An Environmentally Friendly Synthesis of Michler's Ketone Analogues in Water

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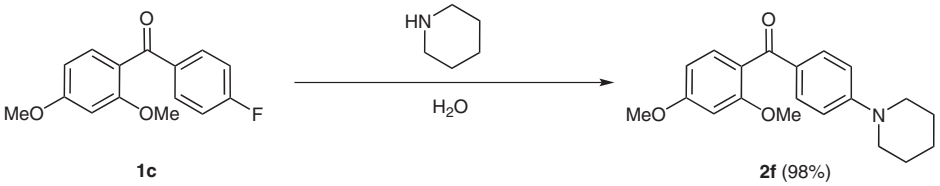
Abstract: An environmentally friendly method for the synthesis of a series of novel, unsymmetrical Michler's ketone analogues, [4-(dialkylamino)phenyl](aryl)methanones, via nucleophilic aromatic substitution of (fluorophenyl)(aryl)methanones with various amines in water is described. The reaction products are formed in high yields and additional purification is not required. The aqueous solvent and unreacted amines can be recycled.

Key words: Michler's ketone, nucleophilic substitution, environmentally friendly, secondary amines, water



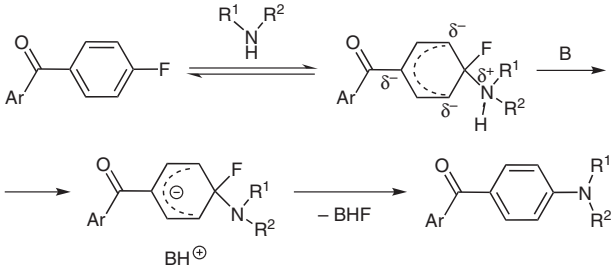
Scheme 1 Synthesis of benzophenone **2f** in water

Michler's ketone, 4,4′-bis(dimethylamino)benzophenone, was originally synthesized by Michler from *N*,*N*-dimethylaniline and phosgene.[1] This particular ketone and its analogs are used in the production of cyanine and triarylmethane dyes and pigments,[2] photochromic naphthopyrans,[3] sensitizers[4] or photoinitiators for polymerization,[5] and are widely studied for their xerographic properties.[6] Some of the dyes prepared from Michler's ketone find application in medicine as cholinesterase inhibitors[7] and antitumor agents.[8]

Michler's ketone and its analogues are synthesized mainly by the reaction of halobenzophenones with secondary amines. Such nucleophilic substitution reactions in aromatic compounds are usually carried out in polar aprotic solvents (DMSO or tetramethylene sulfone,[9] DMF,[10] MeCN[11]) or in the amine itself.[12] The reaction gives the expected arylamines in higher yields when carried out at high pressure.[13] There is also a catalytic variant of the reaction.[14] All these methods utilize rather hazardous and toxic solvents and/or catalysts that are incompatible with regards to green chemistry.[15,16]

In continuation of our studies[17] on the synthesis of new dyes including photochromic compounds, we have developed an environmentally friendly method for the formation of diarylketones bearing dialkylamino groups which can serve as starting materials for the preparation of various dyes including photochromic naphthopyrans. The method involves the reaction of fluorobenzophenones with secondary amines in water (Scheme 1, Table 1).

It is known that this type of reaction occurs via an S_NAr (addition–elimination) mechanism[18,19] (Scheme 2).



Scheme 2 The S_NAr (addition–elimination) mechanism for nucleophilic substitution in aromatic compounds

In most cases of such nucleophilic substitution reactions, sodium or potassium carbonate, triethylamine or 1,4-diazabicyclo[2.2.2]octane are utilized as bases.[19] We found that in this reaction the amine plays the role of both nucleophile and base. A four-fold excess of the amine leads to a significant increase in the reaction rate and target product yields. Another advantage of using the amine as the base in this process is the ability to recover any unre-

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acted amine thereby reducing waste. Thus, after work-up of the reaction mixture and removal of the product by filtration, the mother liquor can be treated with aqueous sodium bicarbonate solution and the resulting suspension of amine in water can be reused.

Table 1 Nucleophilic Substitution of the Fluorine Atom in Benzophenones with Secondary Amines in Water

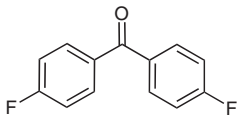
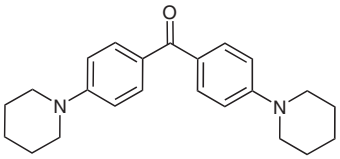
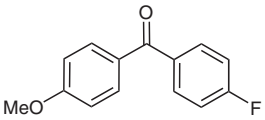
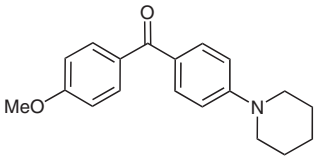
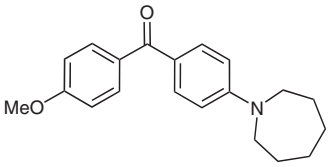
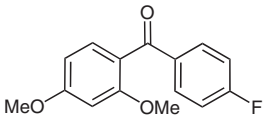
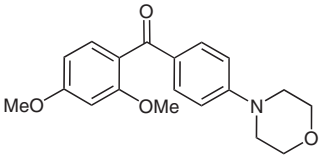
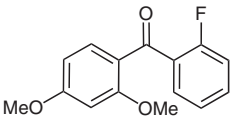
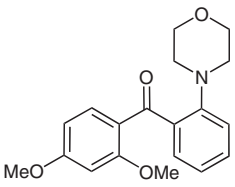
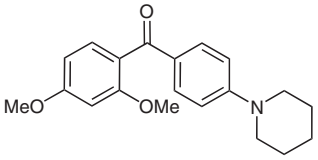
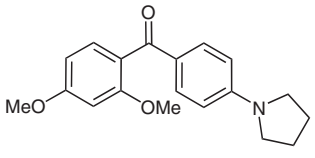
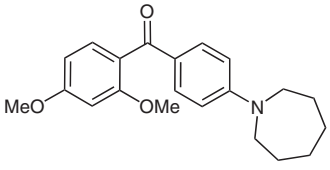
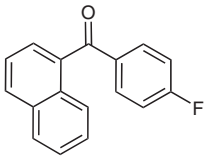
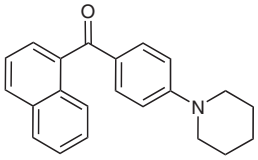
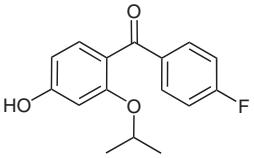
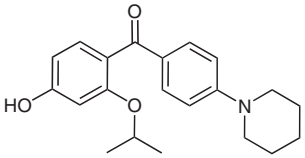
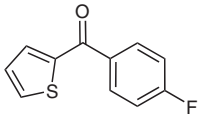
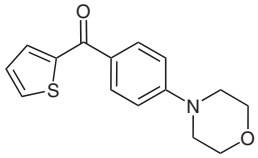
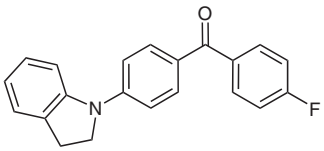
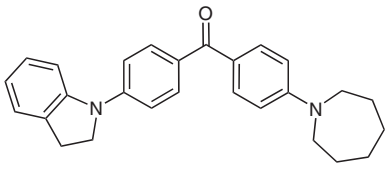
Entry	Substrate	Product	Yield (%)
1	 **1a**	 **2a**	96
2	 **1b**	 **2b**	88
3	**1b**	 **2c**	90
4	 **1c**	 **2d**	93
5	 **1d**	 **2e**	81
6	**1c**	 **2f**	98
7	**1c**	 **2g**	95
8	**1c**	 **2h**	99

Table 1 Nucleophilic Substitution of the Fluorine Atom in Benzophenones with Secondary Amines in Water (continued)

Entry	Substrate	Product	Yield (%)
9	 **1e**	 **2i**	83
10	 **1f**	 **2j**	96
11	 **1g**	 **2k**	90
12	 **1h**	 **2l**	80

The use of water as a solvent not only makes these reaction conditions more environmentally friendly, but in many cases, shows significant beneficial effects in terms of the reaction rates and selectivity.[20] An important role is played by 'on water' processes where the reactants are not soluble in water.[20a] There are several examples of using water as the solvent in nucleophilic substitution in aromatics,[21] and in these cases, the reaction rate increased compared to those in other polar solvents.

In conclusion, we have developed an environmentally friendly method for the preparation of Michler's ketone and its analogues in excellent yields and high purities under mild reaction conditions.

Commercially available reagents (Acros or Merck) were used. Melting points were measured on a Boetius hot stage apparatus and are uncorrected. Benzophenones **1** were prepared by acylation of the appropriate arene with 2- or 4-fluorobenzoyl chloride according to literature procedures.[22] [4-(2,3-Dihydroindol-1-yl)phenyl](4-fluorophenyl)methanone was synthesized by reaction of 4,4′-difluorobenzophenone with indoline and NaH in DMSO.[23] ^{1}H NMR spectra were recorded on a Bruker AM-300 spectrometer. Mass spectra were obtained on a Kratos mass spectrometer (70 eV) with direct sample injection into the ion source. Microanalyses were obtained using a PerkinElmer 2400 Series II CHNS/O Elemental Analyzer. Petroleum ether (PE) refers to the fraction boiling in the 40–70 °C range.

Michler's Ketone Analogues; General Procedure

A mixture of 2- or 4-fluorobenzophenone **1** (5 mmol), secondary amine [20 mmol (40 mmol in the case of morpholine)] and H_2O (5 mL) was heated at reflux temperature for 30 h and then poured into cold H_2O (250 mL). The progress of the reaction was monitored by TLC (eluent: PE–EtOAc, 3:1). The resulting solid precipitate was isolated by filtration, washed with H_2O (50 mL) and PE (50 mL), and dried.

Bis[4-(piperidin-1-yl)phenyl]methanone (2a)

Yellowish powder; yield: 1.7 g (96%); mp 151.5–152.5 °C (PE) (Lit.[9a] 152 °C).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.60–1.76 (m, 12 H, 6 × CH_2), 3.35 (t, *J* = 5.1 Hz, 8 H, 4 × CH_2), 6.89 (d, *J* = 8.8 Hz, 4 H, ArH), 7.75 (d, *J* = 8.8 Hz, 4 H, ArH).

(4-Methoxyphenyl)[4-(piperidin-1-yl)phenyl]methanone (2b)

White powder; yield: 1.3 g (88%); mp 109–110 °C (PE).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.60–1.77 (m, 6 H, 3 × CH_2), 3.37 (t, *J* = 5.5 Hz, 4 H, 2 × CH_2), 3.88 (s, 3 H, CH_3), 6.89 (d, *J* = 8.8 Hz, 2 H, ArH), 6.96 (d, *J* = 8.8 Hz, 2 H, ArH), 7.72–7.82 (m, 4 H, ArH).

MS (EI, 70 eV): *m/z* (%) = 295 (56) $[M]^+$, 280 (77) $[M - Me]^+$, 264 (48) $[M - OMe]^+$, 188 (100).

Anal. Calcd for $C_{19}H_{21}NO_2$: C, 77.26; H, 7.17; N, 4.74. Found: C, 77.41; H, 7.13; N, 4.61.

[4-(Azepan-1-yl)phenyl](4-methoxyphenyl)methanone (2c)

Yellow powder; yield: 1.4 g (90%); mp 85–86 °C (PE).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.50–1.64 (m, 4 H, 2 × CH_2), 1.75–1.89 (m, 4 H, 2 × CH_2), 3.54 (t, *J* = 5.9 Hz, 4 H, 2 × CH_2), 3.88

(s, 3 H, CH_3), 6.69 (d, J = 8.8 Hz, 2 H, ArH), 6.96 (d, J = 8.8 Hz, 2 H, ArH), 7.72–7.82 (m, 4 H, ArH).

MS (EI, 70 eV): m/z (%) = 309 (67) $[M]^+$, 294 (58) $[M - Me]^+$, 278 (39) $[M - OMe]^+$, 202 (100).

Anal. Calcd for $C_{20}H_{23}NO_2$: C, 77.64; H, 7.49; N, 4.53. Found: C, 77.33; H, 7.51; N, 4.65.

(2,4-Dimethoxyphenyl)(4-morpholinophenyl)methanone (2d)
White powder; yield: 1.5 g (93%); mp 86–87 °C (PE).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.29 (t, J = 5.1 Hz, 4 H, 2 × CH_2), 3.68 (s, 3 H, CH_3), 3.73 (t, J = 5.1 Hz, 4 H, 2 × CH_2), 3.84 (s, 3 H, CH_3), 6.62 (dd, J = 2.2, 8.1 Hz, 1 H, ArH), 6.67 (d, J = 2.2 Hz, 1 H, ArH), 6.95 (d, J = 8.8 Hz, 2 H, ArH), 7.19 (d, J = 8.1 Hz, 1 H, ArH), 7.57 (d, J = 8.8 Hz, 2 H, ArH).

MS (EI, 70 eV): m/z (%) = 327 (100) $[M]^+$, 312 (78) $[M - Me]^+$, 296 (44) $[M - OMe]^+$.

Anal. Calcd for $C_{19}H_{21}NO_4$: C, 69.71; H, 6.47; N, 4.28. Found: C, 69.81; H, 6.45; N, 4.44.

(2,4-Dimethoxyphenyl)(2-morpholinophenyl)methanone (2e)
Yellow powder; yield: 1.3 g (81%); mp 82–83 °C (PE).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.87 (t, J = 4.6 Hz, 4 H, 2 × CH_2), 3.34 (t, J = 4.6 Hz, 4 H, 2 × CH_2), 3.60 (s, 3 H, CH_3), 3.86 (s, 3 H, CH_3), 6.42 (d, J = 2.0 Hz, 1 H, ArH), 6.50 (dd, J = 2.2, 8.5 Hz, 1 H, ArH), 6.96 (d, J = 7.9 Hz, 1 H, ArH), 7.07 (t, J = 7.2 Hz, 1 H, ArH), 7.35–7.47 (m, 2 H, ArH), 7.55 (d, J = 8.5 Hz, 2 H, ArH).

MS (EI, 70 eV): m/z (%) = 327 (100) $[M]^+$, 312 (63) $[M - Me]^+$, 296 (56) $[M - OMe]^+$.

Anal. Calcd for $C_{19}H_{21}NO_4$: C, 69.71; H, 6.47; N, 4.28. Found: C, 69.99; H, 6.37; N, 3.96.

(2,4-Dimethoxyphenyl)[4-(piperidin-1-yl)phenyl]methanone (2f)
White powder; yield: 1.6 g (98%); mp 112–113 °C (PE).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.60–1.75 (m, 6 H, 3 × CH_2), 3.30–3.42 (m, 4 H, 2 × CH_2), 3.74 (s, 3 H, CH_3), 3.86 (s, 3 H, CH_3), 6.50–6.56 (m, 2 H, ArH), 6.82 (d, J = 8.5 Hz, 2 H, ArH), 7.30 (d, J = 9.2 Hz, 1 H, ArH), 7.73 (d, J = 8.5 Hz, 2 H, ArH).

MS (EI, 70 eV): m/z (%) = 325 (100) $[M]^+$, 310 (54) $[M - Me]^+$, 294 (47) $[M - OMe]^+$.

Anal. Calcd for $C_{20}H_{23}NO_3$: C, 73.82; H, 7.12; N, 4.30. Found: C, 74.09; H, 7.24; N, 4.47.

(2,4-Dimethoxyphenyl)[4-(pyrrolidin-1-yl)phenyl]methanone (2g)
Yellowish powder; yield: 1.5 g (95%); mp 129–130 °C (PE).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.95–2.09 (m, 4 H, 2 × CH_2), 3.28–3.42 (m, 4 H, 2 × CH_2), 3.74 (s, 3 H, CH_3), 3.86 (s, 3 H, CH_3), 6.44–6.57 (m, 4 H, ArH), 7.28 (d, J = 7.9 Hz, 1 H, ArH), 7.74 (d, J = 8.5 Hz, 2 H, ArH).

MS (EI, 70 eV): m/z (%) = 311 (60) $[M]^+$, 296 (100) $[M - Me]^+$, 174 (57).

Anal. Calcd for $C_{19}H_{21}NO_3$: C, 73.29; H, 6.80; N, 4.50. Found: C, 73.41; H, 6.73; N, 4.30.

[4-(Azepan-1-yl)phenyl](2,4-dimethoxyphenyl)methanone (2h)
Yellowish powder; yield: 1.7 g (99%); mp 98–99 °C (PE).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.47–1.63 (m, 4 H, 2 × CH_2), 1.69–1.88 (m, 4 H, 2 × CH_2), 3.51 (t, J = 6.2 Hz, 4 H, 2 × CH_2), 3.74 (s, 3 H, CH_3), 3.85 (s, 3 H, CH_3), 6.47–6.56 (m, 2 H, ArH), 6.62 (d, J = 9.0 Hz, 2 H, ArH), 7.27 (d, J = 9.0 Hz, 1 H, ArH), 7.72 (d, J = 9.0 Hz, 2 H, ArH).

MS (EI, 70 eV): m/z (%) = 339 (66) $[M]^+$, 324 (100) $[M - Me]^+$, 308 (68) $[M - OMe]^+$.

Anal. Calcd for $C_{21}H_{25}NO_3$: C, 74.31; H, 7.42; N, 4.13. Found: C, 74.24; H, 7.39; N, 4.51.

Naphthalen-1-yl[4-(piperidin-1-yl)phenyl]methanone (2i)
Yellowish powder; yield: 1.3 g (83%); mp 78–79 °C (PE).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.64–1.73 (m, 6 H, 3 × CH_2), 3.35–3.43 (m, 4 H, 2 × CH_2), 6.83 (d, J = 9.2 Hz, 2 H, ArH), 7.44–7.56 (m, 4 H, ArH), 7.78 (d, J = 9.2 Hz, 2 H, ArH), 7.88–8.03 (m, 3 H, ArH).

MS (EI, 70 eV): m/z (%) = 315 (100) $[M]^+$.

Anal. Calcd for $C_{22}H_{21}NO$: C, 83.78; H, 6.71; N, 4.44. Found: C, 83.86; H, 6.68; N, 4.26.

(4-Hydroxy-2-isopropoxyphenyl)[4-(piperidin-1-yl)phenyl]methanone (2j)
Yellow powder; yield: 1.6 g (96%); mp 103.5–104.5 °C (PE).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.38 (d, J = 6.2 Hz, 6 H, 2 × CH_3), 1.64–1.76 (m, 6 H, 3 × CH_2), 3.37 (t, J = 5.1 Hz, 4 H, 2 × CH_2), 4.63 (sept, J = 6.2 Hz, 1 H, CH), 6.38 (dd, J = 2.2, 8.8 Hz, 1 H, ArH), 6.49 (d, J = 2.2 Hz, 1 H, ArH), 6.91 (d, J = 8.8 Hz, 2 H, ArH), 7.57–7.68 (m, 3 H, ArH), 12.51 (br s, 1 H, OH).

MS (EI, 70 eV): m/z (%) = 339 (69) $[M]^+$, 296 (20) $[M - i\text{Pr}]^+$, 161 (100).

Anal. Calcd for $C_{21}H_{25}NO_3$: C, 74.31; H, 7.42; N, 4.13. Found: C, 74.22; H, 7.48; N, 4.07.

(4-Morpholinophenyl)(thien-2-yl)methanone (2k)
Yellow powder; yield: 1.2 g (90%); mp 122–123 °C (PE).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.32 (t, J = 5.0 Hz, 4 H, 2 × CH_2), 3.87 (t, J = 5.0 Hz, 4 H, 2 × CH_2), 6.92 (d, J = 9.1 Hz, 2 H, ArH), 7.15 (dd, J = 3.9, 5.3 Hz, 1 H, ArH), 7.63–7.68 (m, 2 H, ArH), 7.89 (d, J = 9.1 Hz, 2 H, ArH).

MS (EI, 70 eV): m/z (%) = 273 (100) $[M]^+$.

Anal. Calcd for $C_{15}H_{15}NO_2S$: C, 65.91; H, 5.53; N, 5.12. Found: C, 66.03; H, 5.57; N, 5.33.

[4-(Azepan-1-yl)phenyl][4-(2,3-dihydroindol-1-yl)phenyl]methanone (2l)
Yellow powder; yield: 1.6 g (80%); mp 133–134 °C (PE).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.53–1.61 (m, 4 H, 2 × CH_2), 1.77–1.89 (m, 4 H, 2 × CH_2), 3.18 (t, J = 8.3 Hz, 2 H, CH_2), 3.55 (t, J = 5.9 Hz, 4 H, 2 × CH_2), 4.04 (t, J = 8.3 Hz, 2 H, CH_2), 6.71 (d, J = 8.8 Hz, 2 H, ArH), 6.84 (t, J = 7.3 Hz, 1 H, ArH), 7.14 (d, J = 7.8 Hz, 1 H, ArH), 7.19–7.29 (m, 3 H, ArH), 7.32 (d, J = 7.8 Hz, 1 H, ArH), 7.77–7.87 (m, 4 H, ArH).

MS (EI, 70 eV): m/z (%) = 396 (100) $[M]^+$.

Anal. Calcd for $C_{27}H_{28}N_2O$: C, 81.78; H, 7.12; N, 7.06. Found: C, 81.91; H, 7.06; N, 7.23.

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