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One-pot synthesis of 3-hydroxyanthranilate derivatives using furans, bromoalkyne, and secondary amines

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ABSTRACT

A novel and convenient method for synthesizing 3-hydroxyanthranilate derivatives using furans, methyl 3-bromopropiolate, and secondary amines was developed. The synthetic reaction consisted of four steps: the Diels–Alder reaction, a conjugate addition reaction, dehydrobromination, and a ring-opening aromatization reaction. A plausible reaction pathway is described on the basis of the structures of the reaction intermediates. By using this method, sterically hindered 3-hydroxyanthranilate derivatives could be obtained selectively in good yields for four-steps.

Aminohydroxybenzoic acids are important structural units found in a variety of biologically active agents such as natural products[1] and pharmaceuticals.[2] For example, it is well known that 5-aminosalicylic acid (5-ASA) and 4-aminosalicylic acid (PAS) show good medicinal effects against a wide range of diseases.[2a] Furthermore, hydroxyanthranilic acid (HAA) derivatives are used as pharmaceuticals and useful synthetic intermediates for bioactive substances.[3] Therefore, aminohydroxybenzoic acid derivatives are indispensable to modern science, and the development of regioselective, direct, and convenient methods for synthesizing them is of great importance. In particular, methods for synthesizing sterically hindered 3-hydroxyanthranilic acid derivatives are limited, in spite of the wide utility of these compounds.[4]

Recently, we reported a silica gel-promoted facile and direct method for the synthesis of 2-bromo-3-hydroxybenzoates[5] using potentially beneficial 7-oxanorborna-2,5-dienes[6] derived from furans and an electron-deficient bromoalkyne. With the aim of developing a convenient method for the synthesis of polysubstituted benzoates containing different functional groups, further transformations of the 2-position of 2-bromo-3-hydroxybenzoates have been achieved through Pd-catalyzed cross-coupling reactions.[5] As an extension of this research effort, we next focused on introducing an amino group in 3-hydroxybenzoates. Herein, we report the novel and direct synthesis of 3-hydroxyanthranilate derivatives (2-amino-3-hydroxybenzoate derivatives) via the Diels–Alder reaction using furans and methyl 3-bromopropiolate.

A reaction of 2 equiv of *n*-octylamine with the oxanorbornadiene derivative **3a**, which was formed by the Diels–Alder reaction of 2-*n*-pentylfuran **1a** (0.6 mmol) with methyl 3-bromopropiolate **2** (0.5 mmol) in toluene (2 mL) by refluxing for 24 h in a nitrogen atmosphere, resulted in a complex mixture; the expected amination product was not detected. When *N*,*N*-di-*n*-butylamine (**4a**) was employed as a more nucleophilic amine, we observed the formation of tetrasubstituted 3-hydroxyanthranilate **5aa** in 25% isolated yield in one-pot (Table 1, entry 1). In this reaction, a Diels–Alder adduct **3a** (9%), its regioisomer **3a′** (2%),[5,7,8] and a small amount of an unidentified byproduct were also detected. The ^{1}H NMR spectrum of this byproduct showed a set of distinctive signals (δ 6.78 (d, J = 5.4 Hz), δ 6.39 (dd, J = 5.4, 1.8 Hz), and δ 4.76 (d, J = 1.8 Hz)), which would be assigned to the vinyl protons and the allyl proton of the 7-oxanorborna-2,5-diene derivative, respectively. On the basis of this result, we examined the reactions of **1a**, **2**, and **4a** under various conditions.

When 3 equiv of **4a** was employed, the yield of **5aa** increased to 52% (entry 2). By using a sealed test tube as the reaction vessel at 120 °C (condition B: see footnote), **5aa** could be obtained in 57% yield (entry 3). In this case, a few singlet signals assignable to the methyl group of esters were observed in ^{1}H NMR spectrum; these peaks implied the formation of the oligomers of **2**. The

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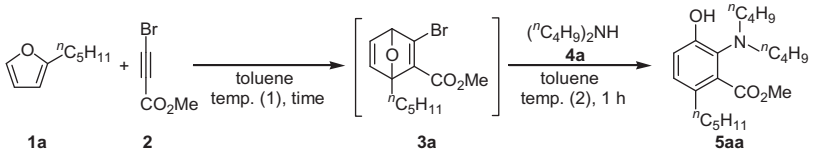
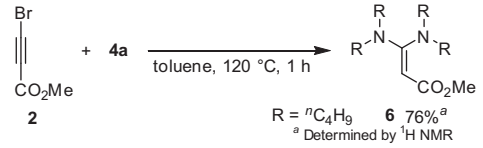
Table 1
Optimization of reaction conditions for the one-pot reaction



1a 2 3a 5aa

Entry	Temp. (1) (°C)	Time (h)	Amine (equiv)	Temp. (2) (°C)	Condition	Yield (%)[a]		
						3a	**3a′**	**5aa**
1	Reflux	24	2.0	Reflux	A	9	2	25
2	Reflux	24	3.0	Reflux	A	—	Trace	52
3	120	24	3.0	120	B	—	—	57
4	90	24	3.0	90	B	6	2	15
5[b]	90	24	3.0	120	B	—	Trace	67 (63)
6	90	48	3.0	120	B	—	Trace	59
7	90	24	3.0	150	B[c]	—	Trace	32

Reaction conditions A: **1a** (0.6 mmol), **2** (0.5 mmol), toluene (2.0 mL), N_2 atmosphere in two-necked round bottom flask. Reaction conditions B: **1a** (0.36 mmol), **2** (0.3 mmol), toluene (1.2 mL), filled with N_2 in sealed test tube.
[a] Determined by ^{1}H NMR (Isolated yield in parentheses).
[b] Ketene aminal **6** (20% yield) was also obtained (see Scheme 2).
[c] *p*-Xylene was used as a solvent.

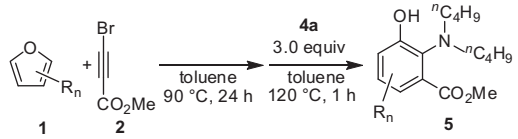


Scheme 1. Synthesis of ketene aminal **6**.

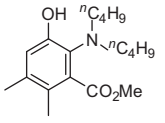
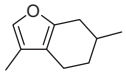
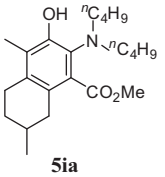
reaction at 90 °C resulted in incomplete latter ring-opening reaction, and the Diels–Alder adducts **3** (6%), its regioisomer **3a′** (2%), and **5aa** (15%) were detected, respectively (entry 4). To our delight, an increase in the reaction temperature for the latter ring-opening reaction to 120 °C proceeded to give **5aa** in 67% yield along with the accompanying ketene aminal **6** (20%), which was derived from the bromoalkyne **2** and **4a** (entry 5). The formation of ketene aminals from the corresponding bromoalkynes using K_3PO_4 has been documented previously.[9] Therefore, we examined the reaction of **2** and **4a** under the same conditions as those for the latter step. The formation of **6** was confirmed (Scheme 1). An increase in the reaction time for the initial Diels–Alder reaction did not have any effect (entry 6). Although the reaction temperature for the latter ring-opening aromatization was increased to 150 °C by using *p*-xylene as a solvent, yield of **5aa** was not improved (entry 7). On the basis of these results, the reaction conditions corresponding to entry 5 were employed as the optimized conditions unless otherwise noted.

Next, we examined the one-pot reactions using several furans and **4a** (Table 2). The reaction of 2-methylfuran (**1b**) proceeded to give the corresponding 3-hydroxyanthranilate **5ba** in 62% yield (entry 2). Furan (**1c**) showed a similar reactivity to give **5ca** in 50% yield (entry 3). 2-Benzyloxymethylfuran (**1d**) was also applicable for the reaction and a desired product **5da** was obtained in 36% yield (entry 4). In the case of 2-benzoyloxymethylfuran (**1e**) owing an electron-withdrawing ester group, however, the Diels–Alder reaction did not proceed, and 43% of ketene aminal **6** was detected (entry 5). Unfortunately, in the case of the reaction of 2-phenylfuran (**1f**), the ring-opening aromatization reaction of **3f** preceded the reaction with the amine **4a** to give the corresponding 2-bromo-3-hydroxybenzoate in 55% yield (entry 6).[5] The reaction of methyl 2-furoate (**1g**), bearing an unfavorable electron-withdrawing substituent as a diene for Diels–Alder reaction, did not take place

Table 2
Synthesis of 3-hydroxyanthranilate **5** using several furans and **4a**



1 2 5

Entry	Furan		Product	Yield[a] (%)
1	R = 2-*n*-pentyl	**1a**	**5aa**	67 (63)
2	R = 2-methyl	**1b**	**5ba**	62 (54)
3	R = H	**1c**	**5ca**	50 (46)
4	R = 2-CH_2OCH_2Ph	**1d**	**5da**	36
5	R = 2-$CH_2OC(O)Ph$	**1e**	**5ea**	Trace[b]
6	R = 2-Ph	**1f**	**5fa**	N.D.[c]
7	R = 2-CO_2Me	**1g**	**5ga**	N.D.[d]
8		**1h**	 **5ha**	58 (42)
9		**1i**	 **5ia**	20[e,f]

Reaction conditions: **1** (0.36 mmol), **2** (0.3 mmol), toluene (1.2 mL), and **4a** (3.0 equiv) placed in sealed test tube in N_2.
[a] Determined by ^{1}H NMR (Isolated yield in parentheses).
[b] 43% of **6** was detected by ^{1}H NMR.
[c] The corresponding 2-bromo-3-hydroxybenzoate was obtained in 55% yield.
[d] 68% of **6** was detected by ^{1}H NMR.
[e] The corresponding 2-bromo-3-hydroxybenzoate was obtained in 48% yield.
[f] Reaction time of latter step was extended to 24 h.

and **6** was obtained in 68% yield (entry 7). In the cases of polysubstituted furans, disubstituted 2,3-dimethylfuran (**1h**) was found to be a good substrate for the one-pot reaction and trisubstituted menthofuran (**1i**) was also applicable. Sterically-hindered penta- and hexasubstituted benzoate derivatives (**5ha** and **5ia**) were obtained in 58% and 20% yields, respectively (entries 8 and 9).