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$AuBr_3$-catalyzed cyclization of *o*-(alkynyl)nitrobenzenes. Efficient synthesis of isatogens and anthranils

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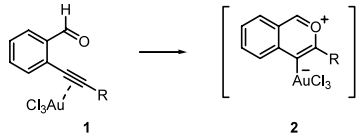
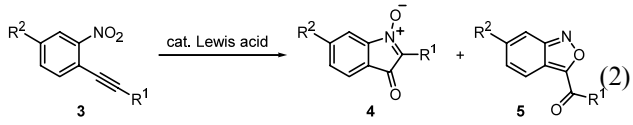
Abstract—The cyclization of *o*-(arylalkynyl)nitrobenzenes was catalyzed by $AuBr_3$ to produce the corresponding isatogens in good to high yields together with small amounts of anthranils. On the other hand, anthranils were obtained selectively when the $AuBr_3$-catalyzed reaction was carried out using *o*-(alkylalkynyl)nitrobenzenes.

2-Substituted-3-*H*-indol-3-one *N*-oxides, which are known as isatogens, have been well investigated due to their useful biological activities against a range of bacteria,[1] mycobacteria[2] and fungi.[3] Some of them are able to antagonize the relaxant response to adenosine-5-triphosphate in mammals.[4] Among many approaches for the synthesis of isatogens, the intramolecular cyclization of an *ortho*-substituted nitrobenzene precursor is one of the most simple and convenient routes.[5,6] However, this cyclization method has some drawbacks, such as poor yields, long reaction times, and high reaction temperatures. It seemed that an efficient and convenient method with wide applicability for the synthesis of isatogens was still needed. We previously reported that the $AuCl_3$-catalyzed reaction of *o*-(alkynyl)benzaldehydes with alkynes produced naphthyl ketone derivatives in good to high yields, in which the first step involves the coordination of the alkyne to $AuCl_3$ **1**, followed by the intramolecular attack of the oxygen of the aldehyde to the electron deficient alkynyl carbon, leading to benzo[*c*]pyrylium type zwitterionic intermediate **2** (Eq. (1)).[7]



(1)

It occurred to us that if we could use, instead of an aldehyde, a heteroatom containing functionality such as a nitro group, we might synthesize a nitrogen containing heterocycle. In this paper, we wish to report that gold-catalyzed cyclization of *o*-(alkynyl)nitrobenzene **3** affords the corresponding isatogens **4** in good to high yields under mild conditions (Eq. (2)).



(2)

Treatment of **3a** with 3 mol% of $AuCl_3$ in 1,2-dichloroethane at rt for 12 h gave **4a**, bearing a phenyl group at the 2-position, in 53% yield together with 3-benzoyl-2,1-benzisoxazole **5a**, which is an anthranil, in 34% yield (entry 1, Table 1). When we used $AuBr_3$ as the catalyst instead of $AuCl_3$, the reaction rate was dramatically accelerated and **4a** was obtained in 67% yield within 1.5 h (entry 2). Other more widely used Lewis acids, such as $BF_3{\cdot}OEt_2$ and $TiCl_4$, were not effective in the present reaction. It should be mentioned that **4a** was obtained in a moderate yield even in the absence of a Lewis acid, although a longer reaction time (5 days) and higher temperature (120°C) were required (entry 3). Optimization experiments revealed that toluene was a suitable solvent for the present reaction (compare entries 2, 4–6). Lowering the reaction temperature to 4°C increased the chemical yield of **4a** up to 81% yield and decreased the yield of **5a** (entry 7). We next examined the cyclization with other *o*-(alkynyl)nitrobenzenes **3b–f**. The reaction of **3b**, bearing a 4-anisyl group at the terminal position of the alkyne, proceeded smoothly to give **4b** in 80% yield together

Keywords: isatogen; anthranil; $AuBr_3$; cyclization; *o*-(alkynyl)-nitrobenzene.

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Table 1. $AuBr_3$-catalyzed cyclization reaction of **3**[a]

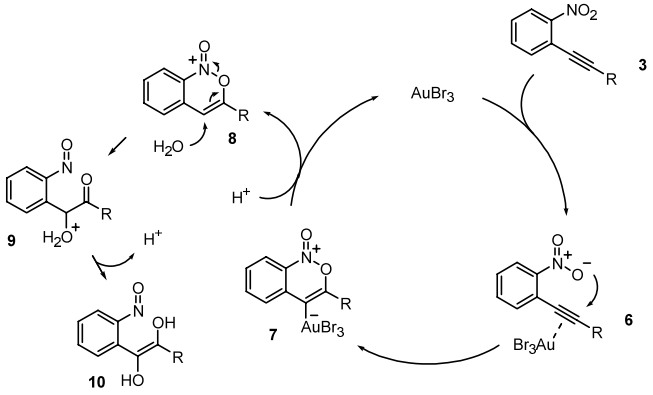
Entry	3	Substrate		Solvent	Conditions	Yield (%)[b]			
		R^1	R^2			4		5	
1[c]	**3a**	Ph	H	$(ClCH_2)_2$	rt, 12 h	**4a**	53	**5a**	34
2	**3a**	Ph	H	$(ClCH_2)_2$	rt, 1.5 h	**4a**	67	**5a**	33
3[d]	**3a**	Ph	H	$(ClCH_2)_2$	120°C, 5 days	**4a**	52	**5a**	39
4	**3a**	Ph	H	Toluene	rt, 1.5 h	**4a**	73	**5a**	23
5	**3a**	Ph	H	1,4-Dioxane	rt, 12 h	**4a**	66	**5a**	34
6	**3a**	Ph	H	CH_3CN	50°C, 21 days	**4a**	43	**5a**	44
7	**3a**	Ph	H	Toluene	4°C, 2 h	**4a**	81	**5a**	17
8	**3b**	4-Anisyl	H	Toluene	4°C, 2 h	**4b**	80	**5b**	16
9	**3c**	2-Pyridyl	H	Toluene	50°C, 9 h	**4c**	86	**5c**	11
10	**3d**	Cyclohexenyl	H	Toluene	rt, 2 h	**4d**	78	**5d**	20
11	**3e**	Ph	MeO	Toluene	4°C, 2 h	**4e**	86	**5e**	14
12	**3f**	Ph	Cl	Toluene	4°C, 2 h	**4f**	78	**5f**	22

[a] The reaction was performed using *o*-(alkynyl)nitrobenzene **3** (1 equiv.) in the presence of $AuBr_3$ (3 mol%) unless otherwise noted.
[b] Determined by ^1H NMR using butanol as an internal standard.
[c] The reaction was carried out in the presence of 3 mol% of $AuCl_3$.
[d] The reaction was carried out in the absence of $AuBr_3$.

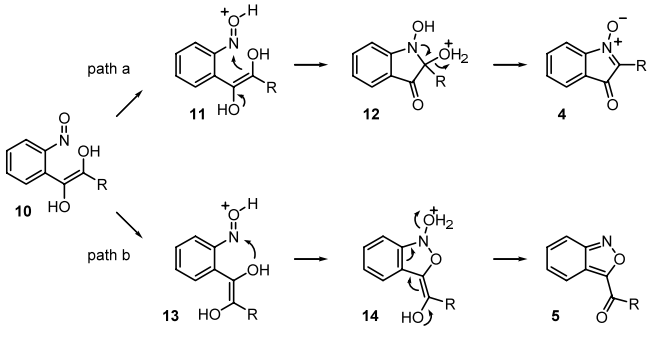
with **5b** in 16% yield (entry 8). 2-Pyridyl-substituted isatogen **4c** was obtained in high yield although the reaction required a longer reaction time (9 h) at 50°C (entry 9). The isatogen **4d**, bearing a cyclohexenyl group at the 2-position, was produced in good yield (entry 10). We also examined the reactions using *o*-(alkynyl)nitrobenzenes having a methoxy group **3e** or a chloro group **3f** at the R^2 position of the benzene ring, and the corresponding products **4e** and **4f** were obtained in high yields (entries 11 and 12).

The preparation of **4a** is representative. To a suspension of $AuBr_3$ (6.6 mg, 3 mol%) in toluene (1 mL) was added a solution of **3a** (112 mg, 0.5 mmol) in toluene (1.5 mL) at 4°C under an Ar atmosphere. After the mixture had been stirred for 2 h, the resulting solution was filtered through a short silica gel column. The solvent was removed under reduced pressure to give the crude product. ^1H NMR analysis of this mixture using butanol as an internal standard showed that **4a** was produced in 81% yield along with **5a** in 17% yield. Each product was isolated by silica gel column chromatography using CH_2Cl_2/hexane = 1/1 as eluent. Isatogen **4a** was obtained as a red solid (84 mg, 0.38 mmol) in 75% yield together with **5a** as a light yellow solid (19 mg, 0.085 mmol) in 17% yield.

A plausible mechanism for the $AuBr_3$-catalyzed cyclization of **3** is shown in Scheme 1. Coordination of the triple bond of **3** to $AuBr_3$ enhances the electrophilicity of the alkyne, and the subsequent nucleophilic attack of the oxygen of the nitro group to the electron-deficient alkyne forms the intermediate auric ate complex **7**.[7] A trace amount of water in the reaction medium will generate a proton due to the presence of the $AuBr_3$. Protonolysis of **7** forms **8**, which may undergo ring opening on treatment with H_2O to produce the nitrosobenzene derivative **10** via **9**. The isatogen **4** would then be formed by cyclization of **10** as shown in structure **11**, followed by dehydration of **12** (path a) (Scheme 2). On the other hand, when the reaction proceeds through path b, anthranil **5** would be produced by the intramolecular nucleophilic addition of the enol oxygen, followed by dehydration.[8]

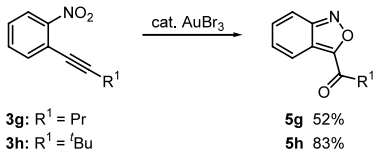


Scheme 1.



Scheme 2.

Interestingly, when the reaction was carried out using *o*-(alkylalkynyl)nitrobenzenes **3g** and **3h**, the corresponding isatogen products were not obtained but the corresponding anthranil derivatives **5g** and **5h** were obtained exclusively. Anthranil derivatives are known as useful precursors for acridones and related heterocycles.[9] The reaction of **3g** (R^1 = Pr) afforded **5g** in 52% yield as the sole product. Moreover, the chemical yield of the anthranil increased when R^1 became bulkier; the reaction of **3h** (R^1 = ^{t}Bu) afforded **5h** in 83% yield (Eq. (3)).



3g: R^1 = Pr
3h: R^1 = ^{t}Bu

5g 52%
5h 83%

(3)

An efficient method for the synthesis of isatogens from *o*-(arylalkynyl)nitrobenzenes and for the synthesis of anthranils from *o*-(alkylalkynyl)nitrobenzenes has been developed. We are now in a position to synthesize isatogens or anthranils, depending on the R^1 substituent of the starting *o*-(alkynyl)nitrobenzene, under very mild conditions. Further studies to elucidate the mechanism of this reaction and to extend the scope of its synthetic utility are in progress in our laboratory.

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