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Metal-free transannulation reaction of indoles with nitrostyrenes: a simple practical synthesis of 3-substituted 2-quinolones†

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Abstract

3-Substituted 2-quinolones are obtained *via* a novel, metal-free transannulation reaction of 2-substituted indoles with 2-nitroalkenes in polyphosphoric acid. The reaction can be used in conjunction with the Fisher indole synthesis offering a practical three-component heteroannulation methodology to produce 2-quinolones from arylhydrazines, 2-nitroalkenes and acetophenone.

3-Substituted 2-quinolones are omnipresent in naturally occurring and synthetic compounds displaying a broad range of pharmacological activities.[1–3] Strong fluorophoric properties coupled with chemical and thermal robustness of 2-quinolones enable them to be used in laser dyes,[4] optical probes,[5] and as donor chromophores in FRET systems.[6] Not surprisingly, synthesis of 2-quinolones has attracted significant attention. Traditional protocols, such as Vilsmeier–Haack (a),[3d,7] Knorr (b),[8] and Friedlander (c) reactions,[9] together with their transition metal-catalyzed variations[10] (Fig. 1) as well as recently emerged alternative approaches including carbonylative cross-coupling reactions (d and f)[11] and RCM (e),[12] provide access to a variety of C3- and/or C4-substituted 2-quinolones. In all these methods, the R^2 substituent originates from costly or synthetically advanced precursors, which narrows the scope of the products, while R^3 is often requisite. Herein, we report convenient access to a broad range of 3-aryl- and 3-alkylsubstituted 2-quinolones *via* a metal-free condensation reaction of readily available 2-substituted indoles with β-nitroalkenes proceeding *via* an unprecedented transannulation pathway. This approach

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allows for easy variability of the R^2 substituent, which comes from readily available aldehydes. Furthermore, we describe a variation of this method involving simple one-pot preparation of the 2-quinolone scaffold by a three-component reaction utilizing all commercially available inexpensive starting materials.

While investigating reactions of heterocyclic compounds in polyphosphoric acid (PPA),[13] we attempted a ring expansion of indole **1** in the presence of electron deficient olefins anticipating the formation of 2(1*H*)-3,4-dihydroquinolinones **4** *via* re-cyclization of hydroxamic acid **3**[14] (Scheme 1). The test reactions between 2-phenylindole (**1b**) and β-nitrostyrene (**2a**) or 4-methoxy-β-nitrostyrene (**2b**) revealed that a facile **5** → **6** ring expansion indeed took place under relatively mild conditions. As predicted, the aromatic substituent from the nitrostyrene was successfully incorporated into the product structure. However, the transannulation reaction took an unexpected turn: the C2 of the indole along with the attached substituent was sacrificed to produce benzamide (**6a**) as a byproduct. Correspondingly, 3-aryl-2-quinolones **5aa** and **5ab** lacking the acyl substituent at C4 were isolated as the main products in high yields (Scheme 1 and Table 1, entries 2 and 4). After thorough optimization, it was found that the best results are achieved when the mixture of a 2-substituted indole and a nitroalkene is heated in 80% PPA at 80–85 °C for 30 min and then at 95–100 °C for additional 2.5–3 hours. We also found it to be more convenient to employ iso-skatole (**1a**) as a precursor, which also provides high yields of 2-quinolones but gives acetamide (**6b**) as a byproduct (Table 1, entries 1 and 3), easily removable by routine aqueous workup. The results of screening of various nitroolefins in this transformation are summarized in Table 1. Good yields were obtained with nitrostyrenes bearing either electron-donating (entries 3–8) or electron-withdrawing (entries 9–13) groups. Aliphatic nitroolefin **2l** reacted uneventfully with both model indoles **1a,b** (Table 1, entries 14 and 15). *N*-Methylindole **1c** also underwent facile transannulation affording the corresponding *N*-Me-2-quinolone **5ca** in high yield (Table 1, entry 16).

Although a detailed mechanistic study is underway in our laboratories, a conjectural, yet reasoned, mechanism for this novel transannulation reaction is provided in Fig. 2. Initially, an electrophilic attack[15] by the nitroalkene at C3 of indole produces alkylideneazinic acid **7**. The aci-species **7** rearranges into hydroxamic acid anhydride **8** in the presence of PPA,[14] which upon aqueous work up provides hydroxamic acid **3**. Indeed, acid **3ab** (R^1 = H, R^2 = R^3 = Ph) was isolated as a sole product if the reaction was carried out below 80 °C. When re-subjected to the standard reaction conditions, **3ab** provided 2-quinolone **5aa** in high yield (91%). Next, intramolecular nucleophilic attack by the *N*-hydroxyl moiety at the iminium functionality in **9** affords imine **10**, which in the presence of acid tautomerizes into enamine **11**. The latter undergoes a retro-Diels–Alder reaction[16,17] to produce anilide **12**. Subsequent migration of the acyl group from aniline to the more nucleophilic imine nitrogen followed by the nucleophilic attack by the aniline at the acyliminium moiety in **13** affords aminoquinoline species **14**, which cyclizes to spiro-dioxaphosphazine **15**. Finally, 2-quinolone **5** is produced after the extrusion of imidic anhydride **16**, which upon the hydrolytic cleavage gives rise to the amide byproduct **6**.

Having optimized the conditions for the transannulation reaction, we explored the possibility of combining this methodology with the Fisher indole synthesis.[18] Since the latter proceeds

efficiently at elevated temperatures in orthophosphoric acid, we anticipated that 80% PPA would also serve as a suitable medium for this reaction. Indeed, a test reaction between phenylhydrazine **17a** and acetophenone (**18**) rapidly produced 2-phenylindole **1b**, which underwent a sequential transannulation reaction with nitrostyrene **2a** to give 2-quinolone **5aa** in high yield (Scheme 2). Several *para*-substituted hydrazines **17d–f** tested reacted with similar facility, affording the corresponding products **5da, 5ea, 5fa** in good isolated yields. Further studies of the scope of this novel three-component heteroannulation reaction are underway in our laboratories.

We have developed a convenient and general approach to 3-substituted 2-quinolones *via* a metal-free transannulation reaction between 2-substituted indoles and 2-nitroalkenes in polyphosphoric acid. This reaction was successfully combined with the Fisher indole synthesis, which led to the development of an efficient sequential three-component heteroannulation methodology for the construction of the 3-aryl-2-quinolone scaffold. In contrast to most other known protocols that employ 1,2-disubstituted precursors, this new method utilizes readily available monosubstituted benzene derivatives. The procedure involves no chromatography and the obtained products are purified by simple recrystallization. The unique features of PPA that serves as a mild proton donor, a source for a good leaving group, a water scavenger, and a heavy-boiling solvent, make it an ideal medium for the described transformation and other analogous cationic rearrangement and condensation cascades yet to come.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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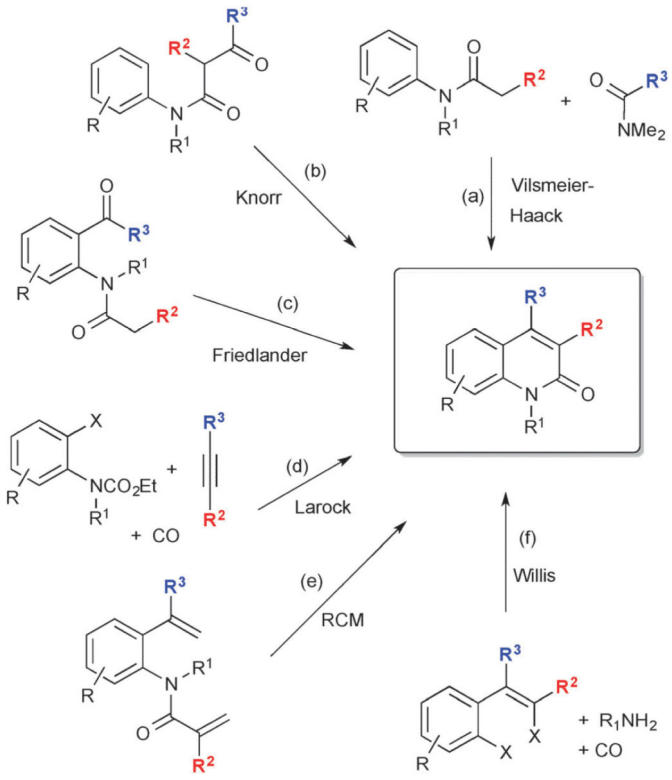
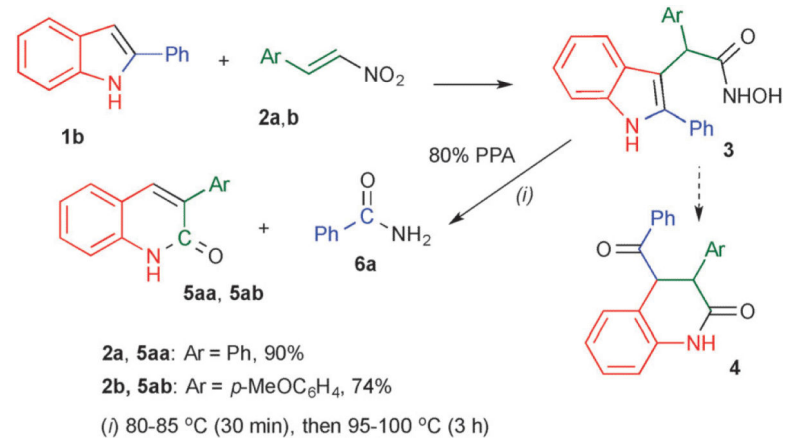


Fig. 1.
General approaches to 2-quinolone scaffolds.



Scheme 1.

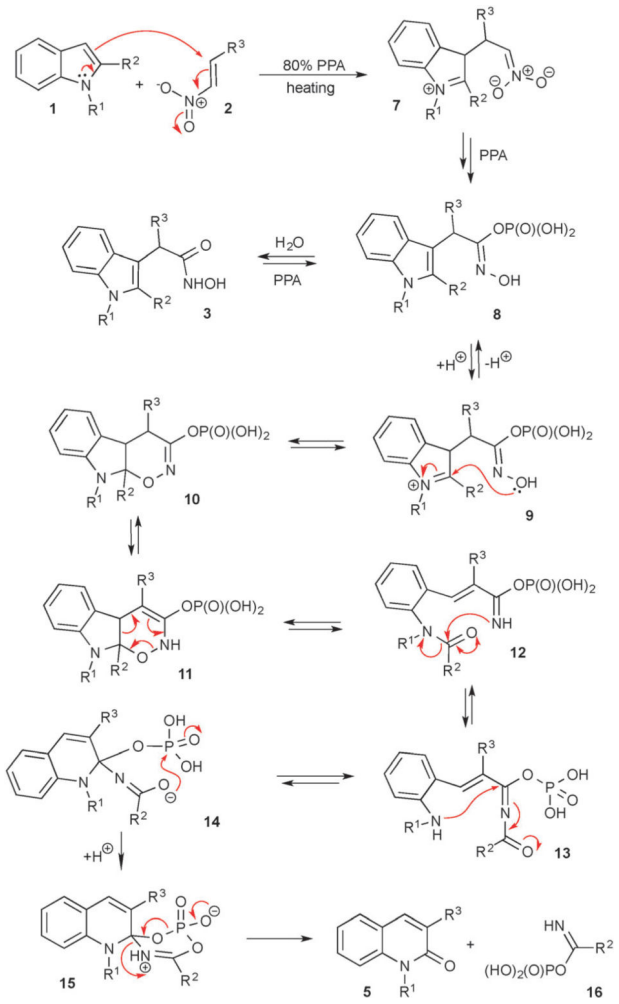
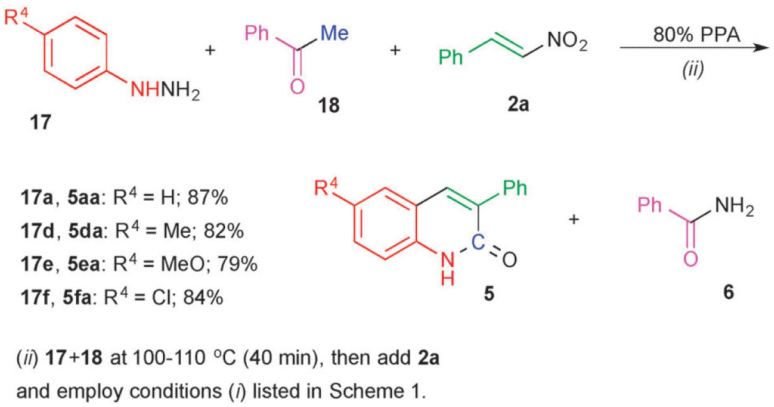


Fig. 2.
Proposed mechanistic rationale for reaction of indoles with nitroalkenes in PPA.

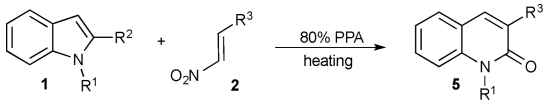


(*ii*) **17**+**18** at 100-110 °C (40 min), then add **2a** and employ conditions (*i*) listed in Scheme 1.

Scheme 2.

Table 1

Synthesis of 2-quinolones from indoles



	1	R^1, R^2	2	R^3	5	Yield[a] (%)
1	**1a**	H, Me	**2a**	Ph	**5aa**	90
2	**1b**	H, Ph	**2a**	Ph	**5aa**	92
3	**1a**	H, Me	**2b**	4-$MeOC_6H_4$	**5ab**	70
4	**1b**	H, Ph	**2b**	4-$MeOC_6H_4$	**5ab**	74
5	**1a**	H, Me	**2c**	4-i-PrC_6H_4	**5ac**	89
6	**1a**	H, Me	**2d**	3,4-$Me_2C_6H_3$	**5ad**	88
7	**1a**	H, Me	**2e**	3,4-$(MeO)_2C_6H_3$	**5ae**	78
8	**1a**	H, Me	**2f**	4-$EtOC_6H_4$	**5af**	79
9	**1a**	H, Me	**2g**	2-FC_6H_4	**5ag**	68
10	**1a**	H, Me	**2h**	3-FC_6H_4	**5ah**	66
11	**1a**	H, Me	**2i**	4-FC_6H_4	**5ai**	72
12	**1a**	H, Me	**2j**	3,4-$Cl_2C_6H_3$	**5aj**	88
13	**1a**	H, Me	**2k**	3-BrC_6H_4	**5ak**	67
14	**1a**	H, Me	**2l**	*n*-Pr	**5al**	63
15	**1b**	H, Ph	**2l**	*n*-Pr	**5al**	62
16	**1c**	Me, Me	**2a**	Ph	**5ca**	84

[a]Isolated yields. Reaction mixtures were heated in 80% PPA at 80–85 °C for 30 min, then at 95–110 °C for 3 h.