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A facile, metal- and solvent-free, autoxidative coupling of quinolines with indoles and pyrroles

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Abstract

A simple, solvent-free, one-pot autoxidative coupling reaction between quinoline and indoles or pyrroles is reported. This atom economic method requires only a stoichiometric amount of inexpensive hydrochloric acid and does not require a catalyst.

Coupling reactions of aza-aromatics, especially quinoline, indole and pyrrole derivatives,¹ are important transformations in organic synthesis, particularly for the preparation of new analogues of these compounds with potential biological activity.² The indolyl-quinoline core is a key structural feature in a large number of biological agents, many with antibacterial properties.³ Thus far, access to coupled indole-quinoline compounds has been achieved in three ways: metal-catalyzed cross coupling,⁴ construction of one or both rings,⁵ or addition of indole to an activated quinoline.^{6,7} All of these strategies require several synthetic steps to achieve the desired C–C bond formation between the two rings. Here we describe a high yielding method for coupling indoles or pyrroles to quinolines in one solvent-free step that does not require a catalyst.^{8, 15a}

We recently discovered that 2-(1-methylindol-3-yl)quinoline (**3a**) could be obtained by heating quinoline (**1a**) and methylindole (**2a**) in the presence of HBr in dioxane followed by neutralization with base (Scheme 1). In this reaction, the oxidative formation of the new C–C bond is remarkable, because no external redox catalyst or oxidizing agent is involved, only a simple mineral acid. This result prompted us to explore and optimize the reaction conditions for this transformation with the aim of developing a new general coupling method, potentially providing rapid access to these interesting products in a simple and economical way.

We chose to pursue the optimization using the isolated quinolinium chloride salt (**1a'**, purified by sublimation) in order to rule out any catalysis by trace metal impurities, and also to confirm its intermediacy in the reaction. In preliminary experiments in dioxane, **1a'** and **2a** were found to yield **3a'**, the chloride salt of **3a**, in modest yield (entry 1, Table 1). The product **3a**, obtained after deprotonation with NaHCO₃, was characterized and the coupling regioselectivity C2–C3' was confirmed by an X-Ray diffraction study (Figure 1).

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Electronic Supplementary Information (ESI) available: Procedure for the synthesis of the compounds and their characterization data, ¹H-NMR, ¹³C-NMR spectra, and crystallographic data are reported. See DOI: 10.1039/b000000x/

Although increasing the concentration of **1a'** and **2a** led to a substantial improvement in yield (entries 1 & 2, Table 1), the addition of 2 equivalents of quinolinium salt **1a'** was more beneficial (entries 1 & 3, Table 1). The combination of higher concentration and the right proportion of reagents (**1a'**/**2a**: 2/1) proved to be optimal (83% yield, Entry 4, Table 1). Under these conditions, the reaction could also be carried out in another solvent (toluene), neat or under air without any significant loss in yield (entries 5–7, Table 1).

A careful examination of the by-products present in the reaction mixture revealed that the quinoline itself acts as an oxidant and is able to abstract hydrogen atoms⁹ to form 1,2,3,4-tetrahydroquinoline (**4**, 5% yield based on total quinoline), and 1',2',3',4'-tetrahydro-2,6'-biquinoline (**5**, 20% yield based on total quinoline) (Scheme 2). Product **5** is most likely the result of the coupling of quinolinium with compound **4**. The quantities of **4** and **5** are consistent with the number of hydrogen atoms abstracted in the coupling.

We reasoned that the need for 2 equivalents of quinolinium was due to its dual role as an electrophile and an oxidant. We thus examined the amount of protonated quinoline necessary in the coupling by running experiments with different relative amounts of quinolinium and quinoline. While monitoring these reactions by ¹H-NMR spectroscopy, we were pleased to observe complete conversion of the indole along with a high yield of **3a'** after 6 h at 175 °C, using the proportion 1:1:1 of quinolinium hydrochloride, free quinoline, and indole (Scheme 3).

In order to simplify the experimental procedure, we carried out the reaction by performing an *in situ* protonation via addition of a solution of HCl in dioxane.¹⁰ The addition of 2 equivalents of quinoline, 1.2 equivalents of HCl, and 1 equivalent of methylindole gave **3a'** in a similar yield and reaction time. We noticed a better reproducibility and higher yields, 83–90%, when the reaction was performed without stirring and in the absence of a solvent (apart from a small quantity of dioxane used to dissolve the HCl). The use of external oxidant, such as DDQ or O₂, combined with or instead of excess quinoline as the oxidant, was not successful.¹¹

Using this simplified procedure, we explored the reaction scope (Table 2). A variety of substituted indoles could be efficiently coupled. The simple indole **2b** was a good nucleophile, reacting with quinoline in 4 h at 155 °C. At the same temperature, substrates bearing both electron-withdrawing (**2c–d**) and electron-releasing (**2e–f**) substituents were effective coupling partners. Pyrroles were also competent substrates in this coupling reaction (**2g–h**), although in these cases lower yields were obtained. Pyrrole itself (**2h**) gave a mixture of the mono- and bis-quinoline coupled products (**3h–i**). Differently substituted quinolines, including tricyclic derivatives, are well tolerated and allowed the coupling with indole to proceed in moderate to good yields. As expected, the more electron-deficient substrate 6-bromoquinoline (**1c**) was the most reactive, affording **6c** in 74% yield in only 4 h. The reaction with 2-quinaldine **1f** resulted in coupling at the *para* position, affording product **6f**, albeit in lower yield.

A tentative mechanism for the coupling reaction is depicted in Scheme 4. First, the nucleophilic electron-rich indole **2b** attacks the electrophilic quinolinium cation (**1a'**). The autoxidative step probably then occurs by intermolecular hydrogen transfer from the indolyl-dihydroquinoline intermediate **A** to quinolinium (**1a'**), leading to the formation of **3a'** and the dihydroquinoline **B**. Intermediate **B** could then enter into a second oxidation step to finally afford the tetrahydroquinoline (**4**).

Similar reactions have been reported in which an electrophile activated as an iminium ion, an *N*-acyliminium ion or a conjugated iminium ion, generated *in situ*, is attacked by an indole. However, none of these reactions yields an aromatic product directly and a second

oxidation step is necessary after isolation.^{6, 12} The autoxidation step is related to the acid-catalyzed disproportionation reaction of 1,2-dihydrolepidine to give lepidine and 1,2,3,4-tetrahydrolepidine;¹³ usually hydrogen transfers involved in C–C bond formation are intramolecular¹⁴ or catalyzed by an external agent.¹⁵

In summary, we have developed a simple, one-pot autoxidative coupling reaction that provides rapid access to indolyl-quinoline and pyrrolyl-quinoline cores in good yields. This process is atom economic, requires only a stoichiometric amount of inexpensive hydrochloric acid, and does not require a catalyst or solvent. The new reactivity of quinoline discovered here holds the potential to be extended to other nucleophiles, which would allow synthetic access to key motifs in a very efficient way.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
ORTEP view of compound **3a**.

Scheme 1.

Autoxidative coupling of quinoline with methylindole.

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Scheme 3. Formation of **3a'** by reaction of quinolinium **1a'**, quinoline **1a** and indole **2a**

Scheme 4.
Possible mechanism for the oxidative coupling of quinoline with indole.

Table 1 Optimization of the reaction conditions for the synthesis of **3a'**.^a

Entry	Solvent	Conc. [1a'] M	Conc. [2a] M	Yield [%] ^b
1	Dioxane	0.3	0.3	20
2	Dioxane	1	1	54
3	Dioxane	0.6	0.3	80
4	Dioxane	1	0.5	83
5	Toluene	1	0.5	80
6 ^c	Toluene	1	0.5	80
7 ^d	Neat	-	-	72

^aReactions were performed on a 0.5 mmol scale for 24 h at 175 °C under an atmosphere of N₂ in a sealed tube. After reaction the product was extracted with a mixture of CH₂Cl₂ and MeOH.

^bNMR yield of **3a'** relative to hexamethylbenzene.

^cUnder Air.

^d**1a'** (1 mmol); **2a** (0.5 mmol).

Table 2

Variation of the substrates^a

Entry	Substrate	Product	Yield (%)
1 ^b	2b	3b	73%
2	2c	3c	46%
3	2d	3d	81%
4	2e	3e	27%
5	2f	3f	54%
6	2g	3g	42%
7	2h	3h	22%
8	1b	6b	41%
9 ^b	1c	6c	74%
10	1d	6d	61%
11	1e	6e	51%
12 ^c	1f	6f	31%
		3i	12%

^aReactions were performed on a 0.5 mmol scale using 2 equiv of quinoline 1a–g and 1.2 equiv of HCl in dioxane in a sealed tube without solvent for 18 h at 155 °C. Isolated yields are reported after work-up with NaHCO₃ and purification by chromatography.

b 4 h. c 175 °C, 36 h.

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