RSC Advances

PAPER

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Cite this: *RSC Adv.*, 2020, **10**, 29109

Water-triggered union of multi-component reactions towards the synthesis of a 4*H*-chromene hybrid scaffold†

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Received 9th June 2020
Accepted 13th July 2020

DOI: 10.1039/d0ra05105e

rsc.li/rsc-advances

An unprecedented union of multi-component reactions to construct pyrazole- and pyranopyrazole-adorned 4*H*-chromene from simple reactants in water at ambient temperature is reported. This innovative tactic has integrated two distinct four-component reactions (4CRs) that occur transiently to form four new heterocycles *via* ten covalent bonds in a single step.

Synthetic organic chemists have reached a level of intricacy, allowing access to any molecule with desired functionalities and stereochemistry. Nevertheless, there is a paucity of transformations for the efficient construction of small biomolecules and their analogs. Multi-component reactions[1] (MCRs) are economical tools for the achievement of this goal, as they inherently involve the formation of several covalent bonds in one operation. MCR proficiency can be further refined by unifying two or more MCRs. In recent decades, the use of higher-order MCRs to construct structurally diverse and complex skeletons has become attractive in organic synthesis and medicinal chemistry.[2]

The union of multi-component reactions (union of MCRs) is an elegant tactic for performing higher-order MCRs and accessing diverse and complex molecular architectures. This approach was first coined by Ugi.[3] The union of MCRs is generally achieved by tandem MCRs[4] or by installing suitable building blocks with orthogonal functionality.[5] The focus of union of MCRs is the orthogonal reactivity of any one of the reactants, which can be combined by two different MCRs without functional-group protection. Nurturing MCRs in water[6] to attain important scaffolds from simple reactants is viewed as a greener approach to populate the chemical space.[7] Diversity-oriented synthesis[8] (DOS), a fascinating area of research in organic synthesis with its sub-disciplines of privileged sub-structure-based diversity-oriented synthesis[9] (pDOS) and biology-oriented synthesis[10] (BIOS), has provided several guiding principles to access biologically relevant small molecules.[11] However, unification of the guiding principles of DOS with union of MCRs in water to access biologically relevant complex scaffold remains a challenge. Very few reports on union of MCRs have focused on the eminent Ugi-4-component reaction (U-4CR) permutation with other MCRs. Indeed, to the best of our knowledge, union of MCRs without the involvement of U-4CRs has not been accomplished so far. The development of new unions of MCR is limited by the compatibility of reactant and reactions in a given solvent.[4i] Herein, we report an innovative strategy that combines two different known 4CRs, which displays solvent compatibilities and produces multiple functional groups in one pot to achieve higher-order MCRs, leading to 4*H*-chromene scaffolds.

At the outset, we established a pyranopyrazole four-component reaction (PP4CR) in water to access a multi-functionalized pyranopyrazole scaffold.[12] To create skeletal diversity, we installed a single-reactant-replacement[13] (SRR) strategy into our PP4CR by orthogonal functionality on the oxo component. Consequently, skeletally diverse and medicinally important 4*H*-chromene[14] and 4*H*-thiochromene[15] derivatives were achieved. Encouraged by these results, we planned to combine these two recent 4CRs in water. As a pDOS approach, we rationally employed 2-hydroxy-5-methylisophthalaldehyde as an oxo component into our PP4CR and performed a pseudo-eight-component reaction to unite these two distinct 4CRs to obtain a complex structure with multi-functionality in a single core possessing the pyranopyrazole and 4*H*-chromene skeletons. Thus, we are the first to describe pseudo-eight-component reactions (8CRs) in water, with unification of two disparate 4CRs to access an unprecedented bioactive pyranopyrazole-substituted 4*H*-chromene scaffold (Scheme 1).

The pseudo-8CR performed in water using two equivalents of hydrazine hydrate 96% (**1**), ethyl acetoacetate (**2**), malononitrile (**3**), and one equivalent of 2-hydroxy-5-methylisophthalaldehyde (**7** and **8**) in the presence of piperidine 10% base at ambient temperature resulted in the formation of product **9a** within 5 min. The product was identified by nuclear magnetic resonance (NMR) as a complex heterocyclic hybrid architecture of 4*H*-chromene adorned with a pyrazole and pyranopyrazole substructure. To verify that this

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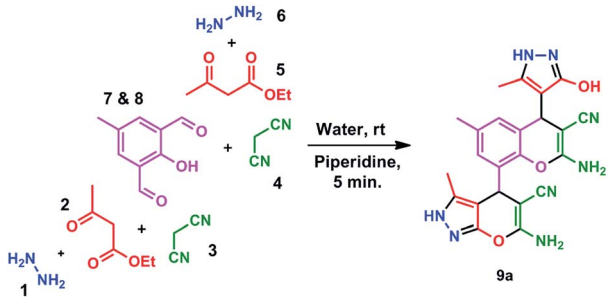
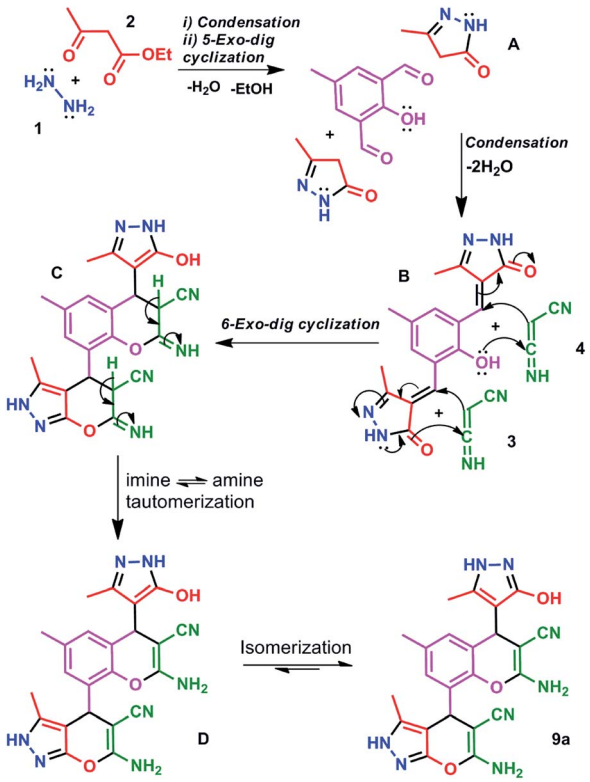
† Electronic supplementary information (ESI) available. See DOI: 10.1039/d0ra05105e



Scheme 1 Pseudo-eight-component reaction in water.



Scheme 2 Plausible mechanism.

union of MCRs occurred either in tandem or in a one-pot manner, we performed an MCR using equimolar hydrazine hydrate 96% (**1**), ethyl acetoacetate (**2**), malononitrile (**3**), and 2-hydroxy-5-methylisophthalaldehyde (**7** and **8**) in water. The reaction yielded **9a** only, which was confirmed by ^{1}H NMR. The result suggests that both 4CRs might occur simultaneously. Thus, the reaction could not be controlled to obtain either a 4*H*-chromene or pyranopyrazole scaffold of a single 4CR while retaining the aldehyde functionality, which can be exploited in other MCRs. This reaction represents an unprecedented example of the true union of MCRs. The reaction occurred according to the mechanism shown in Scheme 2.

Initially, component **1** and **2** are involved in the condensation followed by 5-*exo*-dig azacyclization to yield 3-methyl pyrazolin-5-one (**A**) instantly. **A** undergoes a Knoevenagel condensation

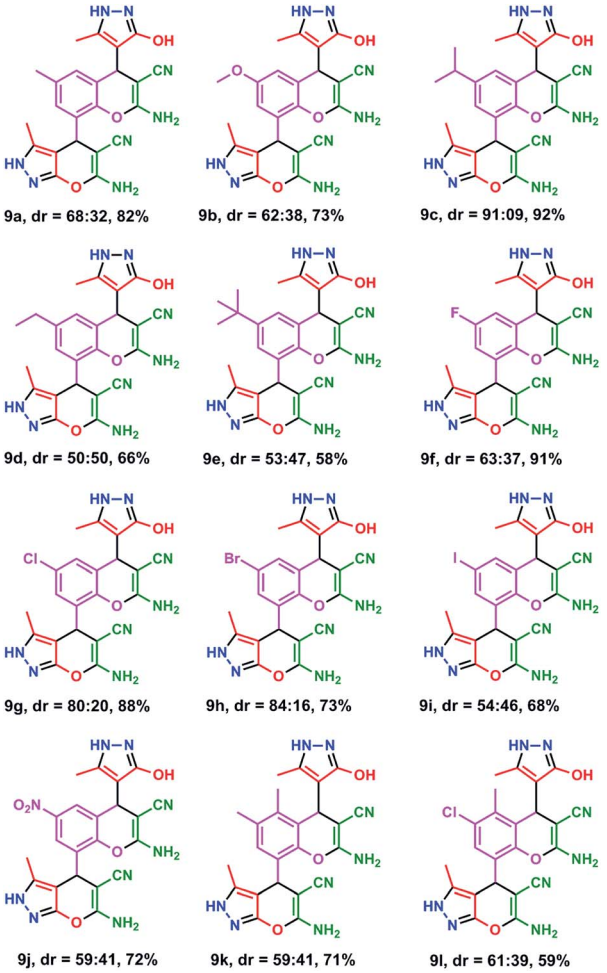


Fig. 1 Library of pyrazole- and pyranopyrazole-adorned 4*H*-chromene scaffolds.

reaction with 2-hydroxy-5-methylisopthalaldehyde to form the intermediate **B**. The malononitrile (**3**) exists in nitrile–ketenimine tauomerism[16] in water medium. The intermediate **B** is involved 6-*exo*-dig-oxocyclization with component **3**. Cumulatively, four heterocycles are formed by 10 covalent bonds, such as C–C, C–N, and C–O. At the final stage, isomerization occurs to obtain the 1*H*-isomer of the pyrazole ring. A deshielding for H_4' and consequent shielding for C_4' of pyranopyrazole were observed in comparison with the corresponding H_4 and C_4 chemical shifts of chromene, indicating the proximity of H_4' to the oxygen of the chromene moiety. The chromene derivatives are adorned with diverse carbo- and heterocyclic motifs, which are ubiquitous in natural products as well as synthetic bioactive molecules, and exhibit vital biological and pharmacological activities.[17]

The reaction showed similar selectivity with good-to-excellent yield when different 2-hydroxyisophthalaldehydes were used as oxo building blocks. The products were created in the course of reactions having two chiral centers. Only two diastereomers of the four possible stereoisomers were distinguishable in ^{1}H and ^{13}C NMR, and were inseparable by column chromatography. The diastereomer ratio was calculated from ^{1}H NMR (Fig. 1).

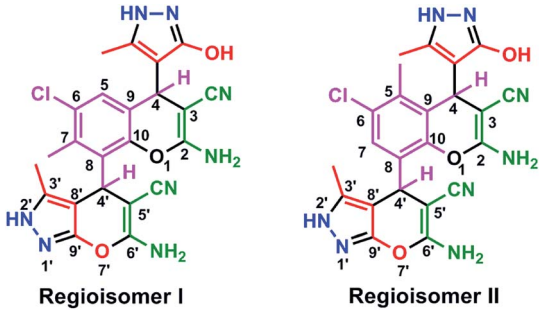


Fig. 2 Possible regio isomers of pyranopyrazole-adorned 4*H*-chromen (**9l**).

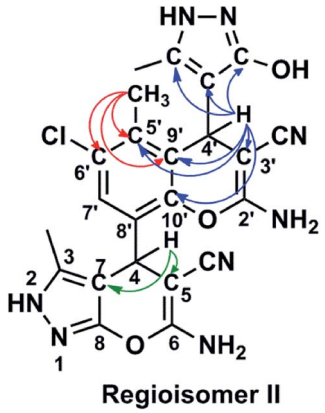


Fig. 3 HMBC correlations of compound **9l**.

We subsequently investigated the use of unsymmetrical disubstituted isopthalaldehydes as an oxo component to this pseudo-8CR. The reaction occurred regioselectively, and the possible regio isomers of **9l** are shown in Fig. 2.

The regio-isomer of **9l** was characterized by heteronuclear multiple bond correlation spectroscopy (HMBC) (Fig. 3). In the ^{1}H NMR of **9l**, the signals at (4.59 + 4.58) and (5.19 + 5.18) ppm were assignable C_4 and C_4' protons, respectively. These proton signals were considered as starting points for analyzing the HMBC correlation spectrum to identify the isomer formed in this reaction.

In HMBC, the C_4' proton correlates with only two carbon (C_8' and C_5') signals at (97.06 + 96.85) and 55.24 ppm. The C_4 proton correlates to four carbon signals at the chromene moiety and three carbon signals at the pyrazole ring C_3 (56.15 + 55.15), C_5 (132.59 + 132.44), C_9 123.57, C_{10} 159.22, C_3'' (135.59 + 135.53), C_4'' (103.87 + 103.59), and C_5'' 145.46 ppm, respectively. The signals at (2.11 + 2.07) ppm, which are assignable to methyl protons attached to aromatic ring, correlate with three carbon signals assignable to the *ipso* carbon C_5 (132.59 + 132.44), two ortho carbons C_6 (128.66), and C_9 (123.57 ppm) of the aromatic ring. The common correlations for C_4 and aromatic methyl protons confirm that the methyl group is adjacent to C_4. The structure of the regio-isomer **II** was assigned unambiguously by HMBC experiments. On cross-matching, the C_4 proton correlates with the aromatic methyl protons correlations two carbon signals at (132.59 + 132.44) and 123.57 ppm are common in both correlations.

Gratifyingly, our union of MCRs is an ideal platform for the rapid construction of privileged scaffolds, introducing both diversity and complexity in a single-step manner with orthogonal functionality.

Conclusions

We have developed a true union of MCRs from simple reactants in water *via* a single step at ambient temperature. This elegant strategy involves the spontaneous formation of ten covalent bonds to access complex and diverse drug-like molecules. The products of union of MCRs also bear orthogonal functionality that may be selectively exploited to create novel compounds having been identified in leads and drugs. Further studies of synthesized scaffolds are in progress in our laboratory.

Experimental

To a stirred aqueous (25 mL) mixture of hydrazine hydrate 96% **1** (107 mg, 2 mmol), ethyl acetoacetate **2** (260 mg, 2 mmol), and malononitrile **3** (132 mg, 2 mmol), 2-hydroxyisophthalaldehyde **4** (1 mmol) and 5 mol% of piperidine catalyst were added successively at room temperature under an open atmosphere with vigorous stirring for 5–10 min. The solid produced from the reaction mixture was filtered, and washed with water and then with ethyl acetate and/or cold ethanol. The products obtained were pure on thin layer chromatography (TLC) and NMR spectra.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

G. V. and K. K thank CSIR (01(2500)/11/EMR-II) and DST (SR/S5/GC-22/2007), the Government of India, for financial support, the Central Instrumentation Facility (CIF), Pondicherry University, for the high-resolution NMR spectroscopy measurements, and the Department of Chemistry (DST-FIST), Pondicherry University, for the FT-IR spectroscopy measurements.

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