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In situ cyclopropanation: a rapid one-pot method for the synthesis of resin bound cyclopropyl phenyl methanones as combinatorial scaffolds☆

Rajesh K. Grover,[a] Ram Chandra Mishra,[b] Bijoy Kundu,[b] Rama Pati Tripathi[b,*] and Raja Roy[a,*]

[a]*Division of SAIF, Central Drug Research Institute, Lucknow 226001, India*
[b]*Division of Medicinal and Process Chemistry, Central Drug Research Institute, Lucknow 226001, India*

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Abstract—An efficient, high yielding one-pot synthesis of 4-substituted cyclopropyl phenyl methanones bound to RAM and WANG resins has been developed. The resin bound cyclopropyl phenyl methanone served as a combinatorial scaffold for the generation of structurally diverse alicyclic compounds.

1. Introduction

The cyclopropane ring is a basic structural element found in a variety of well established drugs used for acute and chronic conditions.[1] Chemists have always been fascinated by this subunit due to its interesting highly strained bonding features.[2] Their bioactive profile makes them useful synthetic scaffolds. Cyclopropanes have also been used as versatile synthetic intermediates in the synthesis of functionally rich cycloalkanes[3] and acyclic compounds.[4] Several reports exist on the synthesis of the cyclopropane moiety in solution.[5] Despite being an interesting class of compound, its synthesis on solid phase has not been carried out except for two reports dealing with trisubstituted cyclopropanes.[6] The motivation for this work stemmed from the identification of novel cyclopropyl phenyl methanone-based compounds exhibiting promising antitubercular activity[7] both in vitro against five clinical MDR strains (H37Rv) of *M. Tuberculosis* isolated from TB patients and in vivo in mice infected with H37Rv. Therefore, the goal of this study was to develop solid phase synthesis of cyclopropyl phenyl methanone-based compounds in order to generate a library of compounds.

Herein, we report an efficient, one-pot synthesis of polymer bound 4-substituted cyclopropyl phenyl methanones on Rink Amide (RAM) and Wang resins in high yields and purities. The resin bound cyclopropyl methanones thus synthesized served as combinatorial scaffolds for the synthesis of a variety of alicyclic compounds. Firstly, we generated the cyclopropyl moiety in situ via base mediated 1,3- substitution[8] of 4-chloro-*p*-fluorobutyrophenone as depicted in Figure 1. The synthetic strategy for resin bound cyclopropyl phenyl methanone is summarized in Scheme 1.

Our synthesis commenced with the loading of 4-formyl benzoic acid on RAM resin (0.64 mol/g) using the DIC/HOBt[9] procedure. Completion of the loading was determined by a negative Kaiser test.[10] Next, the aldehyde group of resin **1** was reduced with sodium borohydride in THF/ethanol mixture to give alcohol **2**. This was then treated with 4-chloro-*p*-fluorobutyrophenone

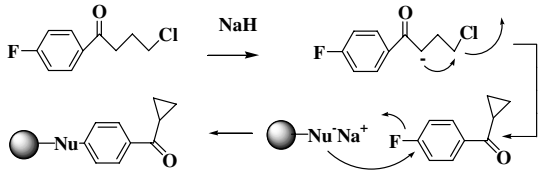

Figure 1. Reaction mechanism for the formation of resin bound cyclopropyl phenyl methanones.

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* Corresponding authors. Tel.: +91 522 212411; fax: +91 522 2223405; e-mail addresses: rpt_56@yahoo.com; rajaroy_cdri@yahoo.com

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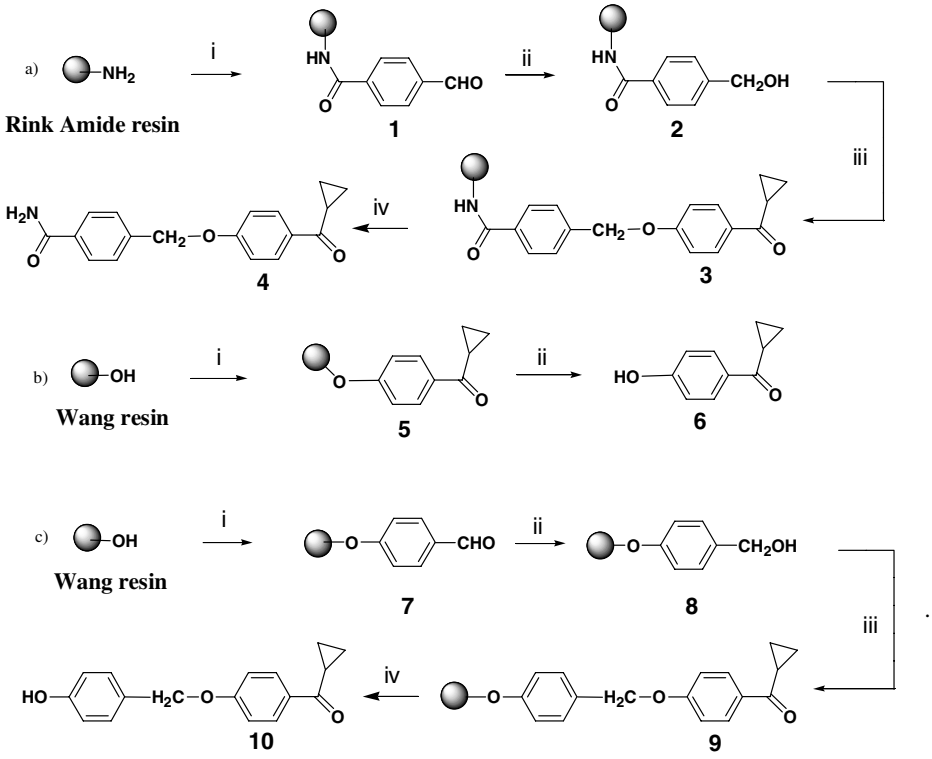


Scheme 1. Reagents and conditions: (a) (i) 4-Formylbenzoic acid, DIC, HOBt, DMF, rt, 12 h; (ii) $NaBH_4$, THF/ethanol (4:1), rt, 12 h; (iii) 4-chloro-*p*-fluorobutyrophenone, NaH, TBAB, DMF, rt, 12 h; (iv) 50% TFA in DCM, rt, 2 h; (b) (i) 4-chloro-*p*-fluorobutyrophenone, NaH, TBAB, DMF, rt, 12 h; (ii) 20% TFA in DCM, rt, 1 h; (c) (i) PPh_3, 4-hydroxybenzaldehyde, DEAD, THF, 0 °C to rt, 12 h; (ii) $NaBH_4$, THF/ethanol (4:1), rt, 12 h; (iii) 4-chloro-*p*-fluorobutyrophenone, NaH, TBAB, DMF, rt, 12 h; (iv) 20% TFA in DCM, rt, 1 h.

in the presence of NaH resulting in **3** along with unreacted **2**. This prompted us to employ tetrabutylammonium bromide (TBAB) as a phase transfer catalyst (PTC) in this reaction. Interestingly, completion of the reaction required 30 equiv of NaH in comparison to 6 equiv when used in combination with TBAB. The reaction mechanism as shown in Figure 1 for the formation of **3** (Scheme 1) involves the intramolecular nucleophilic substitution of the chloro group by the carbanion generated from 4-chloro-*p*-fluorobutyrophenone in the presence of NaH to furnish cyclopropyl *p*-fluorophenyl methanone in situ. This was followed by aromatic nucleophilic substitution (SNAr) at the fluorine bearing carbon of the aromatic ring by the resin bound benzyl alcohol to afford resin **3**. The reaction time was optimized to 12 h for complete conversion to the product.

Generally, a high purity of cleaved product **4** (>90%, as was evident from the ^{1}H NMR spectrum, Fig. 2 and HPLC) was obtained. The course of the reaction was monitored by single bead FT-IR. In compound **1** a strong stretch at 1710 cm^{-1} typical of an aldehyde group was evident while in compound **2**, disappearance of the carbonyl band and the appearance of a stretch at 3600 cm^{-1} due to the –OH group was observed. Finally, formation of the cyclopropyl phenyl methanone **3** was confirmed by the appearance of an IR stretch at 1700 cm^{-1} due to the ketone functionality.

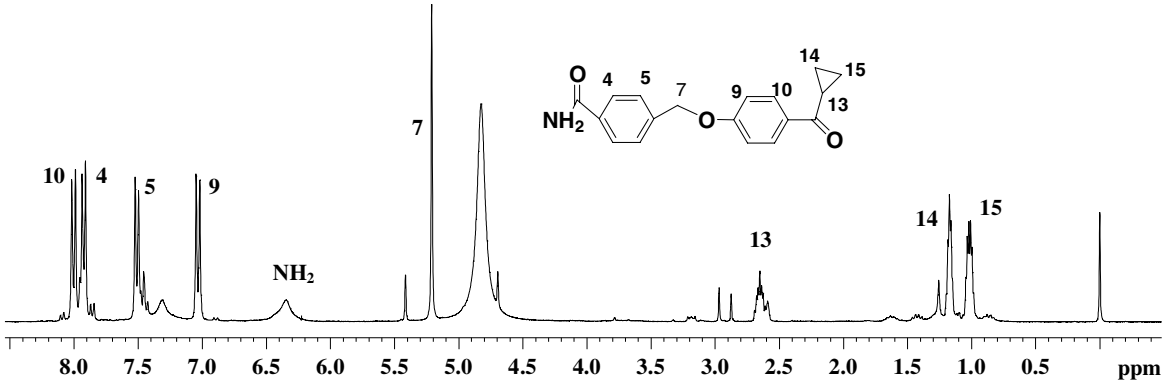
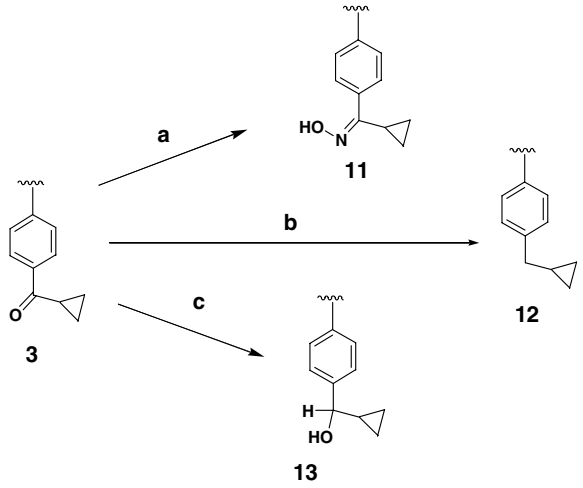


Figure 2. ^{1}H NMR spectrum (DMSO-d_6, 300 MHz) of crude cyclopropyl phenyl methanone **4**.



Scheme 2. Combinatorial scaffolding studies. Reagents and conditions: (a) (i) $NH_2OH{\cdot}HCl$, pyridine, ethanol/DCM (3:1), 40 °C, 56 h, 68%; (ii) 50% TFA in DCM, rt, 2 h; (b) (i) BH_3 stabilized in Me_2S, THF, $BF_3{\cdot}Et_2O$, 0 °C to rt, 16 h, 81%; (ii) 50% TFA in DCM, rt, 2 h; (c) (i) $NaBH_4$, EtOH/THF (4:1), rt, 12 h, 87%; (ii) 50% TFA in DCM, rt, 2 h.

The general applicability of our strategy has been demonstrated by carrying out the same reaction on Wang resin using two different methods (Scheme 1). The first involved loading of 4-chloro-*p*-fluorobutyrophenone directly onto the resin in the presence of NaH and TBAB to give resin **5**. Whereas, in the second method 4-hydroxybenzaldehyde was loaded on Wang resin using the Mitsunobu reaction[11] followed by a similar methodology to that employed in the case of the RAM resin to yield resin **9**.

Combinatorial scaffolding of the resin bound cyclopropyl phenyl methanones was demonstrated by carrying out several classical reactions to provide a variety of alicyclic compounds (Scheme 2). However, attempts at repeating the reactions reported by Bertozzi et al.[12] failed to afford the desired products.

In summary, we have developed a one-pot strategy for the preparation of polymer-bound cyclopropyl phenyl methanones. The protocol developed in this study provides an easy and efficient method for generating cyclopropyl phenyl methanone pharmacophore-based libraries as potential antitubercular agents. A full account with biological evaluations will be presented in due course.

2. Experimental

All compounds gave satisfactory spectral analyses. All resins were purchased from Nova Bio Chem.

2.1. Typical procedure for the preparation of 4-{[4-(cyclopropylcarbonyl)phenoxy]methyl}benzamide 4

To Rink amide resin (100 mg, 0.64 mmol/g) were added 4-formylbenzoic acid (30.6 mg, 3 equiv, 0.189 mmol) and HOBt (30.6 mg, 3 equiv, 0.444 mmol) dissolved in 500 μL of dry DMF followed by DIC (16.4 μL, 3 equiv, 0.189 mmol). The reaction mixture was allowed to stir at room temperature for 12 h. The resin was washed sequentially with DMF (5 × 2 mL), methanol (2 × 2 mL), DCM (3 × 2 mL), diethyl ether (5 × 2 mL) and then dried in vacuo. To the resin **1** in 2000 μL of dry THF/ethanol (4:1) was added sodium borohydride (14 mg, 4 equiv, 0.252 mmol) and the reaction mixture was stirred at rt for 12 h. The resin was then washed sequentially with dry DMF (5 × 2 mL), methanol (3 × 2 mL), DCM (3 × 2 mL) and diethyl ether (3 × 2 mL). After drying under vacuum, resin **2** was treated with sodium hydride (16.0 mg, 10 equiv, 0.63 mmol), 4-chloro-*p*-fluorobutyrophenone (12 μL, 3 equiv, 0.168 mmol) and TBAB (10 mg, 1.5 equiv, 0.84 mmol) in dry DMF 2000 μL. The resulting resin **3** was washed sequentially with DMF (5 × 2 mL), methanol (2 × 2 mL), water (5 × 2 mL), methanol (2 × 2 mL), DCM (3 × 2 mL) and diethyl ether (3 × 2 mL) and dried in vacuo overnight. The compound was cleaved with 50% or 20% TFA in DCM for 15 min to 2 h followed by lyophilization from *t*-BuOH/H_2O (4:1) to afford compound **4** as a white powder.

HPLC purity 98% (C18 reversed-phase column 7.8 × 150 mm, 5 μm) with a linear gradient 0–100% acetonitrile in water (v/v) over 40.0 min, flow rate 1.0 mL/min, t_R 14.99 min), ^{1}H NMR (300 MHz, $CDCl_3$: two drops of DMSO-d_6): δ 8.01 (d, J = 8.8 Hz, 2H, H-10), 7.89 (d, J = 8.8 Hz, 2H, H-4), 7.51 (d, J = 8.8 Hz, 2H, H-5), 7.13 (br s, 2H, H_{2a}NCO), 7.02 (d, J = 8.8 Hz, 2H, H-9), 6.30 (br s, 2H, H_{2b}NCO), 5.20 (s, 2H, H-7), 2.67 (m, 1H, H-13), 1.20 (m, 2H, H-14), 1.01 (m, 2H, H-15).

^{13}C NMR (75 MHz, $CDCl_3$): δ 198.3 (C=O), 173.0 ($CONH_2$), 141.1, 137.1, 134.2, 133.4 (ArC), 130.2, 127.9, 127.1, 114.5 (ArCH), 69.3 (OCH_2Ph), 16.7 (CH), 11.3 (CH_2 Cyclopropyl). MS (FAB): *m/z* 296 $[M+H]^+$, 318 $[M+Na]^+$.

2.2. Cyclopropyl-(4-hydroxy-phenyl)-methanone 6

HPLC purity 96% (C18 reversed-phase column 7.8 × 150 mm, 5 μm) with a linear gradient 10–100% MeOH in water (v/v) over 40 min, flow rate 1.0 mL/min, t_R 11.14 min), ^{1}H NMR (300 MHz, $CDCl_3$: two drops of DMSO-d_6): δ 7.91 (d, J = 8.4 Hz, 2H), 6.90 (d, J = 8.4 Hz, 2H), 4.29 (br s, 1H, –OH), 2.64 (m, 1H), 1.14 (m, 2H), 0.98 (m, 2H). ESMS: *m/z* 163.2 $[M+H]^+$.

2.3. Typical procedure for the preparation of cyclopropyl-[4-(4-hydroxybenzyloxy)-phenyl]-methanone 10

To a solution of PPh_3 (444.0 mg, 15.0 equiv, 1.70 mmol) and 4-hydroxybenzaldehyde (206.8 mg, 15.0 equiv, 1.70 mmol) dissolved in dry THF was added Wang resin (100.0 mg, 1.0 equiv, 1.13 mmol/g). Nitrogen was purged for 5 min and the reaction tube was maintained under ice cold conditions. After 10 min, DEAD (295.0 μL in 1 mL THF, 15.0 equiv, 1.7 mmol) was added dropwise whilst maintaining the temperature at 0 °C under N_2, over a period of 1 h. The reaction mixture was allowed to stir

at room temperature for 12 h. The resin was washed sequentially with DMF (5 × 2 mL), methanol (2 × 2 mL), DCM (3 × 2 mL) and diethyl ether (5 × 2 mL) then dried in vacuo. Completion of the synthesis followed and an identical procedure to that for preparation of compound **4** was used.

HPLC purity 95% (C18 reversed-phase column 7.8 × 150 mm, 5 μm) with a linear gradient 10–100% MeOH in water (v/v) over 40 min, flow rate 1.0 mL/min, t_R = 13.15 min.), ^{1}H NMR (300 MHz, $CDCl_3$: two drops of DMSO-d_6): δ 8.03 (d, J = 8.5 Hz, 2H), 7.10 (d, J = 8.5 Hz, 2H), 6.89 (d, J = 8.5 Hz, 2H), 6.79 (d, J = 8.8 Hz, 2H), 4.56 (s, 2H), 2.61 (m, 1H, H-13), 4.39 (br s, 1H, –OH), 1.15 (m, 2H), 0.96 (m, 2H). ESMS: m/z 269.4 $[M+H]^+$.

3. Compound 11

HPLC purity 88% (C18 reversed-phase 7.8 × 150 mm, 5 μm) with a linear gradient 10–100% MeOH in water (v/v) over 40 min, flow rate 1.0 mL/min, t_R = 10.24 min), ^{1}H NMR (300 MHz, $CDCl_3$: two drops of DMSO-d_6): δ 7.91 (d, J = 8.4 Hz, 2H), 7.49 (d, J = 8.4 Hz, 2H), 7.34 (d, J = 8.4 Hz, 2H), 7.14 (br s, 1H, H_{2a}NCO), 6.91 (d, J = 8.4 Hz, 2H), 6.31 (br s, 1H, H_{2b}NCO), 5.13 (s, 2H), 2.20 (m, 1H), 0.90 (m, 2H), 0.60 (q, J = 5.1 Hz, 2H). ESMS: m/z 311.6 $[M+H]^+$.

4. Compound 12

HPLC purity 75% (C18 reversed-phase 7.8 × 150 mm, 5 μm) with a linear gradient 10–100% MeOH in water (v/v) over 40 min, flow rate 1.0 mL/min, t_R = 20.31 min), ^{1}H NMR (300 MHz, $CDCl_3$: two drops of DMSO-d_6): δ 7.83 (d, J = 8.4 Hz, 2H), 7.56 (d, J = 8.4 Hz, 2H), 7.18 (d, J = 8.4 Hz, 2H), 7.13 (br s, 1H, H_{2a}NCO), 6.30 (br s, 1H, H_{2b}NCO), 6.89 (d, J = 8.4 Hz, 2H), 5.13 (s, 2H), 2.49 (d, J = 7.0 Hz 2H), 0.86 (m, 1H), 0.51 (m, 2H), 0.19 (q, J = 5.1 Hz, 2H). ESMS: m/z 282.1 $[M+1]^+$.

5. Compound 13

HPLC purity 72% (C18 reversed-phase column 7.8 × 150 mm, 5 μm) with a linear gradient 10–100% MeOH in water (v/v) over 40 min, flow rate 1.0 mL/min, t_R = 11.48 min), ^{1}H NMR (300 MHz, $CDCl_3$: two drops of DMSO-d_6): δ 8.0 (d, J = 8.4 Hz, 2H), 7.86 (d, J = 8.4 Hz, 2H), 7.57 (d, J = 8.4 Hz, 2H), 7.14 (br s, 1H, H_{2a}NCO), 7.03 (d, J = 8.4 Hz, 2H), 6.32 (br s, 1H, H_{2b}NCO), 5.23 (s, 2H), 3.76 (d, J = 3.2 Hz, 1H), 2.20 (m, 2H), 0.90 (m, 2H), 0.60 (q, J = 5.1 Hz, 2H). ESMS: m/z 298.5 $[M+H]^+$.

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