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Aromatic amines as nucleophiles in the Bargellini reaction

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ABSTRACT

Aromatic amines can be employed in the Bargellini reaction to generate useful intermediates. Rapid, practical access to functionalised, privileged structures may have significant utility in the synthesis of drug-like molecules. An improved synthesis of carfentanil analogues illustrates this point.

At the start of the 20th Century, Bargellini reported the condensation of phenols with chloroform and acetone in the presence of sodium hydroxide to furnish α-phenoxyisobutyric acids (Scheme 1).[1] This represents an unusual and useful synthesis of ethers α- to sterically hindered carboxylic acids.

Application of the Bargellini reaction to prepare griseofulvin analogues using substituted phenols as nucleophiles was reported by Korger (Scheme 2).[2]

Since the initial report, variants of both nucleophiles and ketones in the Bargellini reaction have been investigated. Youseff used phenols as nucleophiles and cyclopentanone as the ketone.[3] Grella investigated a wider range of cyclic ketones under Bargellini reaction conditions.[4] Reeve and Corey used potassium amide and sodium azide, respectively, as nucleophiles in alternative approaches to α-amino acids.[5,6]

Herein, we report a further extension in the scope of the Bargellini reaction in terms of both nucleophiles and reactive ketones. The examples synthesised through extending the reaction scope may be of utility in the synthesis of privileged drug-like structures. Improvements have also been found in the isolation of the reaction products based on the structure of the nucleophile and ketone.

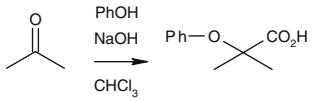
As part of a drug discovery programme, our laboratory has been preparing α-phenoxy carboxylic acids employing the Bargellini reaction using substituted phenols and cyclic ketones (Scheme 3).

The Bargellini reaction offers a multi-component, atom efficient synthesis of molecules with significantly increased complexity, diversity and functionality. It was found that phenols, thiophenols and hydroxy-heterocycles all reacted in acceptable yields with two model ketones (cyclohexanone and *N*-^{t}butyloxycarbonyl-4-piperidone). This expands the scope of nucleophiles that are known to work in the Bargellini reaction (Table 1, entries 1–4).[7]

Significantly, we observed that in the reactions of these nucleophiles with *N*-^{t}butyloxycarbonyl-protected piperidinone and cyclohexanone, the sodium salt of the product precipitated from the reaction mixture allowing easy isolation of the target molecule in very high purity, without the need for crystallisation or chromatography.

We further extended the range of novel nucleophiles by reacting substituted anilines with the Boc-protected piperidinone. Once again, isolation by precipitation of the sodium salt furnished pure products using minimal purification. There are no examples in the chemical literature employing anilines in the Bargellini reaction. The resultant products have four points of diversity and offer the opportunity to explore chemical space in a one-pot, scaleable procedure from readily available starting materials. We have prepared a number of analogues using anilines (Table 1, entries 5–10).[7] The structures of the products were confirmed by NMR studies and accurate mass spectrometry.

It is of note that when using aliphatic or non-aromatic nucleophiles with the Boc-protected piperidinone, sodium salts did not precipitate. For example when benzyl alcohol or trifluoroacetamide was employed as nucleophile product isolation was more protracted and yields were between 10% and 20%.



Scheme 1.

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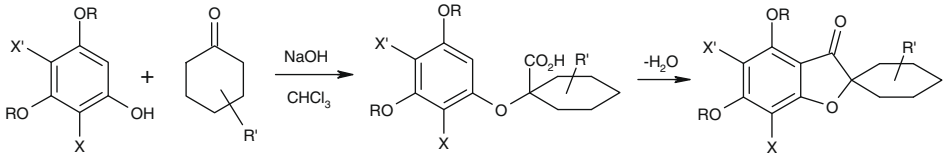
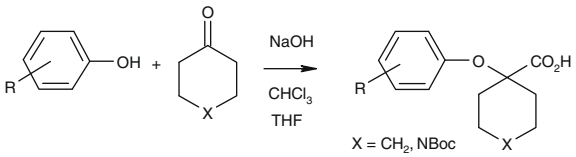


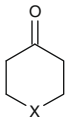
Scheme 2.



Scheme 3.

In order to test the scope of aromatic nucleophiles further with our model ketone we prepared analogues using poorly nucleophilic amino heterocycles (Table 2, entries 1–3). Weak, sterically hindered nucleophiles still gave products in useful yields. The successful reaction with pyrazole showed that the nucleophilic atom need not be restricted to being a substituent on an aromatic ring (Table 2, entry 4).

Table 1
Bargellini reaction of phenols and anilines with ketones



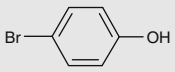
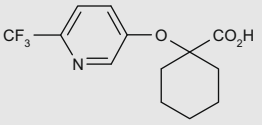
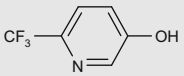
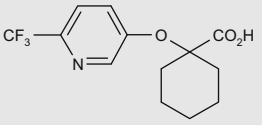
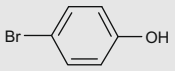
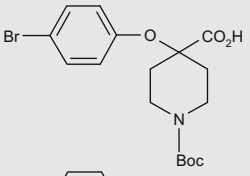
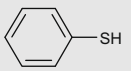
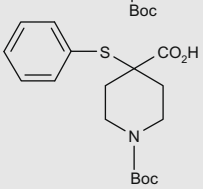
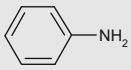
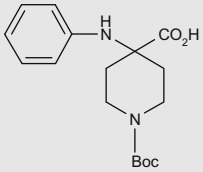
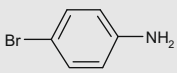
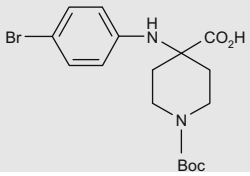
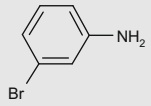
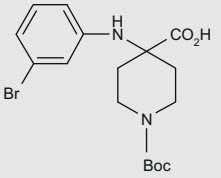
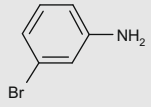
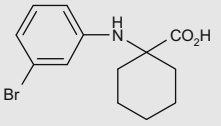
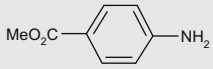
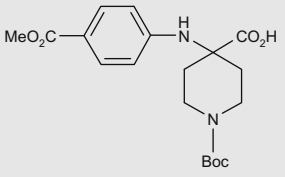
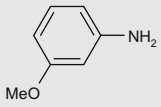
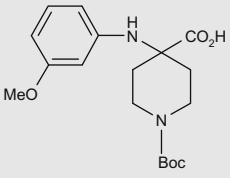
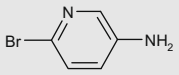
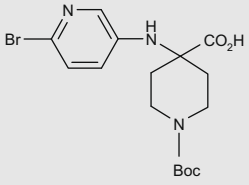
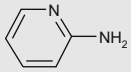
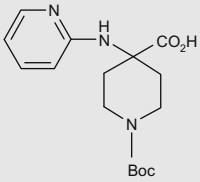
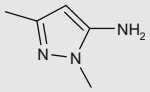
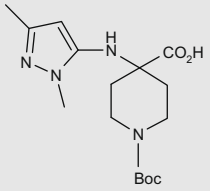
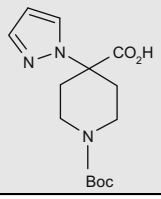
Entry	Nucleophile	X	Product	% Yield
1		CH_2		44
2		CH_2		45
3		NBoc		56
4		NBoc		71
5		NBoc		70
6		NBoc		56

Table 1 (*continued*)

Entry	Nucleophile	X	Product	% Yield
7		NBoc		67
8		CH_2		58
9		NBoc		56
10		NBoc		99

Reaction conditions: nucleophile (6 mmol), ketone (18 mmol), chloroform (30 mmol) and sodium hydroxide (30 mmol) in THF (40 ml) from 0 °C to room temperature.

Table 2
Bargellini reaction of heterocyclic nitrogen nucleophiles with *N*-^{t}butylcarbonyl-4-piperidinone

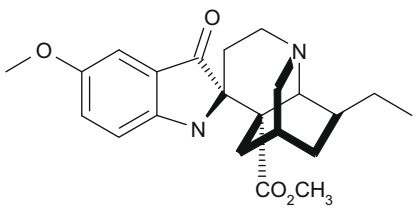
Entry	Nucleophile	Product	% Yield
1			46
2			72
3			35
4			56

Reaction conditions: nucleophile (6 mmol), ketone (18 mmol), chloroform (30 mmol) and sodium hydroxide (30 mmol) in THF (40 ml) from 0 °C to room temperature.

Using this methodology a range of aromatic nitrogen functionality can be used successfully to give products in moderate to good yields. In all cases illustrated, purification by filtration of the precipitated sodium salt was simple and efficient, delivering material of high purity.

The flexibility of this extension of the Bargellini reaction may have application in the synthesis and scale-up of drug-like molecules. An improved synthesis of carfentanil analogues illustrates this point (Scheme 4). The preferable use of Boc over benzyl as a nitrogen-protecting group and the elimination of a Strecker reaction and its use of cyanide are just two examples of how the synthesis of this classical G protein-coupled receptor template[8] has been improved upon.

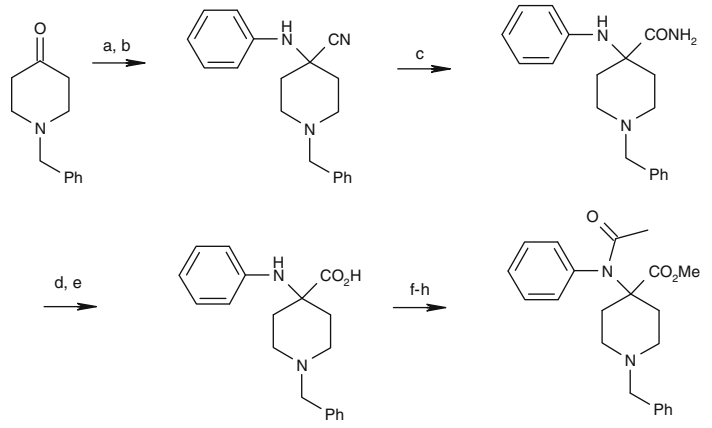
Application in natural product synthesis may also be possible. By analogy to Korger's work on griseofulvin using phenols as nucleophiles, analogues of rupicoline could potentially be accessed using our extension of the Bargellini reaction employing suitably substituted anilines.



Rupicoline

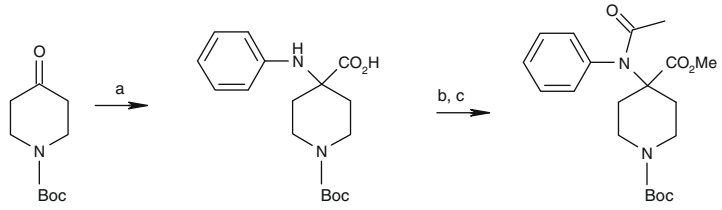
In conclusion, we have discovered that aromatic amines can be employed in the Bargellini reaction to generate useful intermediates. Rapid, practical access to these functionalised, privileged structures may have significant utility in the synthesis of drug-like molecules.

Representative traditional route



a. Aniline, KCN, AcOH, 2 h b. EtOH recryst. c. cH_2SO_4 d. KOH, ethylene glycol, 150 °C 4 d e. H_2O, AcOH f. NaH, DMF g. MeI h. Propionic anhydride, reflux, 3 d.

Improved, aniline Bargellini route



a. Aniline, NaOH, $CHCl_3$, THF, 70% b. Propionic anhydride, Et_3N, EtOAc, 1h c. MeOH, 2 h, 70% over 2 steps.

Scheme 4.

Acknowledgments

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References and notes

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4. Grella, M. P.; Safo, M. K.; Danso-Danquah, R.; Joshi, G. S.; Kister, J.; Marden, M. C.; Abraham, D. J. *J. Med. Chem.* **2000**, *43*, 4726.
5. Reeve, W. *Synthesis* **1971**, 131.
6. Corey, E. J.; Link, J. O. *J. Am. Chem. Soc.* **1992**, *114*, 1906.
7. *Typical procedures*: 4-Bromophenol (1.0 g, 6 mmol) was dissolved in THF (40 ml) and cooled in an ice bath. NaOH powder (1.16 g, 30 mmol) and *N*-^{t}butyloxycarbonyl-4-piperidone (3.58 g, 18 mmol) were added. Chloroform (2.32 ml, 30 mmol) was added dropwise and the reaction mixture was stirred at 0 °C for 1 h and then stirred at room temperature for 18 h. The precipitated solid was filtered off and dissolved in water. The solution was extracted with diethyl ether (3 × 20 ml) and the aqueous layer was separated. The aqueous layer was cooled and acidified with hydrochloric acid (2 M) to pH 1 and extracted with EtOAc (40 ml). The EtOAc layer was separated, washed with brine (3 × 10 ml), dried (Na_2SO_4), filtered and concentrated in vacuo to yield 1.47 g (56%) of a pale yellow solid. An analytical sample was obtained by crystallisation from hexane/ethyl acetate (4:1) as a colourless solid. TLC heptane + AcOH 5%:ethyl acetate 1:1, Rf 0.5. MS (ESI): *m/z* 400 $[^{81}Br\ M\text{-}H]^+$. LC-MS ELSD 100% *m/z* 400 $[^{81}Br\ M\text{-}H]^+$. ^1H NMR (400 MHz, $CDCl_3$) 7.38 (d, 2H, *J* = 9 Hz); 6.79 (d, 2H, *J* = 9 Hz); 3.93–3.80 (m, 2H); 3.19–3.13 (m, 2H); 2.17–2.04 (m, 4H); 1.45 (s, 9H). Microanalysis. calcd C, 51.01; H, 5.54; N, 3.50%. Found C, 51.06; H 5.59; N, 3.49%. 4-Bromoaniline (500 mg, 3 mmol) was dissolved in THF (40 ml) and cooled in an ice bath. NaOH powder (581 mg, 15 mmol) and *N*-^{t}butyloxycarbonyl-4-piperidone (1.79 g, 9 mmol) were added. Chloroform (1.16 ml, 15 mmol) was added dropwise and the reaction mixture was stirred at 0 °C for 1 h and then stirred at room temperature for 18 h. The precipitated solid was filtered off and dissolved in water. The solution was extracted with diethyl ether (3 × 20 ml) and the aqueous layer was separated. The aqueous layer was cooled and acidified with AcOH to pH 3 and extracted with EtOAc (40 ml). The EtOAc layer was separated, washed with brine (3 × 10 ml), dried (Na_2SO_4), filtered and concentrated in vacuo to give 651 mg (56%) of a yellow foam. TLC heptane + AcOH 5%:ethyl acetate 1:1, Rf 0.5. MS (ESI): *m/z* 397 $[^{79}Br\ M\text{-}H]^+$. LC-MS ELSD 100% (ESI) *m/z* 397 $[^{79}Br\ M\text{-}H]^+$. HRMS (ESI) *m/z* 399.0913 $[^{79}Br\ M + H]^+$ for $^{12}C_{17}H_{24}N_2O_4{}^{79}Br$. ^1H NMR (400 MHz, $CDCl_3$) 7.28 (d, 2H, *J* = 9 Hz); 6.54 (d, 2H, *J* = 9 Hz); 3.78–3.71 (m, 2H); 3.29–3.23 (m, 2H); 2.19–2.12 (m, 2H); 1.96–1.90 (m, 2H); 1.45 (s, 9H). Structure was further confirmed by NMR studies using ^{13}C, gCOSY, HSQC and HMBC.
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