



Reaction between anthranilic acids, salicylaldehydes and isocyanides in water: an efficient synthesis of 2-[[2-(alkylimino)-1-benzofuran-3-yliden]amino]benzoic acids

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ABSTRACT

A novel, one-pot and three-component reaction for the preparation of 2-[[2-(alkylimino)-1-benzofuran-3-yliden]amino]benzoic acids is described. Heating a mixture of an anthranilic acid, a salicylaldehyde, and an isocyanide in water affords the title compounds in good to excellent yields.

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Multicomponent reactions (MCRs) are important for generating high levels of diversity, as they allow more than two building blocks to be combined in practical, time-saving one-pot operations, giving rise to complex structures by simultaneous formation of two or more bonds.¹ MCRs contribute to the requirements of an environmentally friendly process by reducing the number of synthetic steps, energy consumption and waste production. MCRs, which lead to interesting heterocyclic scaffolds, are particularly useful for the construction of diverse chemical libraries of 'drug-like' molecules. Isocyanide-based MCRs are especially important in this area.^{2,3}

The high efficiency of isocyanides in MCRs is due to their pronounced reactivity towards C(sp² or sp) electrophilic centres.^{2–5} A prominent example is the Ugi four-component reaction (U-4CR),^{2,3,6} which combines an amine, an aldehyde, an isocyanide and a carboxylic acid to give an α -acylamino amide **1**. In the U-4CR, equilibria between the four components are displaced by a final irreversible Mumm-type rearrangement (Scheme 1). The key C–C bond-forming step in this reaction involves nucleophilic addition of the carbon of an isocyanide to the imine/iminium formed in situ by condensation of the amine and the aldehyde. This reaction has been the subject of intensive research over recent decades.

Through application of these MCRs, many different scaffolds are now readily accessible.^{2,3,7}

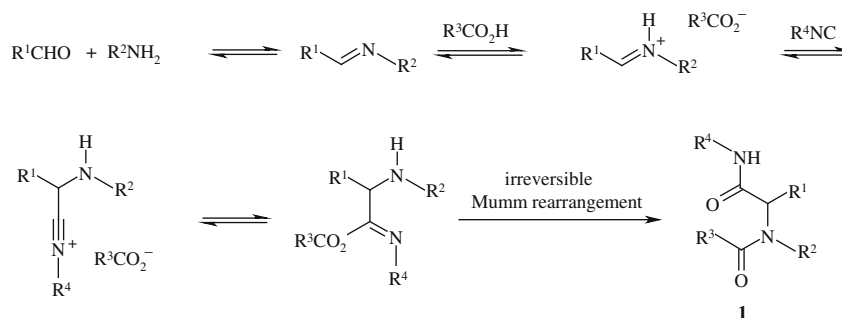
We were prompted to investigate whether the amine and the carboxylic acid, if suitably contained within the same molecule, could undergo the Ugi reaction more efficiently. We also added a more nucleophilic oxygen (phenolic) to compete with the carboxylate nucleophilic attack on the nitrilium ion intermediate in the Ugi reaction. Thus anthranilic acids seemed to be a suitable choice as the amine and carboxylic acid components, and salicylaldehydes were selected as the carbonyl compound. This could allow variation in the skeleton of the U-4CR product, thus increasing the versatility of the Ugi reaction and potentially leading to useful new building blocks for the construction of chemical libraries.

Water is a desirable solvent for chemical reactions because it is safe, non-toxic, environmentally friendly, readily available and cheap compared to organic solvents.⁸ Since the pioneering studies on Diels–Alder reactions by Breslow,⁹ there has been increasing recognition that organic reactions can proceed well in aqueous media and offer advantages over those occurring in organic solvents.⁸

As part of our ongoing program to develop new efficient methods for the preparation of biologically active heterocyclic compounds from readily available building blocks,¹⁰ we report herein a simple new method for the synthesis of 2-[[2-(alkylimino)-1-benzofuran-3-yliden]amino]benzoic acids via a three-component reaction. Thus heating a mixture of an anthranilic acid **2**, a

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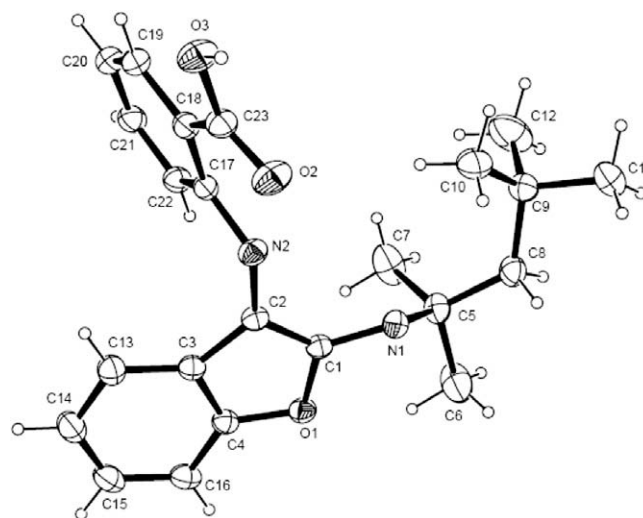
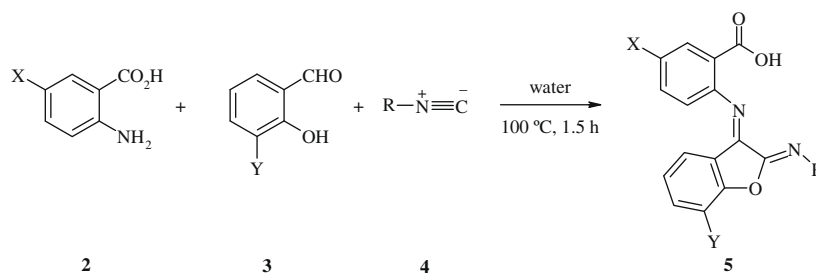
E-mail address: madib@khayam.ut.ac.ir (M. Adib).



Scheme 1. The Ugi four-component reaction mechanism.

salicylaldehyde **3** and an isocyanide **4** in water afforded the corresponding 2-[[2-(alkylimino)-1-benzofuran-3-ylidene]amino]benzoic acids **5a–h** in 77–93% yields (Scheme 2).

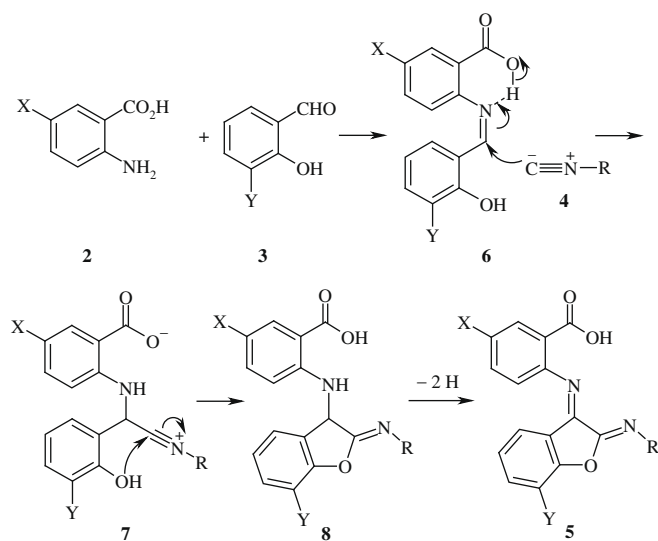
The isolated products **5** were characterised on the basis of IR, ¹H and ¹³C NMR spectroscopy, mass spectrometry and elemental analysis. The mass spectrum of **5c** displayed a molecular ion (M⁺) peak at *m/z* 378, which is 20 mass units (H₂O + H₂) lower than that of a 1:1:1 adduct of anthranilic acid, salicylaldehyde and 1,1,3,3-tetramethylbutyl isocyanide. The IR spectrum of **5c** showed absorptions at 2500–3100 (br) and 1660 cm^{−1} indicative of the acid functionality. The ¹H NMR spectrum of **5c** exhibited three sharp singlets arising from the CMe₃ (δ 1.01 ppm), CMe₂ (δ 1.44 ppm) and methylene (δ 1.71 ppm) groups along with characteristic signals with appropriate chemical shifts and coupling constants for the eight H-atoms of the two aromatic moieties. A fairly broad signal (δ 8.55 ppm) was observed for the carboxylic acid group. The ¹H-decoupled ¹³C NMR spectrum of **5c** showed 20 distinct resonances, in agreement with the adduct structure.¹¹ Single-crystal X-ray analysis of **5c** conclusively confirmed its structure, and by analogy those of compounds **5a,b,d–h**. An ORTEP diagram of **5c** is shown in Figure 1.¹²

Figure 1. ORTEP representation of the molecular structure of **5c**.

5	X	Y	R	% Yield ^a
a	H	H	cyclohexyl	90
b	H	H	^t Bu	93
c	H	H	1,1,3,3-tetramethylbutyl	89
d	H	OCH ₃	cyclohexyl	87
e	H	OCH ₃	^t Bu	85
f	Cl	H	cyclohexyl	83
g	Cl	H	^t Bu	80
h	Cl	OCH ₃	^t Bu	77

^a Isolated yields

Scheme 2.



Scheme 3.

Mechanistically, first the anthranilic acid **2** condenses with the aldehyde **3** to give an imine intermediate **6**. Nucleophilic attack of the isocyanide **4** on the imine, which is facilitated by protonation with the adjacent carboxylic acid, leads to the formation of a nitrilium carboxylate intermediate **7**, which subsequently undergoes intramolecular attack by the adjacent phenol hydroxy group to form γ -iminolactone intermediate **8**. Finally, aerial oxidation of this intermediate affords the product **5** (Scheme 3).

In summary, we have reported an efficient, one-pot, three-component reaction between various anthranilic acids, salicylaldehydes and isocyanides leading to 2-[(2-(alkylimino)-1-benzofuran-3-ylidene)amino]benzoic acids. Simple and readily available starting materials, fairly short reaction times and good to excellent yields of the products are advantages of this reaction.

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- Procedure for the preparation of 2-[(2-[(1,1,3,3-tetramethylbutyl)imino]-1-benzofuran-3-ylidene)amino]benzoic acid (**5c**): A mixture of anthranilic acid (0.137 g, 1 mmol), salicylaldehyde (0.122 g, 1 mmol) and 1,1,3,3-tetramethylbutyl isocyanide (0.139 g, 1 mmol) in H₂O (2 mL) was stirred at 100 °C for 1.5 h. The reaction mixture was cooled to room temperature, the aqueous phase was extracted with CH₂Cl₂ (2 × 5 mL) and dried over magnesium sulfate. The solvent was evaporated and the residue was purified by column chromatography using *n*-hexane–EtOAc (4:1) as eluent. The solvent was removed and the product was obtained as colourless crystals, mp 148 °C (dec.), yield 0.34 g, 89%. EI-MS, *m/z* (%): 378 (M⁺, 14). IR (KBr) ($\nu_{\max}/\text{cm}^{-1}$): 2500–3100 (br) (OH), 1660 (C=O). Anal. Calcd for C₂₃H₂₆N₂O₃ (378.47): C, 72.99; H, 6.92; N, 7.40%. Found: C, 73.14; H, 6.78; N, 7.29%. ¹H NMR (250.1 MHz, CDCl₃): δ 1.01 [9H, s, C(CH₃)₃], 1.44 [6H, s, C(CH₃)₂], 1.71 (2H, s, CH₂), 6.64 (1H, d, *J* = 8.5 Hz, CH), 6.72 (1H, t, *J* = 7.3 Hz, CH), 7.02–7.10 (3H, m, 3CH), 7.25–7.35 (2H, m, 2CH), 8.05 (1H, dd, *J* = 1.3 Hz, *J* = 8.0 Hz, CH), 8.55 (1H, br s, OH). ¹³C NMR (62.9 MHz, CDCl₃): δ 30.0 [C(CH₃)₂], 31.0 [C(CH₃)₃], 31.2 [C(CH₃)₃], 53.9 (CH₂), 56.8 [C(CH₃)₂], 96.6 and 109.2 (2C), 109.8, 113.5, 115.7, 115.9, 120.0 and 122.2 (6CH), 127.3 (C), 131.8 and 135.1 (2CH), 148.8, 150.8 and 154.0 (3C), 173.3 (C=O). 2-[(2-(*tert*-Butylimino)-7-methoxy-1-benzofuran-3-ylidene)amino]benzoic acid (**5e**): Yield 0.30 g, 85%. Colourless crystals, mp 164 °C (dec.). EI-MS, *m/z* (%): 352 (M⁺, 23). IR (KBr) ($\nu_{\max}/\text{cm}^{-1}$): 2500–3150 (br) (OH), 1670 (C=O). Anal. Calcd for C₂₀H₂₀N₂O₄ (352.39): C, 68.17; H, 5.72; N, 7.95%. Found: C, 68.31; H, 5.89; N, 7.80%. ¹H NMR (250.1 MHz, CDCl₃): δ 1.39 [9H, s, C(CH₃)₃], 4.02 (3H, s, OCH₃), 6.62–6.75 (4H, m, 4CH), 7.03 (1H, dd, *J* = 7.8 Hz, *J* = 8.0 Hz, CH), 7.25–7.32 (1H, m, CH), 8.04 (1H, dd, *J* = 1.3 Hz, *J* = 8.0 Hz, CH), 8.59 (1H, br s, OH). ¹³C NMR (62.9 MHz, CDCl₃): δ 30.5 [C(CH₃)₃], 53.8 [C(CH₃)₃], 56.3 (OCH₃), 99.4 (C), 105.2 and 109.7 (2CH), 109.9 (C), 114.1, 116.5 and 123.4 (3CH), 129.5 (C), 132.4 and 135.6 (2CH), 138.2, 144.6, 151.2 and 154.3 (4C), 173.9 (C=O).
- Selected X-ray crystallographic data for compound **5c**: C₂₃H₂₆N₂O₃, triclinic, space group = P1, *a* = 9.4976(9) Å, *b* = 10.7431(10) Å, *c* = 11.9529(11) Å, α = 67.067(3)°, β = 75.900(4)°, γ = 72.271(3)°, *V* = 1058.95(17) Å³, *T* = 295(2) K, *Z* = 2, *D*_{calcd} = 1.187 g cm^{−3}, μ = 0.079 mm^{−1}, 2858 observed reflections, final *R*₁ = 0.052, *wR*₂ = 0.149 and for all data *R*₁ = 0.066, *wR*₂ = 0.163. CCDC 717398 contains the supplementary crystallographic data for the structure reported in this Letter. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.