine (HCQ) [42, 43].

The most commonly used calculation to demonstrate ligand affinity is the energy score (E-score) value. A lower value indicates that the drug is more effective against the active site of the target enzyme. The data obtained refers to there are eight of the Michael addition adducts and pyrano[2,3-*c*]pyrazole derivatives possess E-score values are less than -6.6 kcal/mol compared with the reference ligand hydroxychloroquine. The low E-score values explain that the prepared compounds can serve as good COVID-19 protease inhibitors (Figure 1).



Derivatives	**5a**	**5b**	**5c**	**5d**	**5e**	**5f**	**5g**	**6a**	**6b**	**6c**	**6d**	**6e**	**6f**	**6g**
E-score	-6.93	-6.50	-6.66	-6.61	-6.81	-6.11	-7.02	-6.93	-6.73	-6.87	-6.61	-6.57	-6.14	-6.76

Figure 1. The energy score values of the Michael addition adducts **5a-g** and pyrano[2,3-*c*]pyrazole derivatives **6a-g** compared with HCQ.

The data obtained from the docking software indicate that the most promising ligand in the Michael addition adducts is **5g**, compared with the other ligands in the same class. Similarly, the

most promising in the pyrano[2,3-*c*]pyrazole products is **6a**, compared with the others from the same series. Figures 2 and 3 show the promising compounds **5g** and **6a** inside the COVID-19 protease enzyme.

The protease pocket and the active site protein residues are Thr 45, Asn 142, Leu 167, Thr 26, His 41, Glu 166, Gln 192, Pro 168, Thr 25, Thr 190, Ala 191, Met 165, Leu 141, Met 49, Arg 188, Cys 145, Asp 187, Thr 42, Gly 143, Gln 189, Ser 144, His 164, Ser 46, Leu 27, and Cys 44.

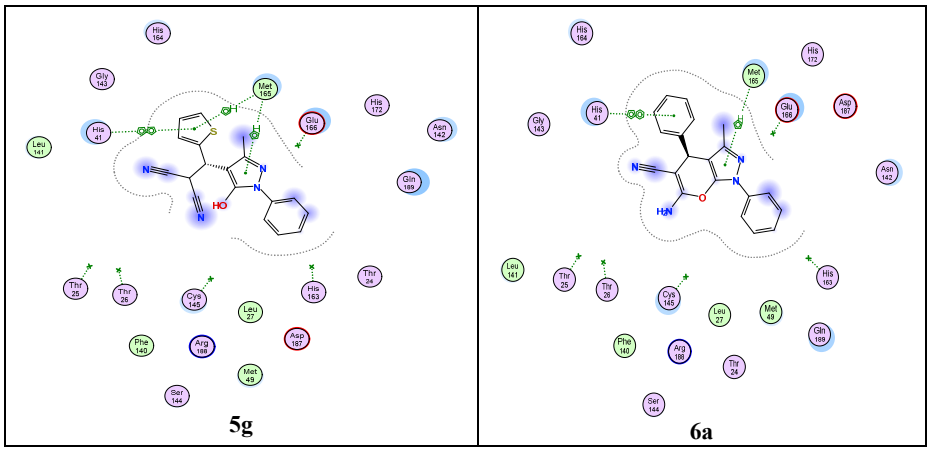


Figure 2. Two-dimensional structure of ligands (**5g** and **6a**) and active sites of COVID-19 protease.

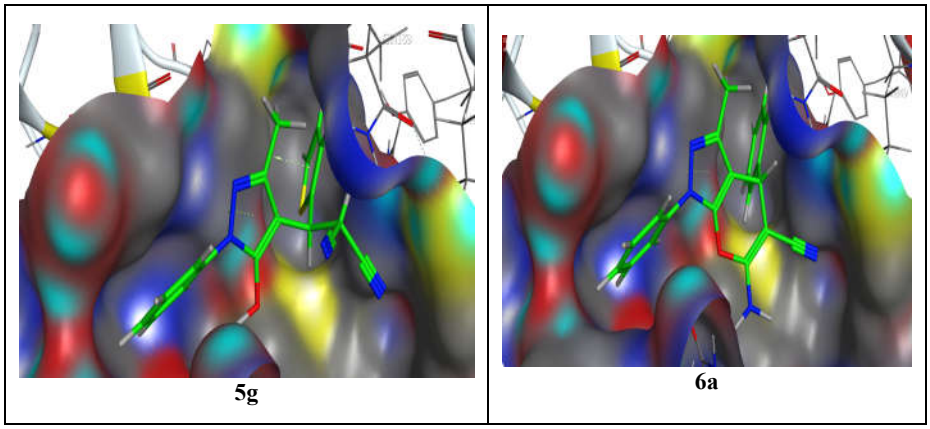


Figure 3. Three-dimensional structure of ligands (**5g** and **6a**) and active sites of COVID-19 protease.

EXPERIMENTAL

Arylidene malononitriles **3a-g** were prepared by the classical method of Knoevenagel condensation through the refluxing of 1 mol of aldehydes **1a-g** and 1 mol of malononitrile (**2**) in ethanol solvent in the presence of a few drops of piperidine base. After extraction and

recrystallization from ethanol solvent, the products dried and were confirmed by their melting points [37].

3-Methyl-1-phenyl-1*H*-pyrazol-5(4*H*)-one (**4**) was prepared by the condensation of phenylhydrazine with ethyl 3-oxobutanoate [38].

*Synthesis of Michael addition adduct **5a-g***

The Michael addition adducts **5a-g** were prepared by mixing 5 mmol of the prepared arylidenes **3a-g** with 5 mmol (0.85 g) of 3-methyl-1-phenyl-1*H*-pyrazol-5(4*H*)-one (**4**) and 20 mL of dichloromethane (DCM) as a solvent in the presence of a catalytic amount of TCS/$ZnCl_2$ and stirring at room temperature (25 °C). After the appropriate time, the final products were precipitated and recrystallized from ethanol solvent, and the products were dried.

*2-((5-Hydroxy-3-methyl-1-phenyl-1H-pyrazol-4-yl)(phenyl)methyl)malononitrile (**5a**)*. ^{1}H NMR ($CDCl_3$, 300 MHz, δ ppm) 2.22 (s, 3H, CH_3), 4.23 (d, 1H, *J* = 10.8 Hz, >(α)CH-CH<), 5.75 (d, 1H, *J* = 11.1 Hz, >CH-(β)CH<), 7.35-7.59 (m, 11H, 10H of aromatic-H + 1H of OH). MS (*m/z*, %): 328 (M^+, 6.3).

*2-((5-Hydroxy-3-methyl-1-phenyl-1H-pyrazol-4-yl)(p-tolyl)methyl)malononitrile (**5b**)*. ^{1}H NMR ($CDCl_3$, 300 MHz, δ ppm) 2.31 (s, 3H, CH_3), 2.45 (s, 3H, CH_3), 4.22 (d, 1H, >(α)CH-CH<), 5.69 (d, 1H, >CH-(β)CH<), 7.15 (t, 1H, aromatic-H), 7.31-7.48 (m, 7H, 6H of aromatic-H + 1H of OH), 7.84 (d, 2H, aromatic-H). MS (*m/z*, %): 341 (M-1, 10.2).

*2-((5-Hydroxy-3-methyl-1-phenyl-1H-pyrazol-4-yl)(4-methoxyphenyl)methyl)malononitrile (**5c**)*. ^{1}H NMR ($CDCl_3$, 300 MHz, δ ppm) 2.53 (s, 3H, CH_3), 3.85 (s, 3H, OCH_3), 5.61 (d, 1H, >(α)CH-CH<), 6.69 (d, 1H, >CH-(β)CH<), 7.15 (t, 3H, aromatic-H), 7.27 (d, 2H, aromatic-H), 7.41 (d, 2H, aromatic-H), 7.59 (t, 2H, aromatic-H), 8.43 (s, 1H, OH).

*2-((4-Chlorophenyl)(5-hydroxy-3-methyl-1-phenyl-1H-pyrazol-4-yl)methyl)malononitrile (**5d**)*. ^{1}H NMR ($CDCl_3$, 300 MHz, δ ppm) 2.10 (s, 3H, CH_3), 4.80 (d, 1H, *J* = 25.8 Hz, >(α)CH-CH<), 6.29 (d, 1H, *J* = 30.9 Hz, >CH-(β)CH<), 7.31-7.84 (m, 10H, 9H of aromatic-H + 1H of OH).

*2-((4-Bromophenyl)(5-hydroxy-3-methyl-1-phenyl-1H-pyrazol-4-yl)methyl)malononitrile (**5e**)*. ^{1}H NMR ($CDCl_3$, 300 MHz, δ ppm) 2.2 (s, 3H, CH_3), 4.78 (d, 1H, *J* = 11.1 Hz, >(α)CH-CH<), 5.87 (d, 1H, *J* = 10.9 Hz, >CH-(β)CH<), 7.18-7.86 (m, 9H, aromatic-H), 8.52 (s, 1H, OH).

*2-(Furan-2-yl(5-hydroxy-3-methyl-1-phenyl-1H-pyrazol-4-yl)methyl)malononitrile (**5f**)*. ^{1}H NMR ($CDCl_3$, 300 MHz, δ ppm) 2.15 (s, 3H, CH_3), 4.82 (d, 1H, >(α)CH-CH<), 6.34 (d, 1H, >CH-(β)CH<), 7.31-7.69 (m, 9H, 5H of aromatic-H + 3H of furan-2-yl ring + 1H of OH). MS (*m/z*, %): 317 (M-1, 16.8).

*2-((5-Hydroxy-3-methyl-1-phenyl-1H-pyrazol-4-yl)(thiophen-2-yl)methyl)malononitrile (**5g**)*. ^{1}H NMR ($CDCl_3$, 300 MHz, δ ppm) 2.06 (s, 3H, CH_3), 4.50 (d, 1H, *J* = 10.5 Hz, >(α)CH-CH<), 5.38 (d, 1H, *J* = 9.9 Hz, >CH-(β)CH<), 6.69 (t, 1H, aromatic-H), 7.17-7.46 (m, 7H, 4H of aromatic-H + 3H of thiophen-2-yl ring), 9.28 (s, 1H, OH). MS (*m/z*, %): 333 (M-1, 5.2)

*Synthesis of pyrano[2,3-c]pyrazole derivatives **6a-g***

The reaction is repeated by a one-pot reaction under the same condition, 5 mmol of aldehydes **1a-g**, 5 mmol of malononitrile (**2**), and 5 mmol (0.85 g) of phenyl pyrazolone **4** with the same catalyst and solvent at room temperature (25 °C). The pyrano[2,3-*c*]pyrazole derivatives **6a-g** were

separated as final products. The final precipitate was recrystallized from ethanol solvent and the products dried. Pyrano[2,3-*c*]pyrazole derivatives **6a-g** were confirmed by their melting points [40, 41].

CONCLUSION

In conclusion, we have synthesized the Michael addition adducts **5a-g** and pyrano[2,3-*c*]pyrazole derivatives **6a-g** using TCS/$ZnCl_2$ as a new catalyst with aldehydes **1a-g**, malononitrile (**2**), arylidene malononitrile **3a-g**, and phenyl pyrazolone **4** as starting materials. All the products were confirmed. Also, a molecular docking study was performed. The eight compounds **5a**, **5c**, **5e**, **5g**, **6a**, **6b**, **6c**, and **6g** possess energy score values less than -6.6 kcal/mol compared with hydroxychloroquine. The two most promising products are **5g** and **6a**. In the future, the two promising products **5g** and **6a** will be studied by extended evaluation.

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