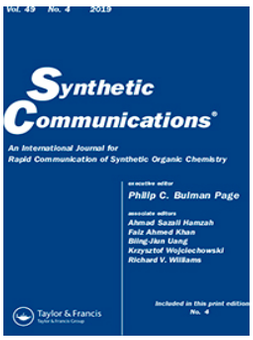

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Synthesis of novel 1,4 naphthoquinone-based molecules by an Ugi-type four-component reaction

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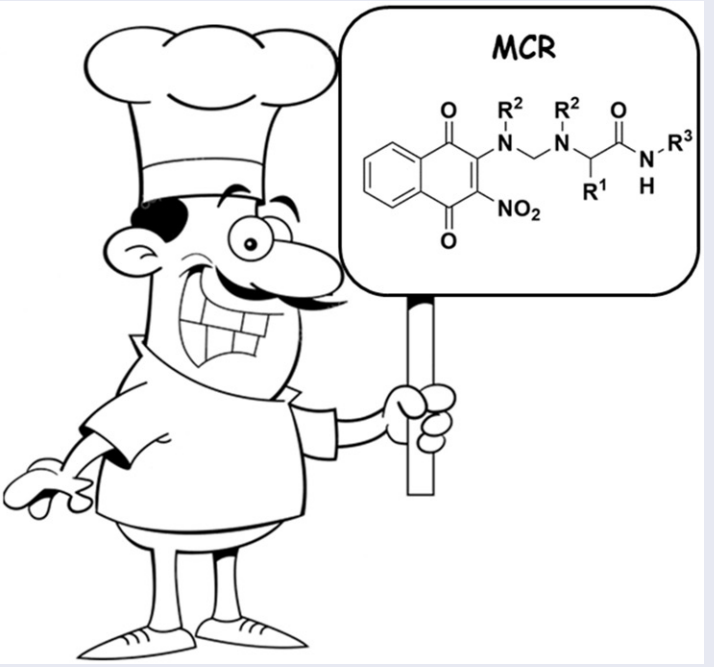
ABSTRACT

In an attempt to further exploit multicomponent reactions in the field of 1,4 naphthoquinone-based compounds, we describe an Ugi-type multicomponent approach for the synthesis of novel 3-substituted 1,4 naphthoquinone molecules. The process relies on the execution of an enol-Ugi reaction between an enol-3-nitro-1,4 naphthoquinone with different secondary diamines and isocyanides. The novel methodology showed great chemical efficiency and versatility.

GRAPHICAL ABSTRACT



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Introduction

The 1,4-naphthoquinone scaffolds have received considerable attention because of the synthetic challenges associated with their interesting biological properties, such as their antifungal, [1] antiviral, [2] and anti-inflammatory activities.[3] In this context, the development of facile methods to access these new targets with structural diversity is very desirable and valuable for drug discovery.

Multicomponent reactions (MCRs) enclose an exciting class of chemical transformations that have been successful in almost all fields of synthetic organic chemistry in the pursuit of novel bioactive small molecules. Isocyanide based multicomponent reactions (IMCR) gained significant interest within the scientific community as an efficient, convenient, time-saving, and atom-economical approach to rapidly generate chemical diversity.[4]

The Ugi four-component reaction (U-4CR) is a widely used IMCR for the synthesis of peptidomimetics.[5] This multicomponent transformation usually refers to the reaction between an amine (usually a primary amine; less often ammonia, or a secondary amine), a carbonyl compound (aldehyde or ketone), an isocyanide, and a carboxylic acid. Carboxylic isosteric replacements like carbonic acids,[6] thiocarboxylic acids,[7] isocyanic acids,[8] phenol, thiophenol,[9] allenic acids[10] and *N*-hydroxyimides[11] were also successfully used in the Ugi-type reaction. More recently, Marcos and coworkers reported that enols containing α,β-unsaturated electron-withdrawing groups readily react as a novel acid surrogate in the U-4CR.[12]

Herein we report the use of 2-hydroxy- 3 nitro-1,4-naphthoquinone as the acid component in the Ugi- type for component reaction (UT-4CR). Similarly, we introduce this multicomponent approach with symmetric secondary diamines which provide a remote Mumm rearrangement.[13] This allows the straightforward synthesis of *N*-substituted naphthoquinone enamines (Figure 1).

Initially, we began our studies by evaluating the reaction between 2-hydroxy-3-nitro-1,4-naphthoquinone (**1**), paraformaldehyde as oxocomponent, 1,3-bis(methylamino)propane and *t*-butyl isonitrile in methanol as a solvent, which provided the desired product **2a** in a 30% yield. Encouraged by this preliminary result, the screening of solvent, time, as well as the influence of temperature was investigated to establish the optimized reaction conditions (Table 1). Solvent effects were first investigated (Table 1, entries 1–4). The polar protic solvents provided higher yields than aprotic ones (Table 1, compare entries 1–4), and the best result was obtained with methanol (entry 1).

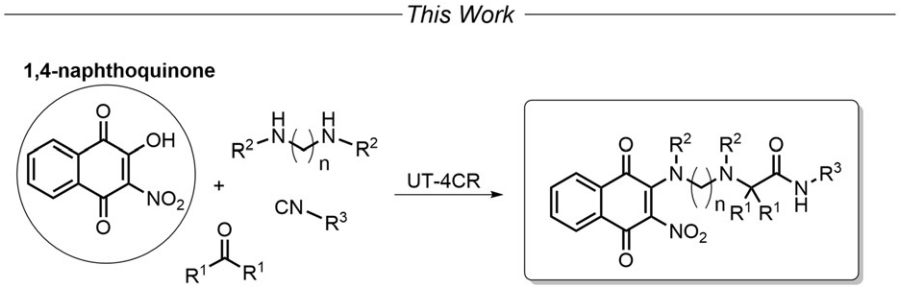
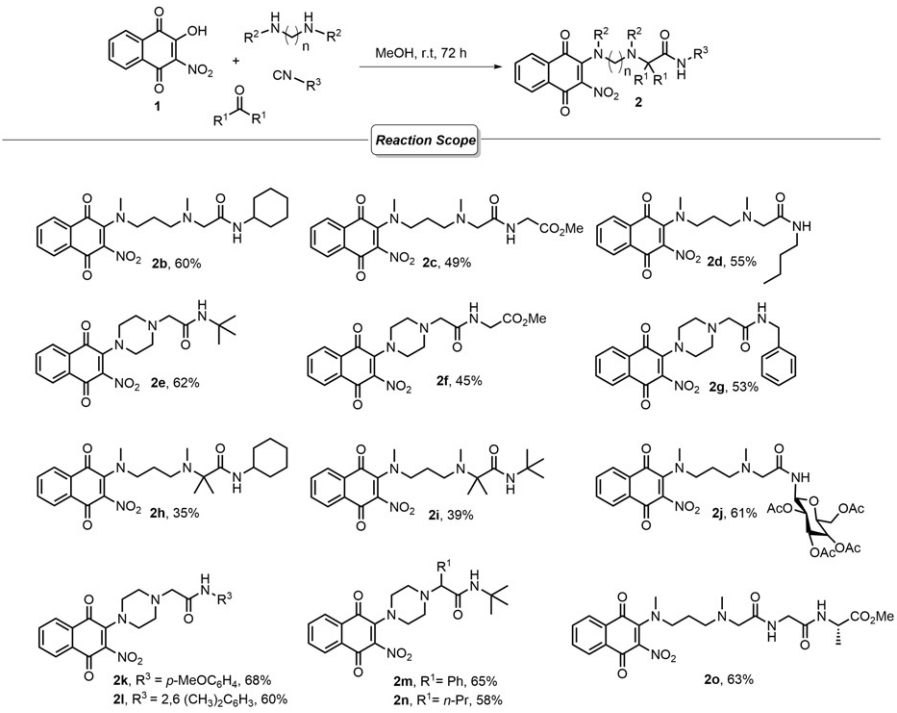


Figure 1. Synthesis of 1,4 naphthoquinones derivatives.

Table 1. Optimization of enol UT-4CR for the synthesis of **2a**.

Entry[a]	Solvent	Temp (°C)	Time(h)	Yield (%)[b]
1	MeOH	25	36	30
2	EtOH	25	36	20
3	CH_2Cl_2	25	36	15
4	Toluene	25	36	Trace
5	MeOH	40	24	25
6	MeOH	50	24	20
7	MeOH	25	72	65
8	MeOH	25	96	52

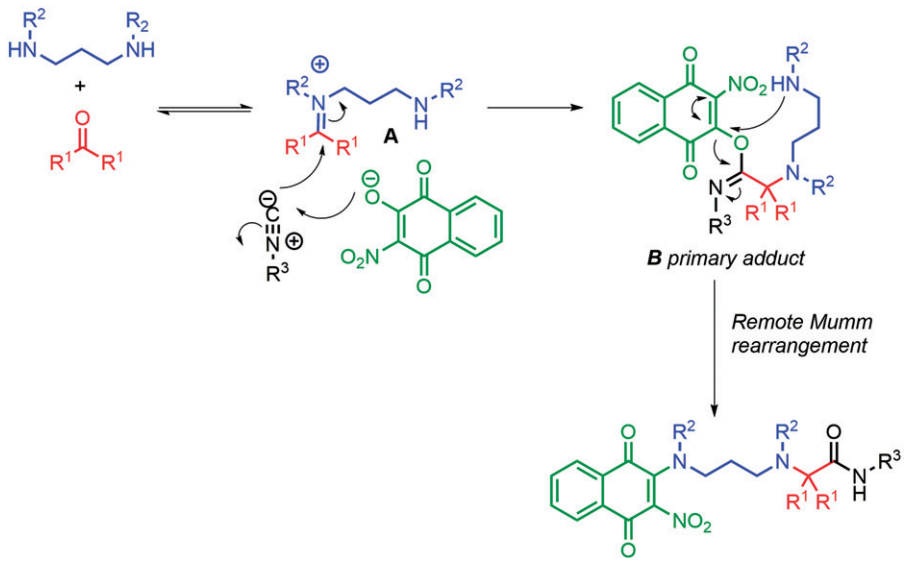
[a]Reaction performed with paraformaldehyde (1.0 equiv) and 1,3-bis(methylamino)propane (1.0 equiv) and, subsequently, the addition of the enol component **1** (1.0 equiv) and tert-butyl isocyanide (1.0 equiv.). [b]Yield of the isolated product after column chromatography.



Scheme 1. Reaction scope for the *N*-substituted naphthoquinone enamines.

The effect of the reaction temperature was investigated; surprisingly, it was observed that increasing the temperature did not reduce the reaction time and lower yields of compound **2a** were achieved (entries 5 and 6). To improve the yields, we then examined the reaction time, it was discovered that 72 h of reaction time afforded the best yield (entry 7); longer reaction times provided complex reaction mixtures. Thus, optimal conditions are the use of methanol as a solvent for 72 h at room temperature.

Under optimal conditions, we widened the scope of the reaction into the achievement of a novel family of naphthoquinone enamines. The Scheme 1 shows the versatility of multicomponent reaction, which through the variation of the amino, oxo, and isonitrile components; made possible the obtention of naphthoquinone derivatives with a wide structural diversity on position 2 of this ring. In all cases, 2-hydroxy- 3 nitro-1,4-naphthoquinone (**1**) was the acid isostere of the Ugi type reaction and reacted with



Scheme 2. Proposed reaction mechanism.

the preformed imine and the isonitrile to render the Ugi products (**2b–2o**). Regarding this, the synthesis was focused on the addition of symmetrical secondary diamines as well as different isocyanides. Secondary diamines participate in an N-split Ugi type four-component reaction as a replacement of primary amines.[14] In this transformation, one nitrogen atom was alkylated and the other was linked to the naphthoquinone core.

As illustrated in Scheme 1, the methodology is suitable for a wide scope of amines and isonitriles, including aliphatic (**2b–2f**), and aromatic (**2k** and **2l**). The incorporation of saccharidic (**2j**) and peptidic fragments (**2o**) was achieved using the corresponding isocyanides, which were prepared as described previously.[15] Remarkably, the efficiency of the reactions carried out with these complex isonitriles proved to be as high as those performed with the simpler, commercially available isocyanides benzyl, cyclohexyl and *t*-butyl isocyanides.

On the other hand, good yields were observed (45–62%) with the exceptions **2 h** and **2i**. Steric hindrance encouraged by the propanone could justify the modest yield in these cases. All compounds were purified by flash column chromatography (n-hexane/AcOEt) and were properly characterized by NMR and MS. The racemic mixtures of compounds **2 m** and **2n** were also corroborated by chiral stationary phase HPLC (see the Supporting information).

The possible reaction mechanism is shown in Scheme 2. The reaction commences with an interaction between one nitrogen of the diamine and the aldehyde to give the corresponding imine A. An α-addition of the imine and enolate give the primary adduct B. The resulting primary intermediate may undergo a subsequent conjugate addition of the second nitrogen atom of the diamine to the naphthoquinone as the first nitrogen atom has already become a tertiary amine and is unable to receive this group.

In summary, we have implemented a multicomponent approach for the 2-substituted-1,4-naphthoquinone enamines formation. The process comprises the execution of

an enol UT-4CR for the decoration of naphthoquinone ring. Also, the present methodology offers a versatile way for introducing higher molecular complexity on naphthoquinone ring.

Experimental

General methods

Reagents and materials were used as received from commercial sources without further purification. Flash column chromatography was carried out using silica gel 60 (230–400 mesh) and analytical thin layer chromatography (TLC) was performed using Merck silica gel 60 F254 aluminum sheets. Visualization of the compounds was achieved by UV or $KMnO_4$. ^1H NMR and ^{13}C NMR spectra were recorded at 400 MHz for ^1H and 100 MHz for ^{13}C, respectively. Chemical shifts (δ) are reported in parts per million relatives to the residual solvent signals, and coupling constants (J) are reported in Hertz. High-resolution mass spectra (HRMS) were recorded using electron spray ionization (ESI) (Hybrid linear ion trap-orbitrap FT-MS/MS – and QqTOF Microtof – QII models).

2-Hydroxy-3-nitro-1,4-naphthoquinone (1)

To a suspension of 2-hydroxy-l,4-naphthoquinone (0.17 g, 1.00 mol) in dry acetonitrile (15 mL) nitronium tetrafluoroborate (0.15 g, 1.15 mmol) was added under nitrogen atmosphere. The resulting reaction mixture was stirred for 30 min during which the light yellow suspension turned into a transparent yellow solution. The solvent was evaporated followed by the addition of HCl (4 M, 50 mL). The resulting aqueous suspension was extracted with ethyl ether (2 × 50 mL). The combined organic layers were dried over $MgSO_4$, filtered off, and evaporated to yield **1** (0.201 g, 92%) as a yellow solid. ^1H NMR (400 MHz, DMSO-d_6) $\delta = 8.68$ (brs, 1 H); 8.25–8.18 (m, 2 H); 7.95–7.82 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) $\delta = 184.2$, 178.4, 161.9, 136.7, 135.4, 135.1, 134.2, 132.0, 131.1, 15.8.

General procedure for the multicomponent conjugation

A suspension of the diamine (0.50 mmol, 1 equiv.) and the carbonyl compound (0.50 mmol, 1 equiv.) in MeOH (1 mL) was stirred for 8 h at room temperature. The 2-hydroxy-3-nitro-1,4-naphthoquinone (0.50 mmol, 1 equiv.) and the isocyanide (0.6 mmol, 1.2 equiv.) are then added and the reaction mixture is stirred at room temperature for 72 h. The volatiles are concentrated under reduced pressure and the resulting crude product is dissolved in 30 mL of $CHCl_3$. The organic phase is washed sequentially with an aqueous saturated solution of citric acid (3 × 10 mL), aqueous 10% $NaHCO_3$ (3 × 10 mL), and brine (30 mL), and then dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product is purified by flash column chromatography (n-hex/AcOEt) on silica to afford the corresponding compound.

Compound ***2a***: A suspension of 1,3-bis(methylamino)propane (63 μL, 0.5 mmol) paraformaldehyde (15 mg, 0.5 mmol) 2-hydroxy-3-nitro-1,4-naphthoquinone 1 (110 mg,

0.5 mmol) and tert-butyl isocyanide (56 μL, 0.5 mmol) in MeOH (1 mL) were reacted according to the general procedure A. Flash column chromatography purification (n-hex/AcOEt 1:1) afforded compound 1a (135 mg, 65%) as an amorphous yellow solid;; ^{1}H NMR (400 MHz, $CDCl_3$) $\delta = 8.28–8.12$ (m, 2 H); 7.89–7.67 (m, 2H); 6.08 (s, 1H); 4.01 (s, 2H); 3.38 (t, $J = 6.9$ Hz, 2H); 2.90 (s, 3H); 2.51 (t, $J = 7.0$ Hz, 2H); 2.39 (s, 3H); 2.04–1.92 (m, 2H); 1.45 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) $\delta = 187.2$, 183.4, 171.6, 147.8, 135.9, 135.0, 134.1, 133.2, 129.5, 127.2, 124.8, 59.6, 55.8, 52.9, 51.7, 42.4, 41.1, 29.1, 24.8. HRMS (ESI-FT-QQTOF) *m/z*: 417.2142 $[M + H]^+$; calcd. for $C_{21}H_{29}N_4O_5$: 417.2138.

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