Divergent Conversion of 4-Naphthoquinone-Substituted 4*H*-Isoxazolones to Different Benzo-Fused Indole Derivatives

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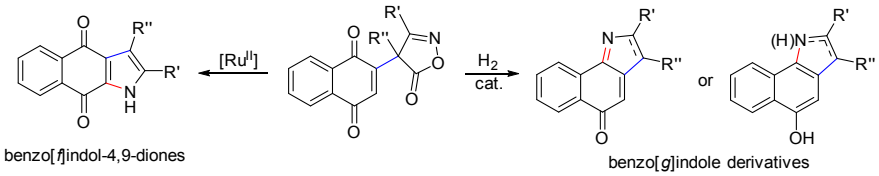
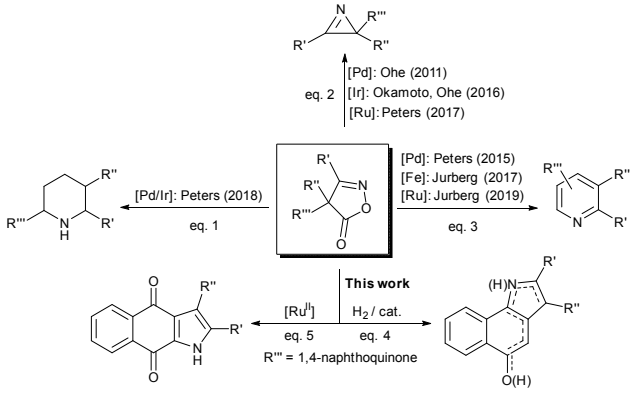
Supporting Information Placeholder



ABSTRACT: 4,4-Disubstituted 4*H*-isoxazol-5-ones bearing a 1,4-naphthoquinone moiety undergo transformation into different type of benzoindolyl products depending on the different reaction conditions. A decarboxylative ring-opening/ring closure promoted by catalytic $[Ru(p\text{-cymene})_2Cl_2]_2$ yields benzo[*f*]indole-4,9-diones. Alternatively, hydrogenation reactions provide the conversion of 4-(1,4-naphthoquinone)-substituted isoxazol-5-ones to benzo[*g*]indole compounds, with the level of reduction depending on the substituents present on the ring. Starting materials have been easily prepared by functionalization of isoxazolinones with naphthoquinone in mild conditions.

4*H*-Isoxazol-5-ones have been identified in organic synthesis as versatile building blocks thanks to their ease of functionalization and of ring opening.[1] In particular, the isoxazolinone ring can be converted into either acylic compounds, such as azadienes[2] and alkynes,[3] or heterocyclic structures such as pyridines,[4] azirines,[5] imidazoles,[6] 1,3-oxazines,[7] pyrazin-2-ones[8] and piperidines.[9]

Following our continuous interest in aza-heterocycles[10] in general, and in isoxazolin-5-ones in particular,[11] and considering the role of transition metal complexes such those based on ruthenium,[4a,4c,5a] iridium,[5b] iron,[4d] and palladium[4b,5c,9] in the decarboxylative conversion of isoxazol-5-ones (Scheme 1, eqs. 1-3), we envisioned the 4-(1,4-naphthoquinone)-substituted 4*H*-isoxazol-5-ones as possible precursors of new benzo-fused indoles. We describe herein their divergent conversion into benzo[*f*]indole-4,9-diones and benzo[*g*]indole derivatives in the presence of Ru(II)-catalysts or by Pd/C-catalyzed hydrogenation, respectively (Scheme 1, eqs. 4,5).



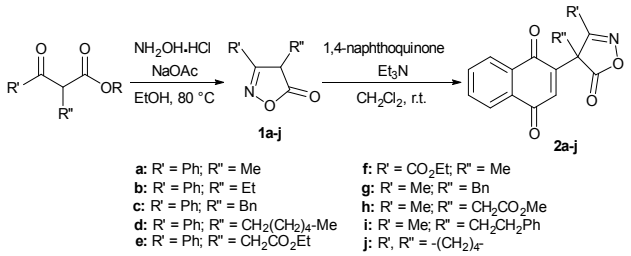
Scheme 1. Transition metal-catalyzed decarboxylative conversion of isoxazol-5-ones to different heterocycles

Benzo-fused indole moieties are key structural blocks in many biologically natural or synthetic compounds. Among them, benzo[*f*]indole-4,9-diones play a relevant role due to their pronounced biological activity as antibacterial, antiviral, antifungal, anticancer, and anti-inflammatory.[12] Benzo[*g*]indole derivatives have shown anticancer, anti-inflammatory and antipsychotic activities.[13] Moreover, the latter compounds have found interest in material sciences.[14] Several methodologies for their preparation have been reported.[15,16] However, in this context, the development of new efficient procedures based on the use of readily available starting materials continues to be a challenging target. Thus, the innovative reactivity herein reported provides step-economic strategies towards benzo[*f*]indole-4,9-diones or

benzo[*g*]indole compounds through decarboxylative ring-opening/ring-closure of 4-naphthoquinonyl isoxazol-5-ones.

Our investigation began with the preparation of the reaction precursors **2a-j**, obtained by treatment of 1,4-naphthoquinone under basic conditions with the corresponding isoxazolones **1a-j**, in turn readily accessible from hydroxylamine and β-ketoesters or malonates, according to a published protocol (Scheme 2).[17]

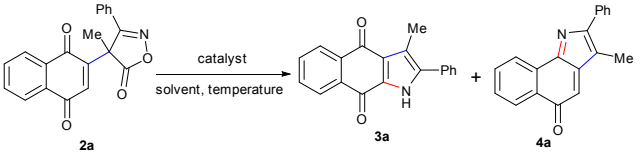
Scheme 2. Preparation of 4-(1,4-naphthoquinone)-substituted isoxazolin-5-ones 2



[a] Reaction conditions: **1a-j** (1.0 mmol), 1,4-naphthoquinone (1.0 mmol), Et_3N (0.10 mmol), CH_2Cl_2 (5 mL).

4-Methyl-4-naphthalene-1,4-dione-2-yl-3-phenyl-substituted isoxazolone **2a** was chosen as the model substrate to carry out preliminary experiments. The reactions tested in search for optimized conditions are summarized in Table 1. Initially, the substrate was treated with the commercial [Ru(*p*-cymene)Cl_2]$_2$ in catalytic amount using different solvents. While heating in toluene at 100 °C left the substrate unchanged (Table 1, entry 1), addition of DMF (20 vol%) led to small amount of the benzo[*f*]indole-4,9-dione **3a**, arising from a decarboxylative ring-opening/ring closure process, beside unaltered starting material (entries 2 and 3, Table 1). Using DMSO as co-solvent strongly increased the formation of compound **3a**, while the loading of catalyst was found to be irrelevant for the reaction (entries 4 and 5, Table 1). Due to the low solubility of the substrates, the yield was improved working in DMSO as the sole solvent at 100 °C (entry 6, Table 1). The addition of phenathroline as a ligand in reactions carried out in toluene/DMSO or DMSO did not provide higher product yields (entries 7 and 8, Table 1). When working at room temperature, no conversion of the substrate was observed, while lowering the reaction temperature from 100 to 80 °C resulted in a drastic decrease of the yield (82% vs 14%) (entries 9 and 10, Table 1). A different type of ruthenium catalyst such as $Ru_3(CO)_{12}$ afforded the product in very low yield (entry 11, Table 1). Then, we turned our attention to other transition metal complexes. The use of [IrCl(cod)]$_2$ afforded **3a** only in moderate yields from a complex mixture of degradation compounds (entries 12-14, Table 1). The palladium complexes $Pd_2(dba)_3$ and $Pd(PPh_3)_4$, applied under different conditions, left the substrate unchanged (entries 15-18, Table 1). Pd-catalysis under hydrogen atmosphere was also tested, in the hope of obtaining reaction through the intermediacy of a vinylnitrene-Pd species.[4b] Although $Pd(PPh_3)_4$ left the substrate unchanged (entry 19, Table 1), the use of catalytic amounts of Pd/C in the presence of H_2 atmosphere provided the benzo[*g*]indole-5-one **4a** as the major product, isolated in 65% yield (entry 20, Table 1).

Table 1. Optimization of decarboxylative cyclization[a]



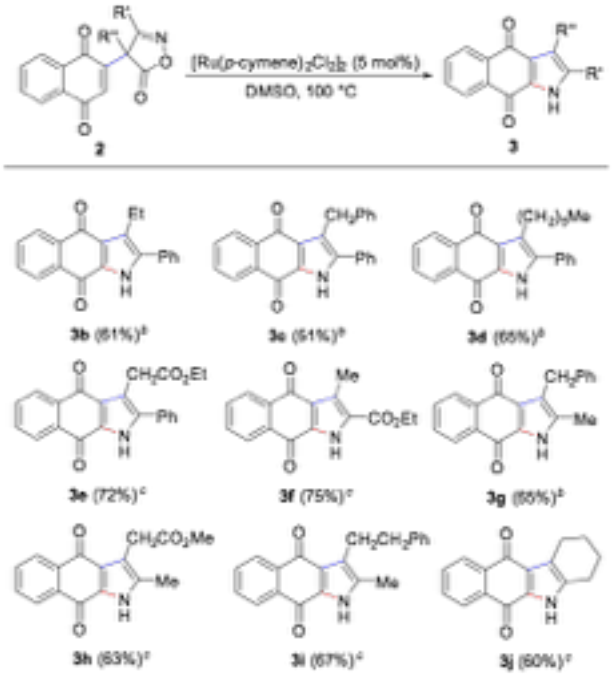
entry	catalyst[b]	solvent	temp. (°C)	product (% yield)
1	[Ru(*p*-cymene)Cl_2]$_2$	toluene	100[c]	S.M.
2	[Ru(*p*-cymene)Cl_2]$_2$	toluene/DMF	100[c]	**3a** (10)
3	[Ru(*p*-cymene)Cl_2]$_2$[d]	toluene/DMF	100[e]	**3a** (41)
4	[Ru(*p*-cymene)Cl_2]$_2$[d]	toluene/DMSO	100[e]	**3a** (79)
5	[Ru(*p*-cymene)Cl_2]$_2$	toluene/DMSO	100[e]	**3a** (78)
6	[Ru(*p*-cymene)Cl_2]$_2$	DMSO	100[e]	**3a** (82)
7	[Ru(*p*-cymene)Cl_2]$_2$[f]	toluene/DMSO	100[e]	**3a** (75)
8	[Ru(*p*-cymene)Cl_2]$_2$[f]	DMSO	100[e]	**3a** (76)
9	[Ru(*p*-cymene)Cl_2]$_2$	DMSO	r.t.[e]	S.M.
10	[Ru(*p*-cymene)Cl_2]$_2$	DMSO	80[e]	**3a** (14)
11	$Ru_3(CO)_{12}$	DMSO	100[e]	**3a** (9)
12	[IrCl(cod)]$_2$	toluene/DMF	100[e]	**3a** (12)
13	[IrCl(cod)]$_2$	toluene/DMSO	100[e]	**3a** (25)
14	[IrCl(cod)]$_2$	DMSO	100[e]	**3a** (38)
15	$Pd_2(dba)_3$	dioxane	80[c]	S.M.
16	$Pd_2(dba)_3$[g]	dioxane	80[e]	S.M.

17	$Pd(PPh_3)_4$	DMSO	100[c]	S.M.
18	$Pd(PPh_3)_4$[g]	DMSO	100[c]	S.M.
19	$Pd(PPh_3)_4$[h]	AcOEt	r.t.[i]	S.M.
20	Pd/C[h]	AcOEt / DMF[j]	r.t.[i]	**4a** (65)

[a] Reaction conditions: **2a** (1.0 mmol), catalyst (0.05 mmol), solvent (3 mL), reported temperature, 24 or 48 h. [b] 5 mol%, unless otherwise indicated. [c] Reaction time: 24 h. [d] 10 mol%. [e] Reaction time: 48 h. [f] Phenanthroline (20 mol%) was added. [g] PPh_3 (20 mol%) was added. [h] H_2 atmosphere. [i] overnight. [j] in 10:1 ratio.

To evaluate the scope of the decarboxylative cyclization to yield benzo[*f*]indole-4,9-dione derivatives, conditions of Table 1, entry 6, were applied to 4*H*-isoxazol-5-ones **2b-j** bearing alkyl and phenyl groups. With exception of the 2-phenyl-3-benzyl-substituted benzo[*f*]indole **3c**, the decarboxylative ring-opening/ring closure products were isolated in a satisfactory range of 60-75% yields (Scheme 3). Interestingly, the decarboxylative cyclization is not precluded by the presence of a carboxylate group at 3-position (substrate **2f**) or a chain at 4-position of the starting isoxazolone ring (substrates **2e** and **2h**).

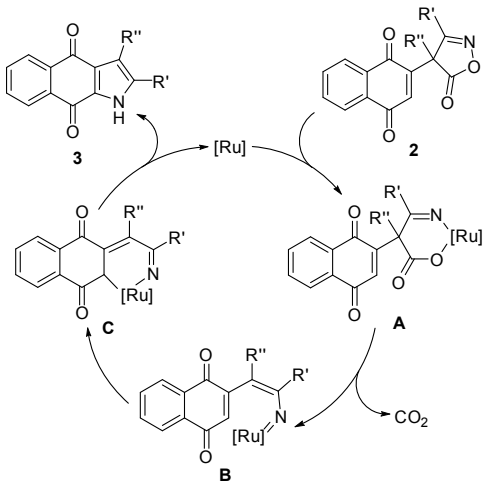
Scheme 3. Scope of the decarboxylative cyclization of the 4*H*-isoxazol-5-ones 2b-j[a]



[a] Reaction conditions: **2** (1.0 mmol), [Ru(*p*-cymene)Cl2]2 (0.05 mmol), DMSO (3 mL), 100 °C. [b] Reaction time: 48 h. [c] Reaction time: 24 h.

A plausible mechanism for this transformation is depicted in Scheme 4. Initial oxidative addition of the ruthenium catalyst to the N-O bond of **2** generates the iminocarboxylate-Ru complex **A**, which converts to the vinyl-nitrene-Ru intermediate **B** by loss of carbon dioxide.[5a] The ring-closure involves an electrocyclic reaction leading to the azaruthenacycle **C**, followed by reductive elimination with formation of the product **3** and regeneration of the Ru-catalyst.

Scheme 4. The proposed mechanism of Ru(II)-catalyzed reaction

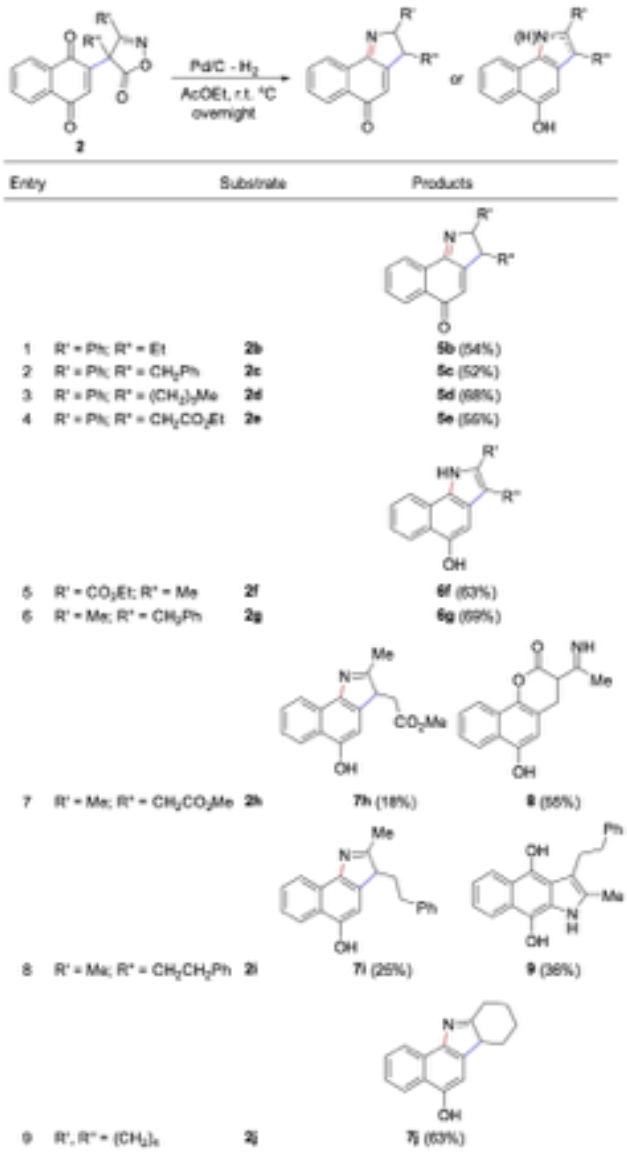


After having confirmed the ability of [Ru(*p*-cymene)Cl2]2 to convert 4*H*-isoxazol-5-ones into benzo[*f*]indole-4,9-diones, we delved into the result of Table 1, entry 20, to verify if a simple protocol change on the same type of substrates allows a general access to benzo[*g*]indole-5-one derivatives.

The applicability of the hydrogenolytic conditions to achieve benzo[*g*]indole-5-one derivatives was evaluated considering the compounds **2b-j** and the results are collected in Scheme 5. In the event, all the substrates tested using the system [Pd/C, H_2 (1 atm)] provided compounds with benzo[*g*]indole structures resulting from an alkene hydrogenation. In particular, while a phenyl group at position 2 generates the 2*H*-benzo[*g*]indol-5(3*H*)-ones derivatives, an alkyl or an alkoxycarbonyl group was found to favor 1*H*-benzo[*g*]indol-5-ols or 3*H*-benzo[*g*]indol-5-ols. Thus, the 2-phenyl-substituted 4*H*-isoxazol-5-ones **2b-e** furnished the 2,3-dihydro-benzo[*g*]indol-5-ones **5b-e** as the major products, isolated in 52-68% (entries 1-4, Scheme 5). An ethoxycarbonyl group at position 2 (**2f**) afforded the 5-hydroxy-1*H*-benzo[*g*]indole **6f** (entry 5, Scheme 5). The same kind of structure was obtained working with the 2-methyl-substituted substrate **2g**, which furnished **6g** in 69% yield (entry 6, Scheme 5). Conversely, 2-methyl-

isoxazolones **2h-j** afforded 3*H*-benzo[*g*]indole structures. In the case of substrates **2h** and **2i**, these compounds were obtained only as the minor products (entries 7 and 8, Scheme 5). In fact, in the former case, the compound **7h** was recovered in 18% yield together with the imino-lactone **8**, isolated in 55% yield, while in the second case the derivative **7i** was formed competitively with the 4,8-dihydroxy-benzo[*f*]indole **9**. Finally, isoxazolone **2j** gave the tetracyclic product **7j** as the major products, isolated in its pure state in 63% yield (entry 9, Scheme 5).

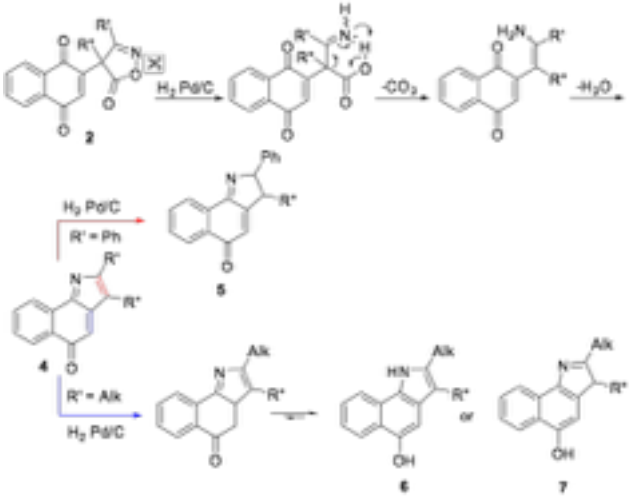
Scheme 5. The scope of the catalytic hydrogenation of the 4*H*-isoxazol-5-ones 2b-j[a]



[a] Reaction conditions: substrate **2b-j** (1.0 mmol), Pd/C (10% weight), AcOEt (30 mL), r.t., H_2 atmosphere, overnight.

A mechanism for this second transformation is depicted in Scheme 6. The initial hydrogenolytic cleavage of the labile N-O bond of the isoxazolone ring[18] affords a β-imino-carboxylic acid intermediate. Subsequent decarboxylation[19] generates an enamine that, through cyclocondensation with the vicinal carbonyl group, generates the corresponding naphthoquinone **4**. The following alkene hydrogenation affords compounds **5** or (**6** or **7**) depending on the nature of the substituent at position 3 of the isoxazolone ring (Scheme 6).

Scheme 6. Proposed mechanism for the Pd/C catalyzed hydrogenation reaction of 4*H*-isoxazol-5-ones 2



In summary, we have disclosed new approaches for the synthesis of two types of benzannulated indoles by the conversion of stable and readily accessible 4*H*-isoxazol-5-ones. The reactions occur either by ruthenium catalysis or Pd/C catalyzed hydrogenation, affording benzo[*f*]indole-4,9-dione and benzo[*g*]indole derivatives, respectively. Both processes involve an initial decarboxylative ring opening of the isoxazolone moiety. The ring closure is expected to proceed through C-H functionalization of the naphthoquinone under Ru catalysis. These strategies represent a valuable alternative to the methods already reported in the literature for the preparation of benzo-indoles and provide wide the possibilities to use the 4*H*-isoxazol-5-ones as building blocks to access heterocyclic products. Further work is aimed to investigate transition metal-based conditions to convert isoxazolone derivatives to pyrroles.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Experimental procedures, compound characterization data including copies of ^{1}H and ^{13}C NMR spectra

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Notes

The authors declare no competing financial interest.

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