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A facile synthesis of antitumoral indeno[1,2-*c*]pyrazole-4-one by mild oxidation with molecular oxygen

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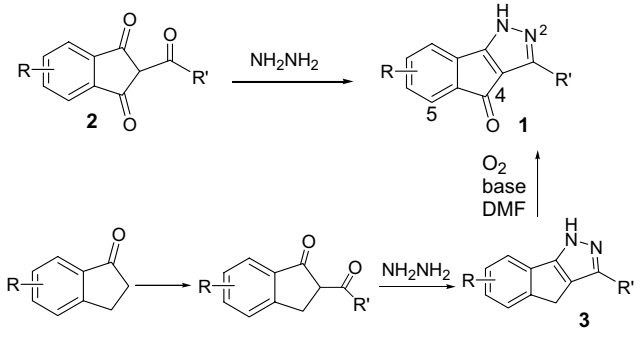
Abstract—An efficient, convenient, and general synthetic method for indeno[1,2-*c*]pyrazole-4-ones through oxidation of indenopyrazoles by treatment with a base and molecular oxygen is described, and a possible mechanism for the oxidation is proposed. The product indeno[1,2-*c*]pyrazole-4-ones were elaborated further by Suzuki coupling and Mitsunobu reaction.

Indeno[1,2-*c*]pyrazole-4-ones are an important class of heterocycles and exhibit a wide range of biological activities such as antidepressive[1,2] and antitumor activities.[3–6] Indeno[1,2-*c*]pyrazole-4-ones (**1**) have recently been explored as a new class of antitumor cyclin dependent kinase inhibitors.[3–6] These compounds show excellent activity against numerous tumor cell lines and show selectivity for proliferating cells versus normal cells. Their synthesis involves a hydrazine-induced cyclization of triketone (**2**) as a key step (Scheme 1).[1–7] However, the triketones are synthetically difficult to access,[4,8] and the cyclization of the unsymmetric triketone may produce two regioisomers, whose separation is usually very tedious. In recent literature, a number of methods have been reported for the preparation of triketones.[4] The yield of indeno[1,2-*c*]pyrazole-4-ones (**1**) is highly dependent on the substituents at the 3-position, and the substituents on the phenyl ring dramatically affect the regioselectivity of the cyclization. Consequently, long synthetic routes or tedious purifications may be necessary to obtain the desired regioisomer.



Scheme 1.

During the course of our studies, we discovered mild conditions for the benzylic oxidation of indenopyrazole **3**, which is easily accessible through numerous organic synthetic methodologies.[9] A mixture of **3** (0.5 mmol) and Cs_2CO_3 (2.0 mmol) (or NaH) in DMF was stirred under molecular oxygen at ambient temperature to produce **1** in quantitative yield as indicated by LC–MS (Scheme 1, and Table 1). A simple filtration, aqueous wash, and evaporation of the solvent provided product **1**, which usually required no further purification.[10] As shown in Table 1, the reaction conditions tolerated a variety of functional groups, including the protecting group SEM (on both N and O, entries A and B), a benzylic alcohol (entry F), and pyridine or pyrazine moieties (entries G and H).

Base-induced benzylic oxidations with molecular oxygen have been described in a variety of substrates such as fluorene and its derivatives,[11] oxazolines,[12] and thioxanthene.[13] Analogous to the reported mechanism for the oxidation of methylene-bridged polyarenes,[11b] a possible mechanism for the conversion of **3** to ketone **1** is depicted in Scheme 2. The methylene carbon at the

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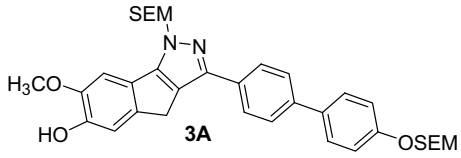
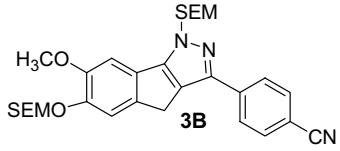
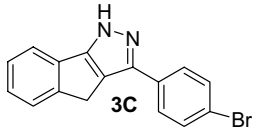
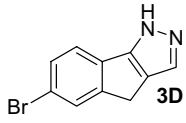
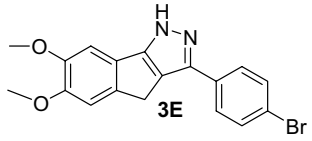
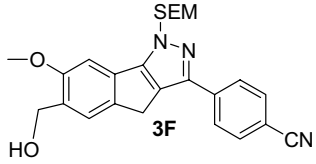
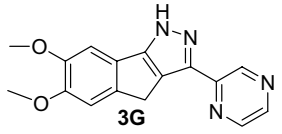
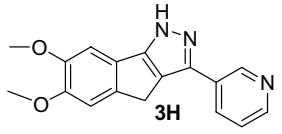
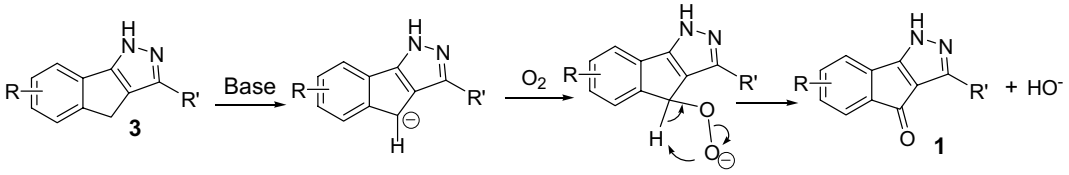
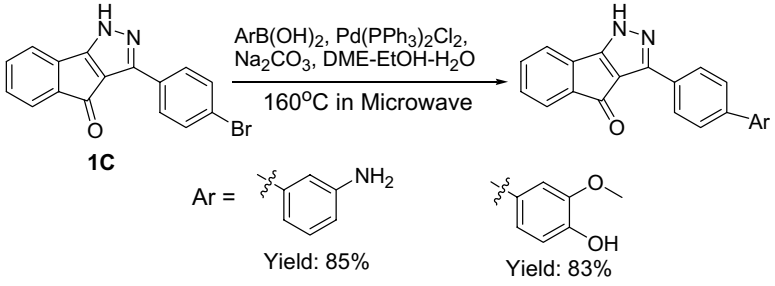
Table 1. Oxidation of indenopyrazole (**3**) in the presence of Cs_2CO_3 and O_2

Entry	Substrate (**3**)	Temperature (°C)[a]/reaction time (h)	Conversion [%][b] (**1**: isolated yield, %)[c]
A[d]	 **3A**	90/24	100 (89)
B[d]	 **3B**	50/12	100 (99)
C	 **3C**	90/7	100 (96)
D	 **3D**	90/12	100 (95)
E	 **3E**	90/3	100 (97)
F[d]	 **3F**	90/3	85[e] (77)
G	 **3G**	90/5	98 (90)
H	 **3H**	90/5	100 (92)

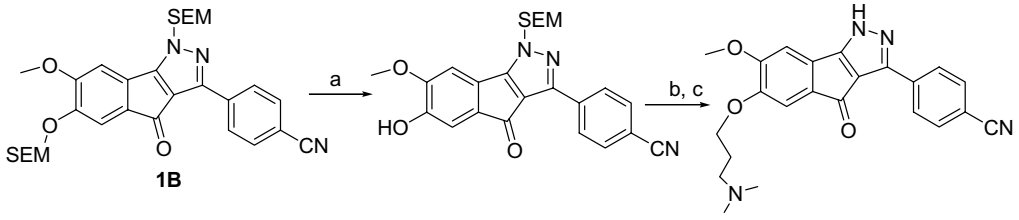
[a] Not optimized.
[b] Indicated by LC–MS.
[c] Purified by flash chromatography or recrystallization.
[d] SEM group could be on either N of pyrazole.
[e] Major side product is the de-SEM ketone (10%).



Scheme 2.



Scheme 3.



Scheme 4. Reagents and conditions: (a) 0.1 N HCl, EtOH–dioxane (35:1), room temperature, 1.5 h, quantitative yield; (b) 3-dimethylaminopropanol, polymer-supported Ph_3P, DBAD, THF, room temperature; (c) 2 N HCl, EtOH–dioxane (1:1), room temperature, 77% yield for two steps.

4-position is deprotonated by base, and the resulting anion is then trapped by molecular oxygen to provide a peroxy anion. The peroxy anion abstracts a proton from the benzylic site of the intermediate in an intermolecular or intramolecular fashion, leading to loss of hydroxide ion and formation of a carbonyl group. The remarkable efficiency of this conversion can be attributed to the relatively high acidity of the doubly activated benzylic protons.[11b]

The ease of derivatization of ketone **1** was demonstrated by the elaboration of the product ketones **1B** and **1C**. As shown in Scheme 3, the Suzuki coupling of **1C** with arylboronic acids went very smoothly under microwave heating conditions. The efficiency of microwave flash heating in accelerating organic transformations (in particular in cross-coupling reactions) has been well documented,[14] and therefore the microwave-accelerated Suzuki coupling could be performed in a combinatorial fashion to provide a large number of biaryl derivatives for biological screening in a short time.

Selective deprotection of SEM group of **1B** at oxygen was achieved in quantitative yield by treatment with HCl (0.1 N) ethanol solution (Scheme 4). The resulting phenol reacted with 3-dimethylamino propanol under Mitsunobu condition in good yield, and removal of SEM group from nitrogen released the critical element for CDK kinase binding.[5] The Mitsunobu reaction could be performed in a parallel manner, providing a large number of compounds for biological screening in a short time.

In conclusion, we developed an efficient, convenient, and general synthetic method for indeno[1,2-*c*]pyrazole-4-ones through oxidation of indenopyrazoles by treatment with a base and molecular oxygen. The mild conditions employed are compatible to a variety of functional groups in the substrates. This methodology should facilitate the exploration of indeno[1,2-*c*]pyrazole-4-ones as important therapeutically useful agents.

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