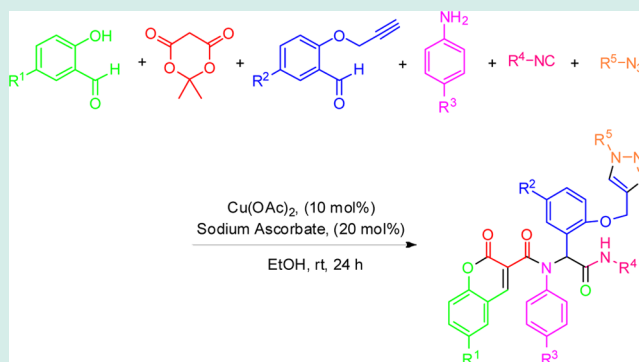


One-Pot Synthesis of Coumarin-3-carboxamides Containing a Triazole Ring via an Isocyanide-Based Six-Component Reaction

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S Supporting Information

ABSTRACT: A facile, efficient, and environmentally friendly approach has been developed for the diversity oriented synthesis of trifunctional coumarin-amide-triazole containing compounds. A wide variety of pharmacologically significant and structurally interesting compounds were synthesized via a one-pot, six-component, tandem Knoevenagel/Ugi/click reaction sequence from readily available starting materials in ethanol at room temperature in excellent overall yields. Substituents could be independently varied at five different positions.



KEYWORDS: coumarin, triazole, multicomponent reaction, click chemistry, isocyanide

INTRODUCTION

Coumarin (2*H*-1-benzopyran-2-one) and its derivatives are important compounds due to their presence in naturally occurring aromatic products found in plants¹ and cinnamon-flavored foods.² It has been reported that coumarin derivatives exhibit anticancer,³ anti-influenza,⁴ anti-HIV,⁵ antialzheimer,⁶ anti-inflammatory,⁷ antituberculosis,⁸ antiviral,⁹ and antimicrobial activities.¹⁰ Novobiocin is a coumarin-derived antibiotic used as a competitive inhibitor of the bacterial ATP binding gyrases B subunit, blocking the negative supercoiling of relaxed DNA.¹¹ Moreover, coumarins constitute an important class of organic fluorescent dyes. These fluorescent properties have been used to study proteins and nucleic acids.¹² It is important to note that the existence of the amide groups in coumarin-3-carboxamides improves the biological activity of these compounds.¹³

In recent years, some works have manifested that a coumarin backbone in combination with some nitrogen-containing heterocyclic moieties such as azetidine, thiazolidine, thiazole, and so on could significantly increase the antimicrobial efficiency and broaden their antimicrobial spectrum.¹⁴ In this context, considerable efforts have been made to develop synthetic strategies to join two structural units, such as coumarin scaffold and triazole moiety, in order to make a new potential therapeutic agent.^{15,10} For example, compounds of formula **I** are useful as pharmaceutical agents to slow or halt atherogenesis,¹⁶ **II** is a potent 5-lipoxygenase (5-LO) inhibitor,¹⁷ and **III** is an anti-inflammatory agent (Figure 1).¹⁸

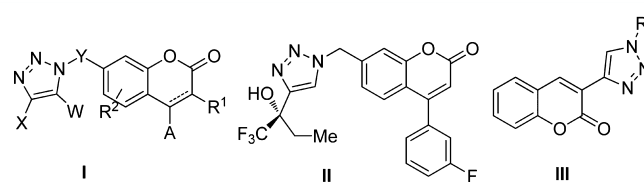


Figure 1. Examples of some biologically active 1,2,3-triazole-coumarins.

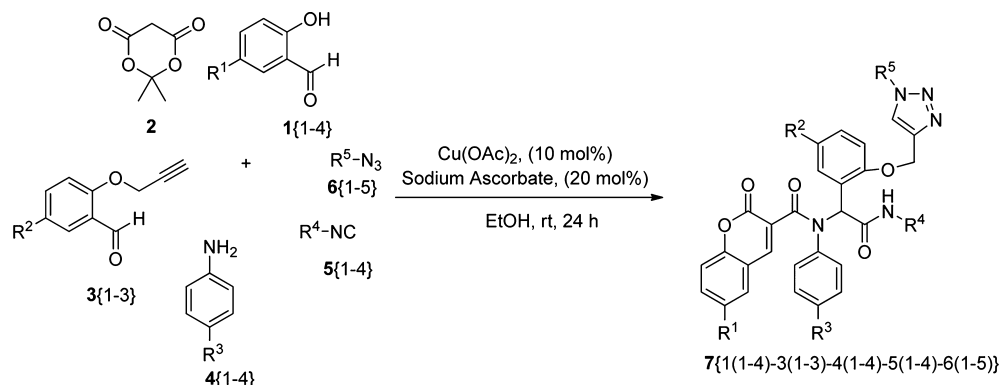
Multicomponent reactions (MCRs) are useful and powerful tools in which three or more different starting materials react to form novel and complex molecules in a one-pot strategy with great efficiency and atom economy. The development of such processes in which several bonds are formed without isolation of intermediates receives considerable attention for the preparation of structurally diverse libraries of drug-like polyfunctional compounds.¹⁹ Although reports on novel MCRs appear regularly in the recent literature, MCRs using more than five components are very rare. A landmark in this context is the seven component reaction (7CR) reported by Domling and Ugi,²⁰ in which thiazolidines are efficiently produced from two different aldehydes, NaSH, NH₃, an isocyanide, CO₂, and a primary alcohol. However, NaSH, NH₃, and CO₂ are invariable components in this reaction.

Received: September 29, 2013

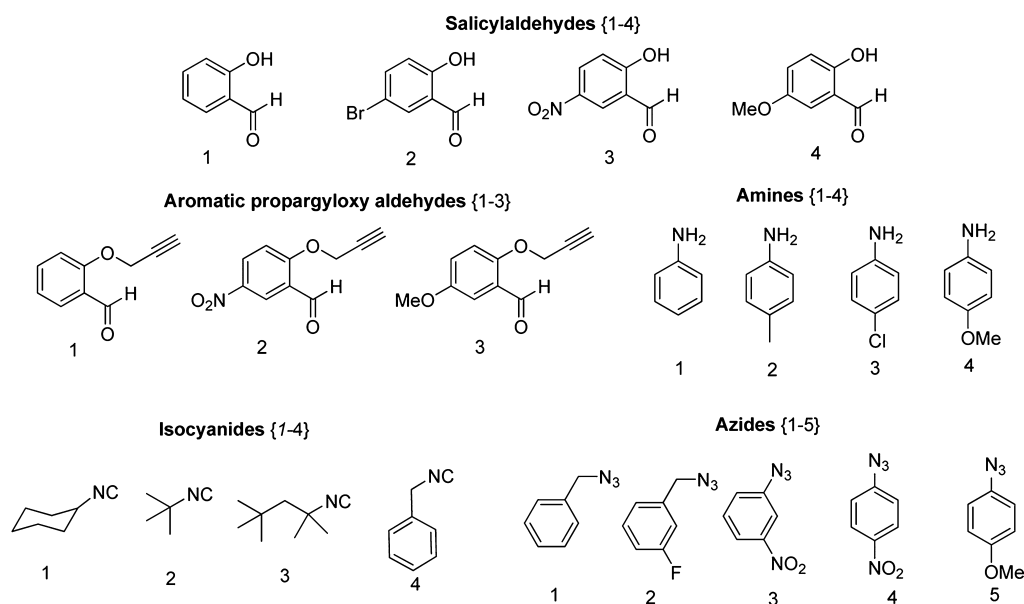
Revised: February 13, 2014

Published: February 14, 2014

Scheme 1. Synthesis of Coumarin-3-carboxamide Derivatives Bearing Substituted 1,2,3-Triazole Moiety 7



$\text{R}^1 = \text{H, Br, NO}_2 \text{ or OMe}$
 $\text{R}^2 = \text{H, NO}_2 \text{ or OMe}$
 $\text{R}^3 = \text{H, CH}_3, \text{Cl or OMe}$
 $\text{R}^4 = \text{Cyclohexyl, } t\text{Butyl, 1,1,3,3-Tetramethylbutyl or Benzyl}$
 $\text{R}^5 = \text{Benzyl, 3-FC}_6\text{H}_4\text{CH}_2, \text{3-NO}_2\text{C}_6\text{H}_4, \text{4-NO}_2\text{C}_6\text{H}_4 \text{ or OMe}$



The Ugi four-component reaction (U-4CR) is one of the most commonly used MCRs, in which a carboxylic acid, an amine, a carbonyl compound, and an isocyanide are reacting to result in peptide-like products.²¹ The combination of U-4CR with secondary transformations is a powerful approach to access highly functionalized heterocyclic structures in few steps. There are some literature examples of using an Ugi reaction in conjunction with click chemistry.²² “Click” chemistry is a highly effective method for functionalization which was coined in 2001 by Sharpless et al.²³ to describe an ideal set of near perfect reactions. Among the various click reactions, the copper(I)-catalyzed 1,3-dipolar azide–alkyne cycloaddition (CuAAC) is a reliable means to form 1,4-disubstituted triazoles²⁴ that has been widely used in synthetic and medicinal chemistry.²⁵ 1,2,3-Triazoles are present in many drugs²⁶ and, because of their interesting biological properties such as antibacterial,^{25b} antiallergic,²⁷ and anti-HIV activity,²⁸ are an important class of target molecules. Compounds with 1,2,3-triazole could actively participate in hydrogen bonding and dipole–dipole interactions due to their strong dipole moments; moreover it is

extremely hard to be hydrolyzed and remain stable under oxidative or reductive conditions.^{25a}

Some articles exposed the use via click chemistry of some coumarin derivatives.²⁹ The well-known biological properties of coumarins and 1,2,3-triazoles prompted us to synthesize molecules in which both nuclei exist. As a part of our ongoing research program on the isocyanide-based MCRs,³⁰ here we report the synthesis of coumarin-3-carboxamides containing triazole ring 7 by a one-pot, six-component, condensation reaction of salicylaldehydes 1, Meldrum’s acid 2, aromatic propargyloxy aldehydes 3, amines 4, isocyanides 5, and azides 6, in the presence of catalytic amounts of $\text{Cu}(\text{OAc})_2$ (10 mol %) and sodium ascorbate (20 mol %) as a reducing agent for the reduction of Cu(II) to Cu(I) in ethanol at room temperature (Scheme 1). Recently, Balalaie et al. synthesized coumarin-3-carboxamides containing lipophilic spacers through the U-4CR.³¹ In this paper, we report the synthesis of coumarin-3-carboxamides containing a triazole ring by preparing the starting coumarine-3-carboxylic acid and a terminal triazole ring *in situ*. It is worth mentioning that in

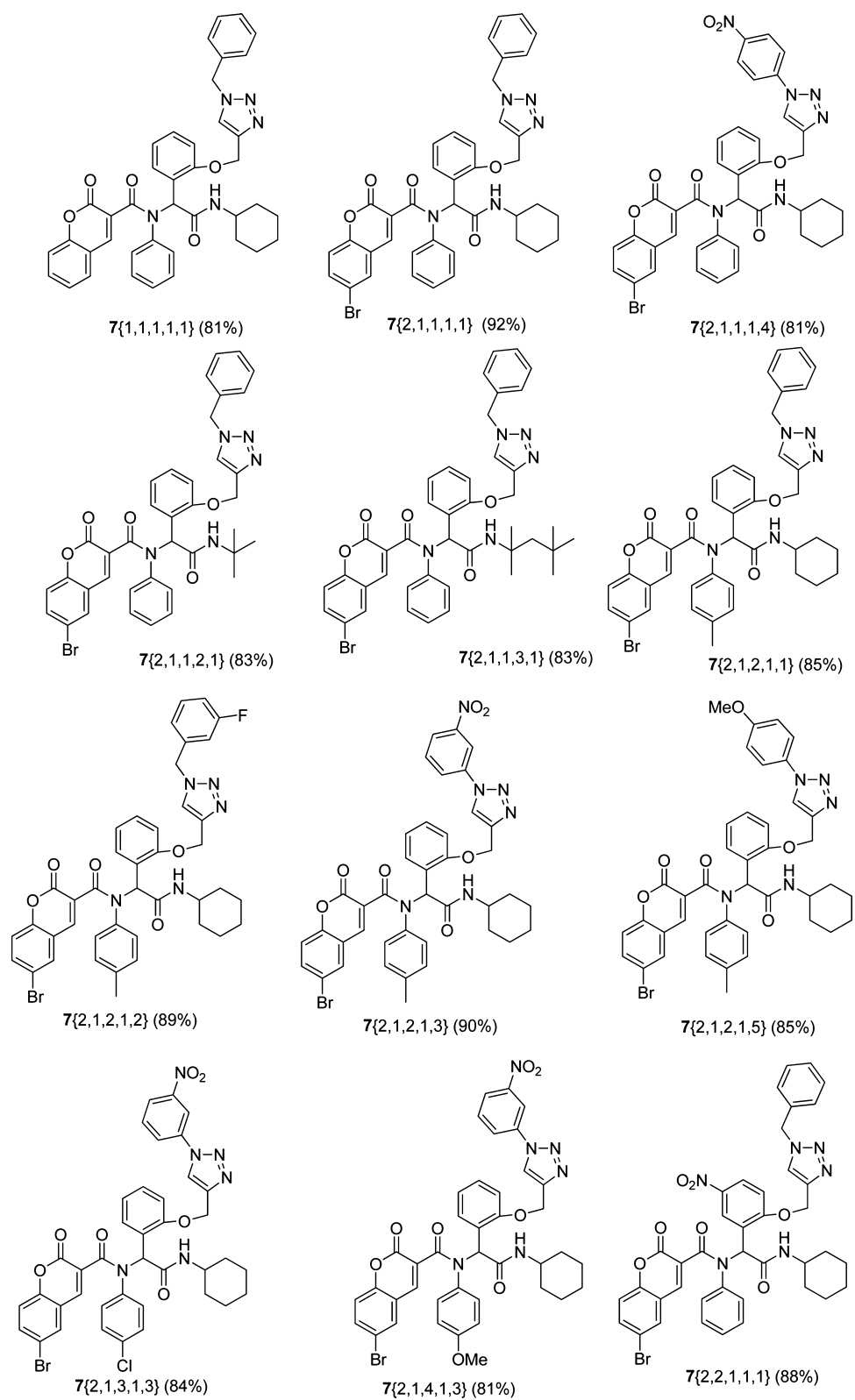


Figure 2. continued

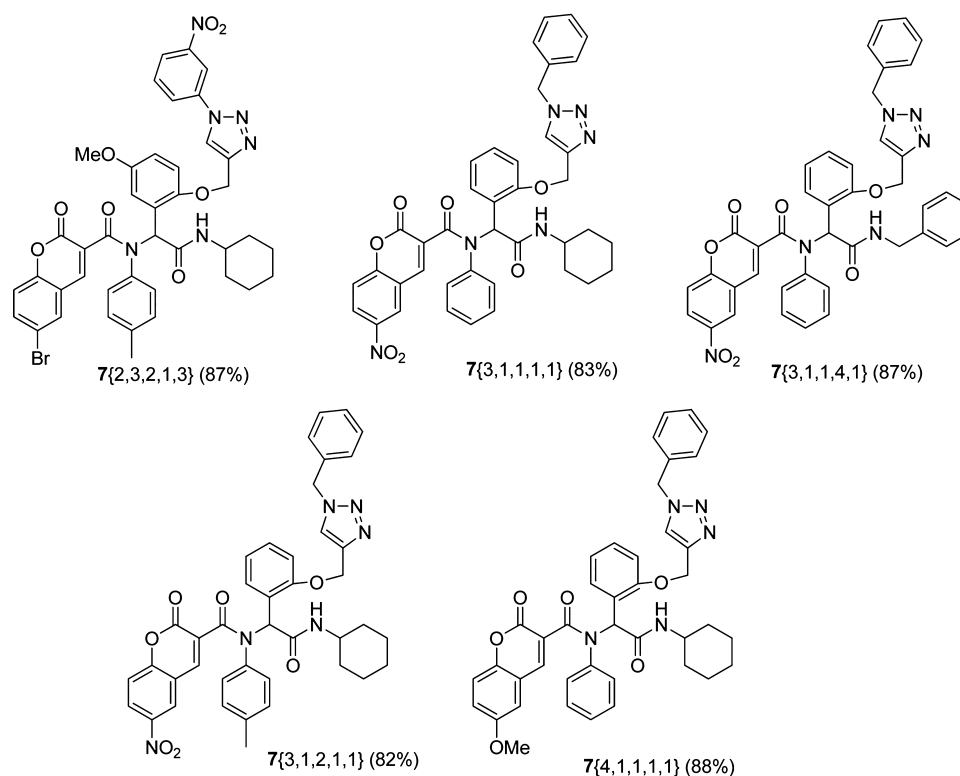


Figure 2. Structure and isolated yields of products 7.

the course of our reaction, two C–C bonds and six heteroatom–C bonds are formed. Also, a triazole ring, a lactose ring, and two amide groups are formed.

RESULTS AND DISCUSSION

In a pilot experiment, 5-bromosalicylaldehyde 1{2} reacts with Meldrum's acid 2 in EtOH to afford 6-bromo-coumarin-3-carboxylic acid. Then, aniline 4{1}, propargyloxy aldehyde 3{1}, and cyclohexyl isocyanide 5{1} were added and the mixture stirred at room temperature. After completion of the reaction, benzyl azide 6{1} and a catalytic amount of Cu(OAc)₂ (10 mol %) and sodium ascorbate (20 mol %) were added. After completion of the reaction (24 h), the desired product 7{2,1,1,1,1} was isolated in 92% yield.

The reaction did not require any optimization. In view of the success of the above reaction, we explored the scope and limitations of this reaction, by extending the procedure to various salicylaldehydes 1{1–4}, aromatic propargyloxy aldehydes 3{1–3}, amines 4{1–4}, isocyanides 5{1–4}, and azides 6{1–5}. As indicated in Figure 2, the reactions proceed very efficiently at room temperature and led to the formation of a new class of the amidated coumarin derivatives containing triazole ring 7 in excellent yields. It is noteworthy that the Ugi and click reaction cannot usually be performed directly in one step. It is well-known that isocyanides are good ligands for transition metals.³² Therefore, copper will be coordinated to the isocyanide C atom, and this complex is not effective as a catalyst for the Huisgen 1,3-dipolar cycloaddition.

The structures of products 7 were deduced from their IR, ¹H NMR, ¹³C NMR, mass spectra, and CHN analysis data. The ¹H NMR spectrum of 7{2,1,1,1,1} consisted of a multiplet for the methylene protons of the cyclohexyl ring ($\delta = 1.04$ – 1.71 ppm, 10H); a broad singlet for the NH–CH cyclohexyl ($\delta = 3.64$ ppm); three singlets for OCH₂ ($\delta = 5.21$ ppm), NCH₂ ($\delta =$

5.67 ppm), and CH ($\delta = 6.42$ ppm); a multiplet for aromatic protons (6.68 – 8.13 ppm, 19H); and a singlet for NH ($\delta = 8.45$ ppm). Also, the ¹H decoupled ¹³C NMR spectrum of 7{2,1,1,1,1} is completely consistent with the product structure. The mass spectra of these compounds displayed molecular ion peaks at the appropriate *m/z* values. Finally, the structure of the products 7{2,1,2,1,1}, 7{2,1,2,1,3}, and 7{2,2,1,1,1} was confirmed unambiguously by single-crystal X-ray analysis (Figure 3 and SI).

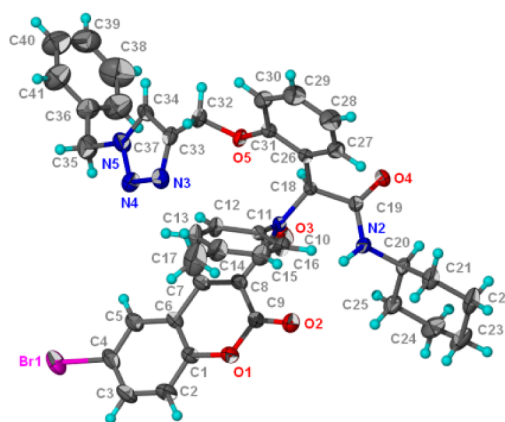
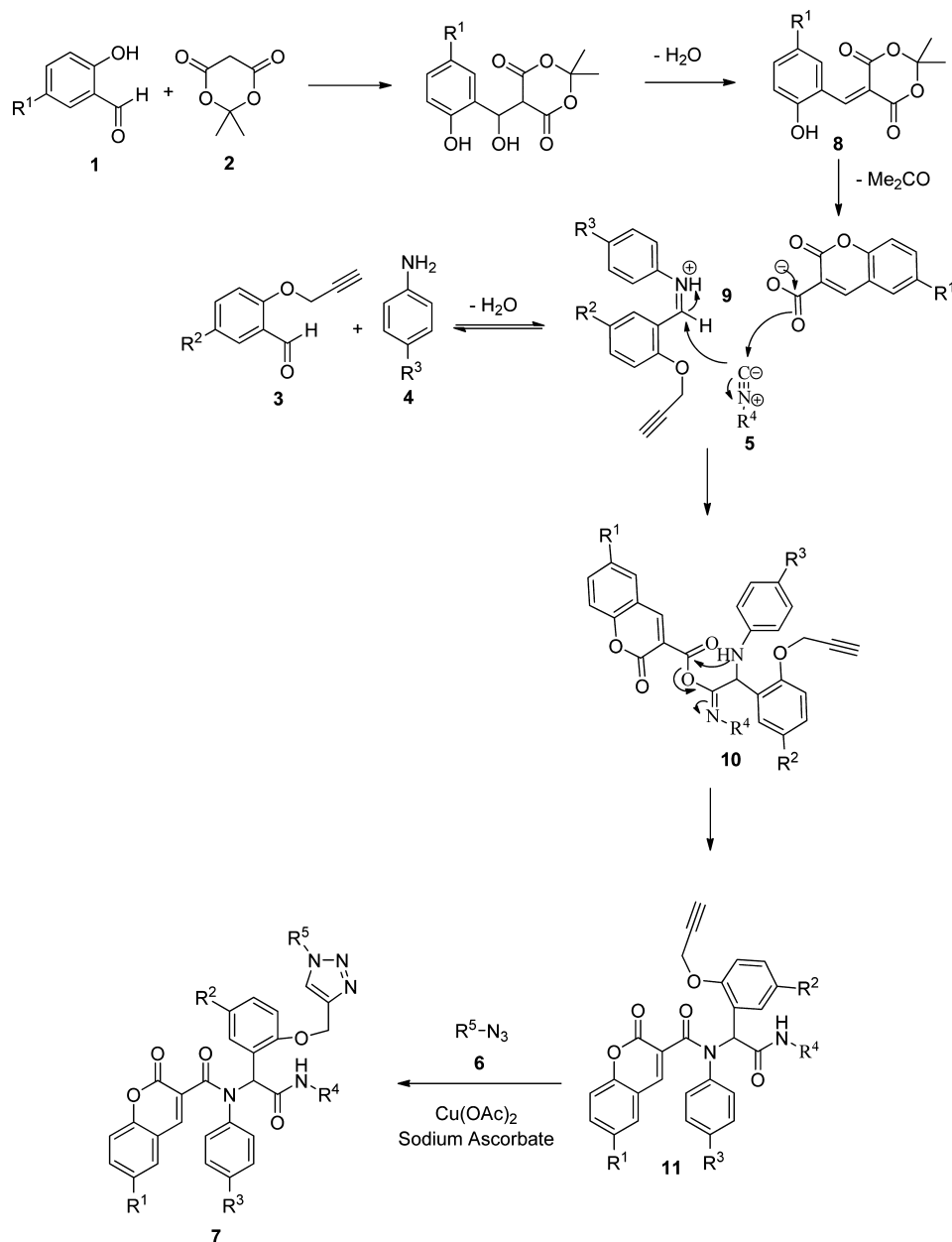


Figure 3. ORTEP diagram for 7{2,1,2,1,1}.

A possible mechanism for the formation of products 7 is shown in Scheme 2. The reaction may be rationalized as by the initial formation of conjugated electron-deficient heterodiene 8 by a standard Knoevenagel condensation of the salicylaldehyde 1 and Meldrum's acid 2. Then nucleophilic attack of the phenolic group onto the carbonyl carbon of Meldrum's acid resulted in the opening of Meldrum's acid ring, and a

Scheme 2. Proposed Mechanism for the Formation of Products 7



subsequent loss of acetone leads to the formation of coumarin-3-carboxylic acid.³³ According to the commonly accepted Ugi-4CR mechanism, the amines, aldehydes, and acids are in equilibrium with iminium carboxylates **9** in the reaction medium. The addition of the carbenoid C atom of the isocyanides onto the iminium group followed by the addition of the carboxylate ion onto the C atom of the nitrilium ion leads to the formation of the adduct **10**, which undergoes an intramolecular acylation known as Mumm rearrangement to give the stable Ugi adduct **11**. Finally, the Huisgen 1,3-dipolar cycloaddition reaction between the propargyloxy group of **11** and azide **6** takes place to produce the bifunctional coumarin-triazole products **7** (Scheme 2).

CONCLUSION

In conclusion, we have successfully developed a novel one-pot six-component condensation reaction strategy leading to

trifunctional containing coumarin-amide-triazole compounds starting from simple and readily available inputs. The reaction shows good functional group tolerance and is high-yielding, and product isolation is very straightforward. The broader substrate scope of this reaction makes it a useful and attractive process for the synthesis of a great library of these important compounds. The potential uses of this route in synthetic and medicinal chemistry may be significant, since the products share structural and functional group properties of the biologically active molecules.

EXPERIMENTAL PROCEDURES

General. Melting points were measured on an Electro-thermal 9200 apparatus. IR spectra were recorded on a Shimadzu IR-470 spectrometer. ^1H NMR spectra were recorded on a Bruker DRX-300 Avance spectrometer at 300.13 MHz; chemical shifts (δ scale) are reported in parts

per million (ppm). ^1H NMR spectra are reported in order: number of protons, multiplicity, and approximate coupling constant (J value) in hertz (Hz); signals were characterized as s (singlet), d (doublet), t (triplet), m (multiplet), br s (broad signal), and Ar (aryl). ^{13}C NMR spectra were recorded on Bruker DRX-400 and DRX-300 Avance spectrometers at 100.64 and 75.47 MHz; chemical shifts (δ scale) are reported in parts per million (ppm). The mass spectra were recorded on an Agilent 5973 mass spectrometer operating at an ionization potential of 70 eV. The elemental analyses were performed with an ElementarAnalysensysteme GmbH VarioEL. All of the products are new compounds, which were characterized by IR, mass, ^1H NMR, and ^{13}C NMR spectra.

General Procedure for the Synthesis of 1,2,3-Triazole-coumarin-3-carboxamides 7. A mixture of salicylaldehyde (1 mmol) and Meldrum's acid (1 mmol) in EtOH (5 mL) was stirred for 10 h. Then, amine (1 mmol), propargyloxy aldehyde (1 mmol), and isocyanide (1 mmol) were added and the mixture stirred at ambient temperature for 8 h. After completion of the reaction, as indicated by TLC, aryl azide (1.2 mmol), $\text{Cu}(\text{OAc})_2$ (0.02 g, 10 mol %), and sodium ascorbate (0.04g, 20 mol %) were added. Then, the resulting mixture was stirred for 6 h at room temperature. After completion of the reaction, as indicated by TLC, the product was filtered off. Then, it was stirred in a solution of ammonia and water for 30 min. Then, the solid was filtered and washed with EtOH and water to give the pure product.

■ ASSOCIATED CONTENT

■ Supporting Information

Experimental procedures; characterization data and spectra of products; IR, mass, and ^1H and ^{13}C NMR spectra for 7; and crystallographic data for 7{2,1,2,1,1}, 7{2,1,2,1,3}, and 7{2,2,1,1,1} (CIF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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■ Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We gratefully acknowledge financial support from the Iran National Science Foundation (INSF) and Research Council of Shahid Beheshti University.

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