A Convenient Synthesis of 1-(4-Fluorophenyl)-2-(4-pyridyl)cyclopentene from Cyclopentanone

Bassam Abu Thaher,[a] Pierre Koch,[b] Vicente Del Amo,[c] Paul Knochel,[c] Stefan Laufer*[b]

[a] Faculty of Science, Chemistry Department, Islamic University of Gaza, Gaza Strip, Palestine

[b] Institute of Pharmacy, Department of Pharmaceutical and Medicinal Chemistry, Eberhard-Karls-University Tübingen, Auf der Morgenstelle 8, 72076 Tübingen, Germany
Fax +49(7071)295037; E-mail: stefan.laufer@uni-tuebingen.de

[c] Institute of Chemistry and Biochemistry, Ludwig-Maximilians-Universität München, Butenandtstraße 5–13, 81377 München, Germany

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Abstract: In the framework of investigating the role of pyridyl-substituted five-membered heterocycles as potential p38 mitogen-activated protein kinase inhibitors, we synthesized the disubstituted carbocyclic analogue, 1-(4-fluorophenyl)-2-(4-pyridyl)cyclopentene. A multistep synthesis of this compound starting from cyclopentanone is reported. Cyclopentanone was converted into 1-cyclopentenyl-4-fluorobenzene using a Grignard reaction. The oxidation of this product with hydrogen peroxide and formic acid gave 2-(4-fluorophenyl)cyclopentanone. This ketone was activated using a neodymium salt ($NdCl_3 \cdot 2LiCl$) and subsequently reacted with a complexed Grignard reagent (pyMgCl·LiCl) to give the corresponding cyclopentanol derivative. Finally, dehydration of the latter alcohol led to the title compound.

Key words: Grignard reactions, carbocycles, medicinal chemistry, neodymium salt, inhibitors

Extensive studies have been carried out on pyridyl-substituted five-membered heterocycles as p38 mitogen-activated protein (MAP) kinase inhibitors.[1] Figure 1 shows the most important interactions between these pyridyl-substituted heterocycles and the adenosine triphosphate (ATP) binding site of p38 MAP kinase.[2] The hydrogen bond between pyridine and Met109 plays a crucial role in the biological activity of the inhibitors. However, the importance of the second hydrogen bond between heteroatom X (N, O) of the heterocycle and Lys53 of p38 MAP kinase is still unclear and rather speculative.[2–6] Herein, we describe the preparation of 1-(4-fluorophenyl)-2-(4-pyridyl)cyclopentene (**5**) as a disubstituted five-membered carbocyclic scaffold, instead of the five-membered heterocycle, which could be considered a key compound for understanding the role of X and its interaction with the active site Lys53 of p38 MAP kinase. A series of symmetrical and unsymmetrical 1,2-disubstituted cycloalkenes have been previously reported.[7–10] Among these cycloalkenes, 1,2-diphenylcyclopentene was prepared by the intramolecular reductive coupling of dibenzoylpropane using titanium(III) chloride ($TiCl_3$)/lithium aluminum hydride by refluxing the reaction mixture for six days.[7] 1-Methyl-2-phenylcyclopentene was also prepared from

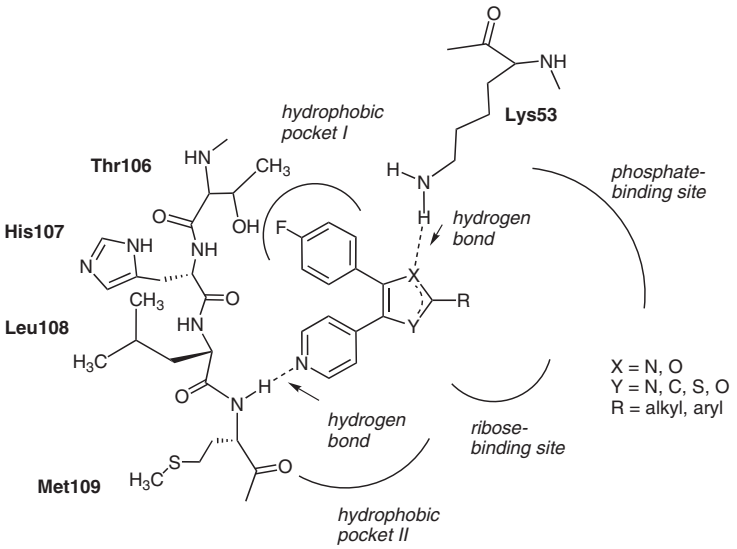

Figure 1 Important interactions between an inhibitor and the ATP binding site of p38 MAP kinase

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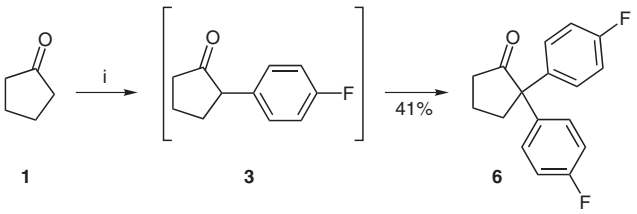
the corresponding dicarbonyl compound using $TiCl_3$/zinc–copper couple.[8] Via another route, disubstituted cyclopentene derivatives were prepared from 1,2-dibromocyclopentene by treatment with alkyl iodide or benzyl bromide in two separate reactions.[10] 1,2-Diphenylcyclopentene has been used as a starting material for preparation of the corresponding alcohol,[10] or to characterize the structure of its radical anion by electron spin resonance spectroscopy.[11] To the best of our knowledge, the synthesis of compound **5** has not yet been described. Accordingly, we report herein a new synthetic route for the preparation of the unsymmetrical pyridyl-substituted cyclopentene **5**.

The first step was accomplished easily by the addition of 4-fluorophenylmagnesium chloride to cyclopentanone (**1**). The reaction led to 1-cyclopentenyl-4-fluorobenzene (**2**), which was converted into 2-(4-fluorophenyl)cyclopentanone (**3**) by oxidation. The preparation of compound **4** was challenging. We eventually overcame this problem by treatment of the reactive reagent 4-pyridylmagnesium chloride–lithium chloride complex (pyMgCl·LiCl)[12] with ketone **3** in the presence of a neodymium salt ($NdCl_3$·2LiCl),[13] leading to the corresponding disubstituted cyclopentanol **4**. Finally, dehydration of alcohol **4** led to 1-(4-fluorophenyl)-2-(4-pyridyl)cyclopentene (**5**) as the major product (Scheme 1). Further work on the preparation of analogues of this compound for biological testing is currently underway.

The synthesis of compound **5** was quite challenging with the most-demanding step being the addition of the pyridyl substituent to cyclopentanone derivative **3**. After a long list of unsuccessful attempts we prepared this alcohol **4**, as mentioned above, and dehydrated it to yield the target molecule **5**.

We also tried to prepare 2-(4-fluorophenyl)cyclopentanone (**3**) by the palladium-catalyzed α-arylation of ketone **1**.[14] Heating ketone **1** with 1-bromo-4-fluorobenzene in the presence of a palladium catalyst [$Pd(dba)_2$], the ligand tri-*tert*-butylphosphine, and a base (K_3PO_4) in toluene yielded the disubstituted ketone 2,2-bis(4-fluorophenyl)cyclopentanone (**6**) instead of **3** (Scheme 2). Surprisingly, the disubstitution took place at the same carbon atom. Even the use of 1.5 equivalents of the base instead of 3 equivalents gave product **6**.

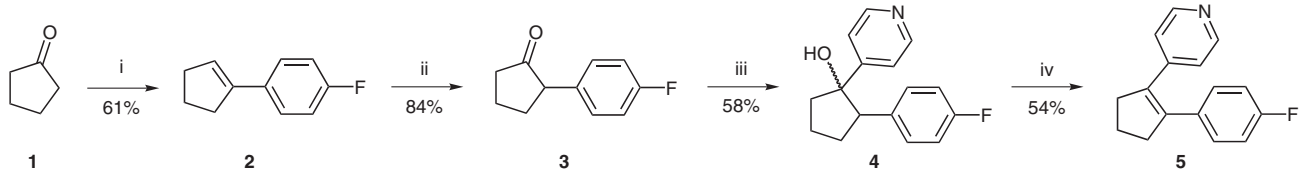
Starting from cyclopentanone (**1**), 1-cyclopentenyl-4-fluorobenzene (**2**) was obtained under standard Grignard reaction conditions. The oxidation of cyclopentene derivative **2** with hydrogen peroxide in the presence of formic acid yielded 2-(4-fluorophenyl)cyclopentanone (**3**) (Scheme 1).



Scheme 2 Palladium-catalyzed α-arylation of ketone **1**; *Reagents and conditions*: (i) 1-bromo-4-fluorobenzene (1 equiv), compound **1** (1.2 equiv), $Pd(dba)_2$ (1 mol%), P(*t*-Bu)$_3$ (1.2 mol%), K_3PO_4 (3 equiv), toluene, 100 °C, 7 h.

Many attempts to prepare the disubstituted alcohol **4** from the enolizable ketone **3** using the standard Grignard reagent (pyMgCl) were unsuccessful. Attempts to prepare 4-pyridylmagnesium chloride, bromide, and iodide from their corresponding 4-halopyridines using active Rieke magnesium[15] followed by the addition of ketone **3** gave no result. After workup of the reaction, only the starting material ketone **3** was recovered. Itami et al. reported the bromine–magnesium exchange of 4-bromopyridine with isopropylmagnesium chloride to give 4-pyridylmagnesium chloride.[16] The reaction of the Grignard reagent prepared by this method with ketone **3** was also unsuccessful. Another possible method of halogen–metal exchange described by Furukawa et al. involves the reaction of 4-iodopyridine with ethylmagnesium bromide in tetrahydrofuran (THF) at room temperature;[17] however, this approach was also unsuccessful, even when the reaction time and temperature were changed. Using an analogous method to Wibaut and Heeringa,[18] a red color appeared during the synthesis of pyMgCl which was a good indication of the formation of the organomagnesium compound. After adding ketone **3** to this Grignard solution, no product was detected.

To pave the way for obtaining alcohol **4**, we used recently reported THF-soluble lanthanide halides ($LnCl_3$·2LiCl, Ln = La, Nd). These convenient reagents were found to be very helpful for the addition of various Grignard reagents to inert and/or enolizable ketones.[13] The reaction of the more-reactive Grignard reagent pyMgCl·LiCl with ketone **3** in the presence of $LaCl_3$·2LiCl was unsuccessful. However, on addition of $NdCl_3$·2LiCl, ketone **3** was activated sufficiently. The addition of Grignard reagent pyMgCl·LiCl to the activated ketone **3** was complete after 10 hours at room temperature to give the disubstituted cyclopentanol **4** in about 60% yield. The addition is highly stereoselective and the *trans*-alcohol **4** is formed because of steric hindrance, as determined by X-ray crystal analysis.[19]



Scheme 1 *Reagents and conditions*: (i) 4-fluorophenylmagnesium bromide, Et_2O, reflux; (ii) H_2O_2, HCO_2H; (iii) $NdCl_3$·2LiCl, 1 h at r.t., then pyMgCl·LiCl (2 equiv), 0 °C, then 8–10 h at r.t.; (iv) TsOH, H_2SO_4, toluene, reflux, 1 h.

Attempts to dehydrate alcohol **4** with hydrochloric acid[20] or *p*-toluenesulfonic acid (TsOH)[21] under reflux failed. Dehydration of **4** by treatment with triphenylphosphine/iodine in dichloromethane was also unsuccessful,[22] as was the use of phosphorus pentoxide in dry diethyl ether. Finally, the dehydration of alcohol **4** with TsOH and few drops of concentrated sulfuric acid in toluene under reflux gave the desired alkene **5** as the major product.

All commercially available reagents and solvents were used without further purification. Melting points were determined with a Büchi melting point B-545 apparatus. IR spectra were recorded with a Perkin–Elmer Spectrum One [attenuated total reflection (ATR) technique] spectrometer, and ^{1}H and ^{13}C NMR spectra were obtained with a Bruker Advance 200 instrument. Chemical shifts are reported relative to the residual solvent peak. GC-MS analysis was carried out on a HP6890 series GC system to which a HP5973 mass selective detector was attached, and MS and HRMS were carried out on a Thermo Finnigan TSQ70 instrument.

1-Cyclopentenyl-4-fluorobenzene (2)[23]

To a stirred solution of 4-fluorophenylmagnesium bromide, synthesized from 1-bromo-4-fluorobenzene (17.5 g, 0.1 mol) and magnesium (2.4 g, 0.1 mol) in Et_2O, was added cyclopentanone (**1**) (6.73 g, 0.08 mol) in Et_2O (10 mL) dropwise. After the addition was complete, the mixture was refluxed for 2 h. The product was hydrolyzed by adding ice (10 g) and a precipitate formed. Then 6 M HCl was added until the precipitate dissolved. The organic phase was separated and the aqueous layer was extracted with Et_2O (3 × 50 mL). The combined organic phases were washed consecutively with sat. $NaHSO_3$ soln, sat. $NaHCO_3$ soln, and H_2O, dried (Na_2SO_4), and evaporated under vacuum. The crude product was purified by vacuum fractional distillation (79.1 °C, 240 Pa) and the collected colorless oil was crystallized in the refrigerator to afford the product.

Yield: 7.95 g (61%).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.98–2.16 (m, 2 H, H-4 cyclopentenyl), 2.58–2.64 (m, 2 H, H-5 cyclopentenyl), 2.72–2.80 (m, 2 H, H-3 cyclopentenyl), 6.15–6.20 (m, 1 H, H-2 cyclopentenyl), 7.03–7.14 (m, 2 H, H-3/H-5 4-FC_6H_4), 7.41–7.51 (m, 2 H, H-2/H-6 4-FC_6H_4).

2-(4-Fluorophenyl)cyclopentanone (3)

A mixture of 85% HCO_2H (20 mL) and 30% H_2O_2 (4.5 mL) was stirred and warmed at 40 °C for 10 min. Cyclopentene **2** (5.34 g, 30 mmol) was added portionwise while maintaining a temperature of 30–35 °C. The mixture was stirred for 1 h and then left without stirring at r.t. overnight. Then, Et_2O (50 mL) was added and the mixture was washed with sat. $NaHCO_3$ soln (3 × 30 mL). The aqueous layer was extracted with Et_2O (3 × 30 mL), and the collected organic phases were dried (Na_2SO_4) and evaporated under vacuum. The crude product was purified by flash chromatography (silica gel, hexane–EtOAc, 3:1). A thick colorless oil was obtained and was crystallized in the refrigerator to afford the product.

Yield: 4.50 g (84%).

IR (ATR): 2966, 2880, 1738, 1602, 1509, 1406, 1221, 1159, 1141, 1120, 866, 836, 818, 800 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.85–2.26 (m, 4 H, H-3/H-4 cyclopentyl), 2.41–2.49 (m, 2 H, H-5 cyclopentyl), 3.24–3.34 (m, 1 H, H-2 cyclopentyl), 6.96–7.05 (m, 2 H, H-3/H-5 4-FC_6H_4), 7.12–7.19 (m, 2 H, H-2/H-6, 4-FC_6H_4).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 20.6 (C-4 cyclopentyl), 31.6 (C-3 cyclopentyl), 38.1 (C-5 cyclopentyl), 54.4 (C-2 cyclopentyl), 115.3 (d, *J* = 21.3 Hz, C-3/C-5 4-FC_6H_4), 129.5 (d, *J* = 7.9 Hz, C-2/C-6 4-FC_6H_4), 133.9 (d, *J* = 3.4 Hz, C-1 4-FC_6H_4), 161.7 (d, *J* = 243.5 Hz, C-4 4-FC_6H_4), 217.6 (C-1 cyclopentyl).

GC-MS: *m*/*z* = 178.1 [M$^+$].

HRMS (EI): *m*/*z* calcd for $C_{11}H_{11}OF$: 178.0794; found: 178.0804.

2-(4-Fluorophenyl)-1-(4-pyridyl)cyclopentanol (4)

In a dried, argon-flushed 50-mL Schlenk flask equipped with a septum and a magnetic stirring bar was placed 0.33 M $NdCl_3$·2LiCl in THF (3.2 mL, 1.05 mmol). Neat cyclopentanone **3** (178 mg, 1.0 mmol) was added, and the resulting mixture was stirred for 1 h at r.t. To another dried, argon-flushed 50-mL Schlenk flask equipped with a septum and a magnetic stirring bar was added 4-iodopyridine (410 mg, 2.00 mmol). After cooling this second flask to 0 °C, *i*-PrMgCl·LiCl (1.39 M in THF, 1.6 mL, 2.20 mmol) was added and the mixture was stirred for 1 h at 0 °C. The flask containing the activated ketone was then cooled to 0 °C, and the prepared pyMgCl·LiCl in the second flask was quickly added to it dropwise. The resulting mixture was then stirred for 10 h at r.t. After the reaction was finished, sat. aq NH_4Cl (2 mL) and H_2O (10 mL) were added. The aqueous layer was extracted with Et_2O (4 × 10 mL), and the combined extracts were dried (Na_2SO_4) and evaporated to dryness. The crude product was purified by flash column chromatography (silica gel, hexane–EtOAc, 3:1) to give colorless needlelike crystals.

Yield: 148 g (58%).

Mp 147–148 °C.

IR (ATR): 3066 (br), 2968, 1602, 1554, 1507, 1410, 1311, 1214, 1157, 1060, 1022, 1005, 990, 818 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.93–2.47 (m, 7 H, H-3/H-4/H-5 cyclopentyl, OH), 3.37 (2d, J_1 = 11.2 Hz, J_2 = 7.7 Hz, 1 H, H-2 cyclopentyl), 6.81–6.97 (m, 4 H, 4-FC_6H_4), 7.26 (d, *J* = 4.55 Hz, 2 H, H-3/H-5 py), 8.46 (d, *J* = 4.55 Hz, 2 H, H-2/H-6 py).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 22.4 (C-4 cyclopentyl), 30.0 (C-3 cyclopentyl), 42.8 (C-5 cyclopentyl), 57.2 (C-2 cyclopentyl), 82.9 (C-1 cyclopentyl), 115.0 (d, *J* = 20.9 Hz, C-3/C-5 4-FC_6H_4), 120.3 (C-3/C-5 py), 130.0 (d, *J* = 7.9 Hz, C-2/C-6 4-FC_6H_4), 132.8 (d, *J* = 16 Hz, C-1 4-FC_6H_4), 149.0 (C-2/C-6 py), 156.1 (C-4 py), 161.9 (d, *J* = 244.2 Hz, C-4 4-FC_6H_4).

MS (FAB): *m*/*z* = 258.1 [M$^+$ + 1].

HRMS (EI): *m*/*z* calcd for $C_{16}H_{16}NOF$: 257.1216; found: 257.1226.

1-(4-Fluorophenyl)-2-(4-pyridyl)cyclopentene (5)

Alcohol **4** (100 mg, 0.39 mmol), one crystal of TsOH in toluene (15 mL), and 3–5 drops of concd H_2SO_4 were refluxed for 1 h. The mixture was then cooled to r.t., sat. $NaHCO_3$ soln (30 mL) was added, the mixture was extracted with EtOAc (3 × 30 mL). The organic phase was washed with H_2O (20 mL), dried (Na_2SO_4), and evaporated. The crude product was purified by thick-layer chromatography (silica gel, hexane–EtOAc, 1:1). The plates were put in the eluent 3 × for good separation to give a thick, colorless oil that solidified in the refrigerator to afford the product.

Yield: 50 mg (54%).

IR (ATR): 2954, 1593, 1508, 1409, 1222, 1158, 819 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.00–2.15 (m, 2 H), 2.70–2.77 (m, 4 H), 6.84–6.98 (m, 2 H), 7.04–7.15 (m, 4 H), 8.41–8.43 (m, 2 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 21.9 (cyclopentenyl), 37.8 (cyclopentenyl), 39.8 (cyclopentenyl), 115.3 (d, *J* = 21.3 Hz, C-3/C-5 4-FC_6H_4), 122.8 (C-3/C-5 py), 129.5 (d, *J* = 7.9 Hz, C-2/C-6 4-FC_6H_4), 133.2 (d, *J* = 3.5 Hz, C-1 4-FC_6H_4), 134.5, 141.9, 146.5, 148.6 (C-2/C-6 py), 161.9 (d, *J* = 245.7 Hz, C-4 4-FC_6H_4).

MS (FAB): *m*/*z* = 240.2 [M$^+$ + 1].

HRMS (EI): *m*/*z* calcd for $C_{16}H_{14}NF$: 239.1110; found: 239.1096.

2,2-Bis(4-fluorophenyl)cyclopentanone (6)

In a dried, argon-flushed Schlenk flask equipped with a magnetic stirring bar was placed K_3PO_4 (9.50 g, 45 mmol). Toluene (40 mL), 1-bromo-4-fluorobenzene (2.62 g, 15 mmol), cyclopentanone (1.51 g, 18 mmol), P(*t*-Bu)$_3$ (0.04 M in toluene, 4.5 mL, 0.18 mmol), and Pd(dba)$_2$ (86 mg, 0.15 mmol) were added, and the mixture was stirred at 100 °C for 7 h and then cooled to r.t. The mixture was filtered through Celite, washed with toluene, and concentrated in vacuo. Purification by chromatography (silica gel, hexane–EtOAc, 3:1) afforded a colorless oil.

Yield: 0.54 g (41%).

IR (ATR): 3050, 2050, 1891, 1737, 1596, 1495, 1395, 1321, 1226, 1158, 1125, 1108, 1015, 1005, 819, 803, 764.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.87–2.01 (m, 2 H, H-4 cyclopentyl), 2.45 (t, *J* = 7.6 Hz, 2 H, H-3 cyclopentyl), 2.68 (t, *J* = 6.6 Hz, 2 H, H-5 cyclopentyl), 6.95–7.03 (m, 4 H, H-3/H-3′/H-5/H-5′ 4-F C_6H_4), 7.17–7.22 (m, 4 H, H-2/H-2′/H-6/H-6′ 4-F C_6H_4).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 18.7 (C-4 cyclopentyl), 37.9 (C-3 cyclopentyl), 38.2 (C-5 cyclopentyl), 61.1 (C-2 cyclopentyl), 115.2 (d, *J* = 21.2 Hz, C-3/C-3′/C-5/C-5′ 4-FC_6H_4), 129.5 (d, *J* = 7.9 Hz, C-2/C-2′/C-6/C-6′ 4-FC_6H_4), 137.7 (d, *J* = 3.2 Hz, C-1/C-1′ 4-FC_6H_4), 161.6 (d, *J* = 244.7 Hz, C-4/C-4′ 4-FC_6H_4), 217.3 (C-1 cyclopentyl).

HRMS (EI): *m*/*z* calcd for $C_{17}H_{14}OF_2$: 272.1013; found: 272.1015.

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