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Reaction of 3-(2-nitrophenyl)-1-arylprop-2-en-1-ones with triethylphosphite in microwave revisited: One-pot synthesis of 2-aroylindoles and 2-arylquinolines

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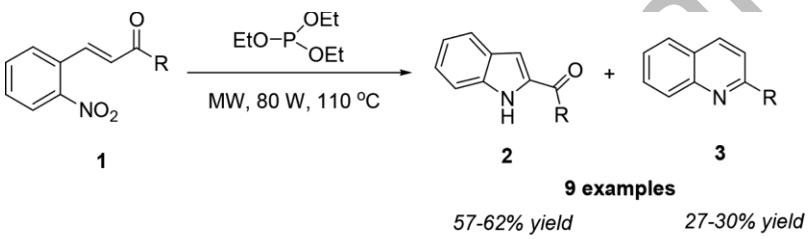
Abstract

One-pot synthesis of 2-aroylindoles and 2-arylquinolines has been achieved by the reductive cyclization of 3-(2-nitrophenyl)-1-arylprop-2-en-1-ones with triethylphosphite [$P(OEt)_3$] under microwave irradiation. The formation of 2-arylquinolines by this method is unprecedented.



R = Ph, 4-$CH_3C_6H_4$, 4-$OCH_3C_6H_4$, 3-$OCH_3C_6H_4$, 4-ClC_6H_4, 4-BrC_6H_4, 4-FC_6H_4, 3,4-$(OCH_3)_2C_6H_3$, 2-furyl

KEYWORDS: 3-(2-Nitrophenyl)-1-arylprop-2-en-1-ones, $P(OEt)_3$, 2-aroylindoles, 2-arylquinolines, microwave irradiation

INTRODUCTION

Indole is one of the most commonly encountered heterocyclic units in a variety of biologically significant molecules [1]. C2–carbonyl indole derivatives have proven to be important building blocks for the synthesis of natural and pharmacologically active compounds [2]. In particular, C2–aroyl indole derivatives without any substituent at N1 and C3 positions have been identified as potent small molecular modulators for diverse

biological targets such as cell surface receptors (receptor tyrosine kinase) [3], histone deacetylases [4] and controlling the polymerization of tubulin [5]. Quinoline, on the other hand is another heterocyclic scaffold of paramount importance to human race. Quinoline moiety is present in the framework of many natural products and pharmacologically active compounds and have long been known for their wide range of biological [6] and chemotherapeutic activities [7]. 2-arylquinolines are found to be biologically active and found as substructure in many anti-malarial, anti-bacterial and anti-tumor agents [8]. In addition to the medicinal importance, quinolines also find applications in dyestuffs, photographic sensitizers [9] and are valuable precursors for the synthesis of nano and mesostructures with enhanced electronic and photonic properties [10]. Due to their wide range of applications, the synthesis of indole and quinoline derivatives has attracted the attention of many organic chemists and biochemists. Some of the methods for the synthesis of indole derivatives involves reductive cyclization of *o*-nitrochalcones using triethylphosphite [11], Pd catalyzed synthesis from *o*-nitrochalcones [12], reductive N-heterocyclization of 2-nitrovinylarenes catalyzed by ionic diamine rhodium complex [13] and CuI-catalyzed S_NAr reaction of *o*-bromochalcones with sodium azide [14]. For the synthesis of 2-arylquinolines some of the reported methods are molecular iodine catalyzed reaction between imines and aldehyde [15], one-pot Fe catalyzed synthesis from *o*-nitroarylcarbaldehyde [16], base mediated cyclization reaction between 2-aminobenzylalcohol and ketone [17], solid acid catalyzed microwave assisted reaction between anilines and cinnamaldehydes [18], hydrotalcite-bound ruthenium catalyzed reaction between 2-aminobenzyl alcohol and acetophenone [19].

It is pertinent to mention here, that Creencia *et al*. obtained 2-benzoylindole from 3-(2-nitrophenyl)-1-phenylprop-2-en-1-one in good yield using triphenylphosphine (PPh_3) in microwave (MW) and observed poor yields of the product with $P(OEt)_3$ in MW [20]. We have successfully synthesised pyrrole derivatives by $P(OEt)_3$ mediated reductive cyclization of ethyl 2-nitro-5-oxo-3,5-diarylpentanoates in MW [21]. Therefore, we wished to revisit the Creencia's protocol, which, surprisingly has not been successful for the synthesis of 2-benzoylindole from 3-(2-nitrophenyl)-1-phenylprop-2-en-1-one while using $P(OEt)_3$ in MW.

RESULTS AND DISCUSSION

3-(2-Nitrophenyl)-1-phenylprop-2-en-1-one (**1a)** upon MW irradiation with $P(OEt)_3$ (6 eq.) at 90 ˚C resulted in the formation of two products which were isolated in 42% and 20% respective yields. The major product was characterized as 2-benzoylindole, while the minor product was found to be 2-phenylquinoline. This result is in variance to those reported in the literature [11,20] where the formation of 2-phenylquinoline has not been noticed. Raising the temperature of the above reaction to 110 ˚C, resulted in the overall improvement of the yields of 2-benzoylindole and 2-phenylquinoline to 62% and 28% respectively. No improvement in the yields of products (**2a**) and (**3a**) as well as their ratio (~ 2 : 1) was noticed by further raising the temperature of the reaction to 120 ˚C, 130 ˚C and 140 ˚C. Thus, the optimized reaction condition involves the MW irradiation of 3-(2-nitrophenyl)-1-phenylprop-2-en-1-one with 6 eq. of $P(OEt)_3$ at 110 ˚C for 60 min (Scheme 1).

To check the versatility of this reaction, various 3-(2-nitrophenyl)-1-arylprop-2-en-1-ones (**1a-i**) bearing various electron-withdrawing and electron-releasing groups in 1-aryl were examined and found to yield the desired products *viz*. 2-aroylindoles (**2a-i**) and 2-arylquinolines (**3a-i**) in satisfactory yields (Scheme 2, Table 1). Heterocyclic ring at 1-position (Table 1, entry 9) also gave the expected products in good yields. The requisite starting propenones (**1a-i**) were, in turn prepared by an aldol/dehydration reaction of 2-nitrobenzaldehyde and various substituted ketones under basic conditions [22].

In order to have a mechanistic insight into the formation of 2-aroylindoles and 2-arylquinolines, ^{31}P NMR was recorded on the aliquots of the reaction at time 0 min and 30 min. In ^{31}P NMR of the aliquot at 30 min, appearance of a singlet at δ: -0.87 ppm and disappearance of singlet at δ: 138.7 ppm spoke in favour of formation of triethylphosphate from triethylphosphite (Figure 1). Based on this information coupled with that reported in literature[23,24], following mechanism is proposed for the formation of 2-aroylindoles (**2**) and 2-arylquinolines (**3**) (Scheme 3). Formation of (**2**) and (**3**) occurs *via* a nitrene intermediate (**4** and **6**) formed by deoxygenation of nitro group with 2 eq. of $P(OEt)_3$. Following path **A**, nitrene intermediate (**4**) rearranges to cyclic zwitterion (**5**), which undergoes proton transfer to give 2-aroylindoles (**2**). Nitrene (**4**) on isomerisation gives *cis*-nitrene which eventually collapses to 2-arylquinoline (**3**) *via* path **B**. Phosphorimidate (**7**) formed by the reaction of (**6**) with $P(OEt)_3$ undergoes [2+2] cycloaddition to produce four-membered heterocycle (**8**) which disproportionates to 2-arylquinolines (**3**) owing to the strong affinity of phosphorus for oxygen. The synthesis of

2-arylquinolines (**3**) *via* path **B** is in line with the mechanism proposed by Ogasawara *et al.* [24].

EXPERIMENTAL

General

All the commercially available reagents were purchased from Aldrich and were used without further purification. The reactions were performed with a Discover™ single mode cavity MW synthesizer (CEM Corporation). Melting points (°C) were measured in open glass capillaries using Perfit melting point apparatus and are uncorrected. The progress of the reaction was monitored by thin layer chromatography (TLC) using silica gel pre-coated aluminium sheets (60 F254, Merck). Visualization of spots was effected by exposure to ultraviolet light (UV) at 254 nm, iodine vapours, 2% 2,4-dinitrophenylhydrazine in methanol containing few drops of H_2SO_4 and draggendroff reagent. Column chromatography was performed on silica gel (60-120 mesh). IR spectra (ν, cm^{-1}) were recorded on Perkin-Elmer FTIR spectrophotometer using KBr discs. ^{1}H NMR and ^{13}C NMR spectra in $CDCl_3$ as solvents were recorded on Burker AC-400 spectrometer operating at 400 MHz for ^{1}H and 100 MHz for ^{13}C, with tetramethylsilane (TMS) as internal standard. Electron impact mass spectra (EIMS) were recorded on Micro Mass VG-7070 H mass spectrometer at 70 ev. Elemental analysis were performed on Leco CHNS-932 analyzer.

General Procedure For The Synthesis Of 2-Aroyl Indoles (2a-I) And 2-Arylquinoline (3a-I)

A solution of 3-(2-nitrophenyl)-1-arylprop-2-en-1-ones (1 mmol) in $P(OEt)_3$ (6 mmol) in a capped vial was exposed to MW irradiation at 110 °C (80 W). After the completion of the reaction (TLC), the reaction mixture was cooled to room temperature, transferred to a 10 mL round-bottomed flask and concentrated under vacuum at 80 °C in a rotary evaporator. The residue so obtained upon column chromatography yield pure products **2(a-i; 57-62% yield)** and **3(a-i; 27-30% yield)**.

Spectral Characterization Of (2a) And (3a)

Compound (1*H*-indol-2-yl)(phenyl)methanone **(2a)** was obtained as yellow solid, yield: 62%, m.pt. 145-147 °C (lit. 150-151 °C) [25], ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.65 (br s, 1H, NH), 8.04 (d, *J* = 7.8 Hz, 2H), 7.76 (d, *J* = 8.1 Hz, 1H), 7.66 (t, *J* = 7.0 Hz, 1H), 7.60 – 7.52 (m, 3H), 7.41 (t, *J* = 7.6 Hz, 1H), 7.20 (t, *J* = 7.4 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 187.3, 138.0, 137.6, 134.3, 132.4, 129.2, 128.5, 127.7, 126.5, 123.2, 121.0, 112.9, 112.2. IR (KBr, υ_{max} cm^{-1}): 3315, 1618, 1577, 1512, 1328, 1261, 1132, 734. MS(ESI) (m/z) : 222. Anal. calcd. for $C_{15}H_{11}NO$: C, 81.43; H, 5.01; N, 6.33%. Found: C, 81.52; H, 5.02; N, 6.31% and compound 2-phenylquinoline **(3a)** was separated as oil, yield: 28%, ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.44 – 8.08 (m, 4H), 7.89 (dd, *J* = 18.8, 8.3 Hz, 2H), 7.77 (t, *J* = 7.6 Hz, 1H), 7.59 – 7.51 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.4, 148.2, 139.7, 136.8, 129.7, 129.3, 128.8, 128.3, 127.6, 127.4, 127.2, 126.3, 119.0. IR (KBr, υ_{max} cm^{-1}): 3053, 2958, 1710, 1596, 1551, 1446, 1282, 1074, 828, 765. MS(ESI) (m/z) : 206. Anal. calcd. for $C_{15}H_{11}N$: C, 87.77; H, 5.40; N, 6.82%. Found: C, 87.65; H, 5.38; N, 6.81.

CONCLUSION

In summary, we have successfully developed a strategy for the one-pot synthesis of 2-aroylindoles and 2-arylquinolines from 3-(2-nitrophenyl)-1-arylprop-2-en-1-ones and $P(OEt)_3$ under microwave irradiation. Formation of 2-arylquinolines has been reported for the first time using 3-(2-nitrophenyl)-1-arylprop-2-en-1-ones and $P(OEt)_3$.

SUPPLEMENTAL MATERIAL

Experimental data, ^{1}H NMR and ^{13}C NMR spectra of all the synthesized compounds can be accessed on the publisher's website.

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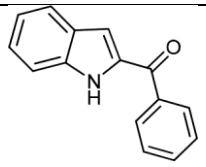
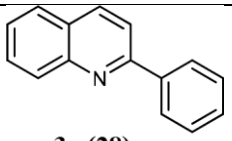
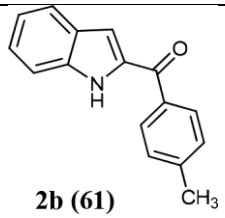
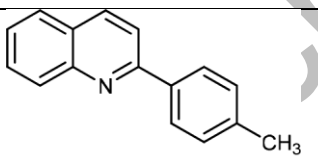
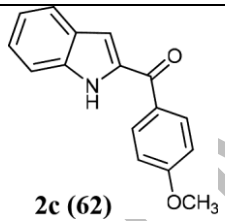
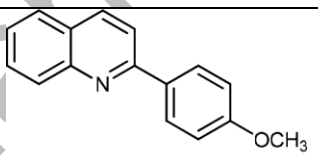
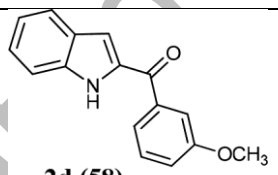
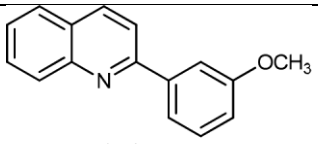
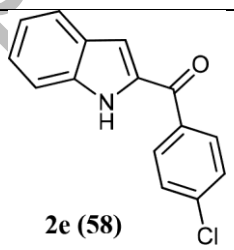
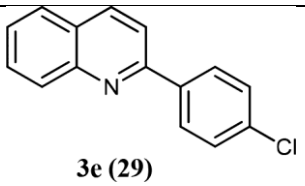
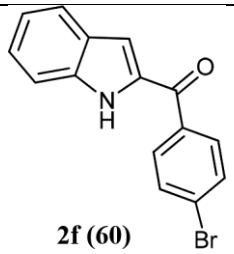
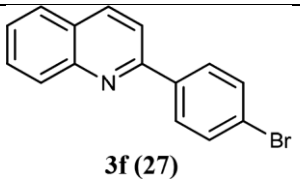
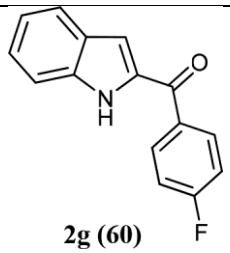
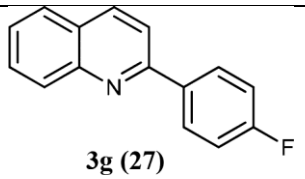
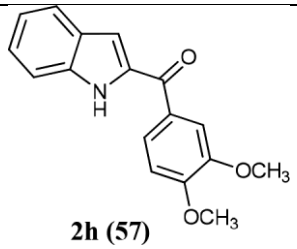
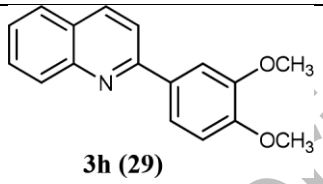
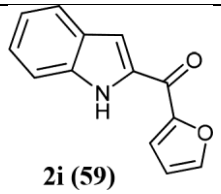
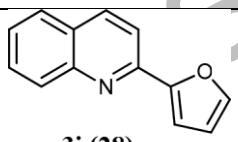
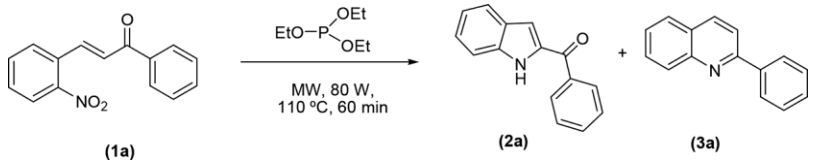
Table 1 Triethylphosphite mediated synthesis of 2-aroylindoles and 2-arylquinolines.

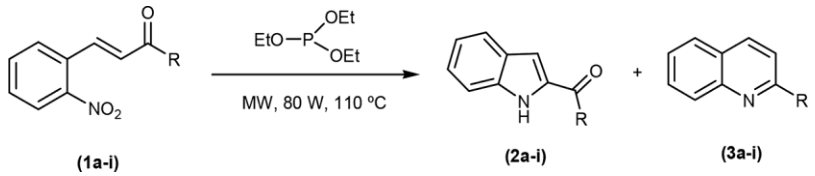
S. No.	R	2-aroylindoles (yield %)	2-arylquinolines (yield %)	Time (min)
1	C_6H_5	 **2a (62)**	 **3a (28)**	60
2	4-$CH_3C_6H_4$	 **2b (61)**	 **3b (28)**	50
3	4-$OCH_3C_6H_4$	 **2c (62)**	 **3c (30)**	45
4	3-$OCH_3C_6H_4$	 **2d (58)**	 **3d (28)**	55
5	4-ClC_6H_4	 **2e (58)**	 **3e (29)**	45
6	4-BrC_6H_4	 **2f (60)**	 **3f (27)**	40

7	4-FC_6H_4	 **2g (60)**	 **3g (27)**	50
8	3,4- $(OCH_3)_2C_6H_3$	 **2h (57)**	 **3h (29)**	60
9	2-Furyl	 **2i (59)**	 **3i (28)**	45

Scheme 1. Triethylphosphite mediated one-pot synthesis of 2-benzoylindole **(2a)** and 2-phenylquinoline **(3a)**.



Scheme 2. Triethylphosphite mediated one-pot synthesis of 2-aroylindoles **(2a-i)** and 2-arylquinolines **(3a-i)**.



(1a-i) **(2a-i)** **(3a-i)**

Scheme 3. Plausible mechanism for the synthesis of 2-aroylindoles (**2**) and 2-arylquinolines (**3**)

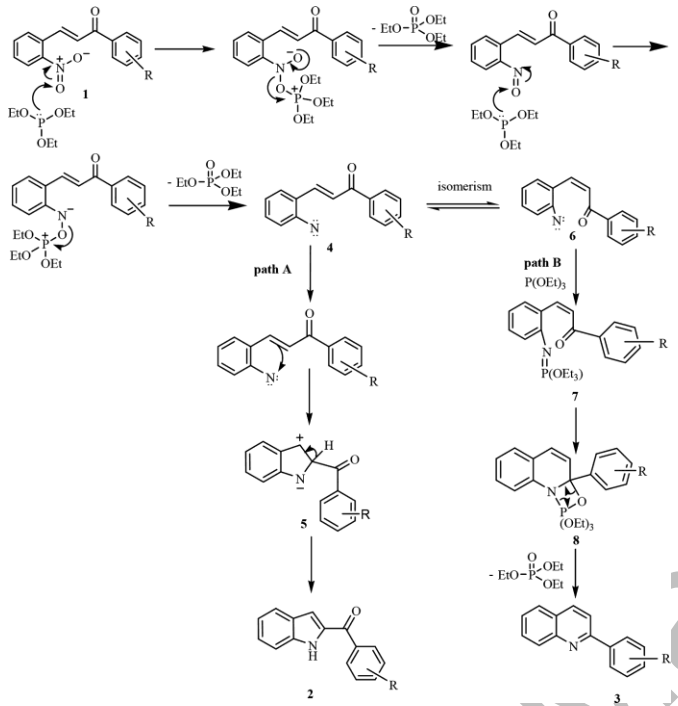


Figure 1. ^{31}P NMR study of reaction mixture at 0.0 min and 30 min for mechanistic proof.