Microwave assisted synthesis of phenyl(2-phenyl-5,6,7,8-tetrahydro-4-
quinolinyl)methanone and its derivatives

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The 4-benzoyltetrahydroquinoline related heterocycles, phenyl(2-phenyl-5,6,7,8-tetrahydro-4-quinolinyl)methanone and its derivatives have been synthesized by one-pot amination-cyclization reaction under microwave conditions. The reaction can be performed conveniently in polyethylene glycol-200 within 5 min.

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The quinoline nucleus and its partially reduced forms can be readily recognized as structural motifs in many physiologically active alkaloids. Therefore, the synthesis and characterization of various quinoline derivatives is of continuing interest. We have been particularly interested in the synthesis and characterization of 5,6,7,8-tetrahydroquinoline derivatives as possible precursors for the aza-steroid type compounds. The 5,6,7,8-tetrahydroquinoline moiety is found in alkaloids isolated from the plants belonging to Aizoaceae, Rutaceae and Rutaceae families. In addition, a few of the 5,6,7,8-tetrahydroquinoline derivatives also have therapeutic importance. In an effort to develop a convenient and environment friendly synthesis of the 5,6,7,8-tetrahydroquinoline derivatives, we attempted the amination-cyclization reaction on the 1,4,2'-triketones 3a derived from the conjugate addition of cyclohexanone 2 to (E)-1,4-diphenyl-2-butene-1,4-diones 1 (trans-dibenzoylethlenes). We wish to report herein that 1,4,2'-triketones 3 generated from trans-dibenzoylethylene (trans-DBE) and its analogs can be converted to the corresponding hitherto unreported phenyl(2-phenyl-5,6,7,8-tetrahydro-4-quinolinyl)methanone derivatives 4 using amination-cyclization-aromatization protocol. This multi-step one-pot transformation can be conducted within a few minutes under environmentally benign microwave mediated reactivity enhancement conditions.

Conjugate addition (Michael reaction) of the anion generated from cyclohexanone 2 to trans-DBE 1a in the presence of barium hydroxide in ethanol medium furnished diastereomeric mixture of triketones 3a in 60% yield in 3:1 ratio (Scheme I). Kaupp and coworkers reported the isolation of triketone 3a as a byproduct in their study on the synthesis of eage compounds from trans-DBE. The 1H NMR and 13C NMR (seven sets of signals in the aliphatic region) spectra matched well with the expected structure. Previously, we have isolated carbocyclic products along with expected 1,5-diketones from barium hydroxide mediated reaction of some α,β-unsaturated ketones, viz. chalcone or phenyl vinyl ketone derivatives with cyclopentanone. However, in the present case we did not detect the formation of any carbocyclic products. Similarly, we found only the triketone 3a when the reaction was conducted in the presence of different bases such as sodium ethoxide, potassium hydroxide and sodium hydroxide in ethanol medium. The Ba(OH)2 mediated condensation of 4,4'-dichlorobenzoylethylene 1b and 4,4'-dimethylbenzoylethylene 1c with cyclohexanone 2 resulted in the corresponding diastereomeric triketones 3b-c in good yields.

The triketone of the type 3 has two aromatic and one aliphatic keto-groups. Molecular stitching involving two carbonyl groups on C-1 and C-4 in 3 in the dehydrative amination-cyclization sequence is expected to generate 2,3,5-trisubstituted pyrrole derivatives 5 (Scheme II). On the other hand, similar transformation involving two carbonyl groups on C-1 and C-2' lead to 2,3-disubstituted-4,5,6,7-tetrahydroindole derivative 6. Finally, the cyclization
involving C-4 and C-2' carbonyl groups in 3 furnish the 2,4-disubstituted-5,6,7,8-tetrahydroquinoline derivatives 4. To test the above possibilities, we conducted the amination-cyclization reaction on the triketones 3 with ammonium acetate. Literature search revealed that 4-aroyl-5,6,7,8-tetrahydroquinoline derivatives of the type 4 are not known.

Initially the triketone 3a was treated with ammonium acetate in dry methanol under reflux for 18 hr to result in phenyl(2-phenyl-5,6,7,8-tetrahydro-4-quinolinyl)methanone 4a as a single product in moderate yield (13%). The reaction time could be reduced to 5 min when it was conducted in polyethylene glycol-200 (PEG-200) under microwave irradiation using domestic microwave oven (BPL-Sanyo, India; mono-made, multi power; power source: 230V, 50Hz; Microwave Frequency: 2450 MHz). However, in spite of best efforts to optimize the reaction conditions the yield of the desired product did not go above 15%. Extensive decomposition was observed when the reaction was conducted in polyethylene glycol-400 (PEG-400) possibly because of its high viscosity. In addition, ammonium acetate was found to be sparingly soluble in PEG-400.

We have attempted to conduct the microwave-assisted reaction under solvent-free conditions, on silica gel, alumina and acid clay solid support. In all the conditions except in PEG-200, the yield of the desired product 4a was lower than 10%. PEG-200 is an environmentally benign solvent. It has several desirable characteristics for a solvent. It is miscible in water; it shows high-boiling point, low viscosity, low vapour pressure and reasonably high dielectric constant (\(\varepsilon = 20\)). Furthermore, PEG has been approved for use in food materials\(^9\), and it is non-halogenated with low toxicity\(^10\). Keeping the desirable characteristics in view, we selected to conduct microwave-mediated reactions in PEG-200.
The 5,6,7,8-tetrahydroquinoline 4a was characterized by its spectral analyses. The IR spectrum of 4a showed the carbonyl group absorption at 1650 cm⁻¹. The ¹H NMR spectra showed two triplets (δ 2.33, J = 6.2 Hz and δ 2.58, J = 6.3 Hz) and two multiplets (δ 1.64-1.72 and δ 1.76-1.86) for eight hydrogens in the aliphatic region accounting for cyclohexane ring hydrogens. The C₂-H aromatic hydrogen appeared as a singlet at δ 7.33 ppm. The presence of an aromatic keto group (IR) and four methylenes (¹H NMR) in 4a ruled out the formation of the pyrrole derivatives of the type 5 or 6 in the amination-cyclization step.

Having established the structure of 4a, next, we studied the scope of the amination-cyclization reaction by transforming the triketones 3b-c having electron withdrawing (C₆, 3b) and electron donating (Me, 3c) groups located on the aryl rings to the corresponding phenyl-(2-phenyl-5,6,7,8-tetrahydro-4-quinolyl)methane derivatives 4b-c. Formation of 4b-c took place without any event but only in moderate yield. No other product was detected in the reaction mixture. The spectral data for 4b-c matched well with the quinoline 4a.

Thus, in this study we demonstrated that triketones of the type 3 could be transformed to 5,6,7,8-tetrahydroquinoline derivatives of the type 4 via one-pot oxidative amination-cyclization sequence. However, the yield of the tetrahydroquinoline product 4 was found to be moderate, possibly because the system 4 is behaving like highly reactive acid halides. We have found that the rate of the formation of the product 4 from triketones 3 is promoted by microwave heating methods when PEG-200 is used as a solvent.

**Experimental Section**

**General.** Progress of all the reactions was monitored by TLC (TLC silica gel: Qualigens or TLC alumina: SRL, India) using hexane-EtOAc as eluent. Column chromatography was accomplished on silica gel (100-200 mesh, Acme synthetic chemicals) using hexane-EtOAc as eluent. IR spectra were recorded neat using JASCO FT-IR or Perkin-Elmer or Bomem MB-104 FT-IR spectrophotometer. ¹H NMR and ¹³C NMR spectra were recorded in CDCl₃ with JEOL 400 MHz and Varian 300 MHz NMR spectrometer. Mass spectra and High Resolution Mass Spectra were recorded on Finnigan MAT 8230 Mass spectrometer. The microwave reactions were carried out using BPL-Sanyo, India; mono-made, multi power; power source: 230V, 50Hz, Microwave Frequency: 2450 MHz microwave oven. trans-DBE and derivatives Ia-c were prepared according to literature procedure. The tetrahydroquinoline products 4a-c were found to be unstable and therefore satisfactory mass spectra and analysis could not be obtained.

**Reaction of trans-dibenzoylethylene with cyclohexanone under basic conditions. General procedure.** To a stirred suspension of freshly activated Ba(OH)₂ (heated to 100 °C for 2 hr and cooled in a desiccator, 136 mg, 0.8 mmole) in 10 mL of absolute alcohol, cyclohexanone (432 mg, 4.4 mmoles) was added dropwise at room temperature and stirred for 10 min. trans-Dibenzoylethylene (944 mg, 4 mmoles) was added to the reaction mixture in three portions during 15 min and the mixture was stirred for 12 hr at room temperature. The reaction mixture was diluted with dichloromethane (25 mL), washed with ice water (2x20 mL), brine (2x10 mL), dried (anhydrous Na₂SO₄) and concentrated. The crude product was purified through column chromatography using silica gel (100-200 mesh) using 5 to 15% EtOAc-hexane as an eluent to give an inseparable diastereomeric mixture of triketones 3a. The spectral data of the major isomer culled from the mixture is given below.

**2-(2-Oxocyclohexyl)-1,4-diphenyl-1,4-butanedione 3a:** Viscous oil; yield 815 mg (61%); R₉ 0.45 (15% EtOAc-hexane); IR (neat): 1700, 1670, 1590, 1450, 1440, 1210, 995, 740, 680 cm⁻¹; ¹H NMR (300 MHz, CDCl₃/CCI₄): δ 1.54-1.62 (m, 3H), 1.89-2.03 (m, 3H), 2.28-2.46 (m, 2H), 2.72-2.78 (m, 1H), 3.18 (dd, J = 18.0, 4.5 Hz, 1H), 3.48 (dd, J = 12.6, 3.9 Hz, 1H), 3.92 (dd, J = 12.9, 3.7 Hz, 1H), 4.66-4.72 (m, 1H), 7.30-7.51 (m, 6H), 7.92 (dd, J = 8.7, 8.4 Hz, 2H), 8.06 (dd, J = 8.4, 6.9 Hz, 2H); ¹³C NMR (75 MHz, CDCl₃/CCI₄): δ 25.3, 27.2, 29.3, 36.9, 39.6, 42.0, 51.3, 128.1, 128.4, 128.6, 128.8, 133.0, 136.1, 136.6, 138.3, 197.3, 201.5, 209.3; LRMS: 334 (M⁺, 8), 316 (6), 229 (3), 212 (10), 133 (4), 105 (100), 77 (56), 51 (8); HRMS: Calcd for C₂₂H₂₂O₂; 334.1569. Found: 334.1562.

**1,4-Di(4-chlorophenyl)-2-(2-oxocyclohexyl)-1,4-butanedione 3b.** Following the general procedure described as above, the reaction of 1,4-di-(4-chlorophenyl)-2-buten-1,4-dione (1.0 g, 3.3 mmoles) and cyclohexanone (356 mg, 3.63 mmoles) in the presence of activated barium hydroxide (113 mg, 0.66 mmoles) in absolute ethanol (10 mL) resulted in 701 mg (53%) of inseparable mixture of 1,4-di(4-chlorophenyl)-2-(2-oxocyclohexyl)-1,4-butanedione 3b. The spectral data of the major isomer culled from the
mixture is given as follows: viscous oil; Rf 0.47 (15% EtOAc-hexane); IR (neat): 1700, 1670, 1560, 1480, 1210, 1085, 840, 750 cm⁻¹; ¹H NMR (300 MHz, CDCl₃/CCL₃): δ 1.52-1.64 (m, 3H), 1.91-2.07 (m, 3H), 2.29-2.48 (m, 2H), 2.71-2.78 (m, 1H), 3.13 (dd, J = 18.0, 4.2 Hz, 1H), 3.42 (dd, J = 18.0, 8.7 Hz, 1H), 4.57-4.60 (m, 1H), 7.36-7.47 (m, 4H), 7.83 (dd, J = 8.7, 8.4 Hz, 2H), 7.99 (dd, J = 8.7, 8.4 Hz, 2H); ¹³C NMR (75 MHz, CDCl₃/CCL₃): δ 25.3, 27.3, 29.4, 37.0, 39.7, 42.0, 51.4, 128.9, 129.0, 129.5, 130.1, 134.5, 134.8, 139.6, 139.7, 196.2, 200.5, 209.3; LRMS: 402 (M⁺, 7), 384 (6), 263 (5), 248 (5), 117 (4), 116 (4), 115 (15), 75 (10); HRMS: Calcd for C₂₂H₂₀Cl₂O₃:

Phenyl(2-phenyl-5,6,7,8-tetrahydro-4-quinolinyl)methanone 4a: Viscous oil; Rf 0.51 (10% EtOAc-hexane); IR (neat): 1650 cm⁻¹; ¹H NMR (300 MHz, CDCl₃/CCL₃): δ 1.64-1.72 (m, 2H), 1.76-1.86 (m, 2H), 2.33 (t, J = 6.2 Hz, 2H), 2.58 (t, J = 6.3 Hz, 2H), 7.05-7.56 (m, 6H), 7.73 (s, 1H), 7.70 (d, J = 7.5 Hz, 2H), 7.93 (d, J = 7.5 Hz, 2H).

4-Chlorophenyl(2-(4-chlorophenyl)-5,6,7,8-tetrahydro-4-quinolinyl)methanone 4b. Following the general procedure described as above, the reaction of 1,4-di(4-chlorophenyl)-2-(2-oxocyclohexyl)-1,4-butanedione (265 mg, 0.66 mmol) and ammonium acetate (508 mg, 6.6 mmol) in dry methanol (5 mL) resulted in 4b as viscous oil, yield 36 mg (17%); Rf 0.49 (10% EtOAc-hexane); IR (neat): 1655 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 1.77-1.81 (m, 2H), 1.91-1.94 (m, 2H), 2.65 (t, J = 6.4 Hz, 2H), 3.07 (t, J = 6.4 Hz, 2H), 7.35 (s, 1H), 7.40 (d, J = 8.4 Hz, 2H), 7.47 (d, J = 8.4 Hz, 2H), 7.71 (d, J = 8.4 Hz, 2H), 7.90 (d, J = 8.4 Hz, 2H); ¹³C NMR (100 MHz, CDCl₃): δ 22.3, 22.7, 26.1, 33.2, 115.2, 127.8, 128.2, 128.9, 129.3, 131.4, 134.3, 135.1, 137.3, 140.8, 146.7, 153.2, 158.8, 195.9.

(4-Methylphenyl)[2-(4-methylphenyl)-5,6,7,8-tetrahydro-4-quinolinyl)methanone 4c. Following the general procedure described as above, the reaction of 1,4-di(4-methylphenyl)-2-(2-oxocyclohexyl)-1,4-butanedione (347 mg, 0.96 mmol) and ammonium acetate (739 mg, 9.6 mmol) in dry methanol (5 mL) resulted in 4c as viscous oil, yield 49 mg (15%); Rf 0.53 (10% EtOAc-hexane); IR (neat): 1650 cm⁻¹; ¹H NMR (300 MHz, CDCl₃/CCL₃): δ 1.76-1.80 (m, 2H), 1.93 (m, 2H), 2.39 (s, 3H), 2.44 (s, 3H), 2.65 (t, J = 6.3 Hz, 2H), 2.60 (t, J = 6.3 Hz, 2H), 7.20 (d, J = 8.1 Hz, 2H), 7.25 (d, J = 8.1 Hz, 2H), 7.33 (s, 1H), 7.72 (d, J = 8.1 Hz, 2H), 7.83 (d, J = 8.1 Hz, 2H); ¹³C NMR (75 MHz, CDCl₃/CCL₃): δ 21.2, 21.7, 22.4, 22.7, 25.9, 33.2, 115.3, 127.0, 129.4, 130.5, 131.4, 133.6, 136.2, 138.7, 145.1, 147.3, 154.2, 158.2, 196.8.

Reaction of triketone 3a with ammonium acetate under microwave irradiation

The triketone 3a (165 mg, 0.49 mmol) and ammonium acetate (377 mg, 4.9 mmol) were dissolved in 2 mL PEG-200 and the mixture kept under microwave irradiation at 370 W for 5 min. The reaction mixture was diluted with dichloromethane.
(20 mL), washed with water (2×20 mL), brine (2×10 mL), dried over anhydrous Na$_2$SO$_4$ and concentrated in vacuo. The crude product was purified by column chromatography with silica gel (100-200 mesh) using hexane-EtOAc (95:5) as an eluent to furnish 4a (23 mg, 15%).

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