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Microwave-enhanced Goldberg reaction: a novel route to *N*-arylpiperazinones and *N*-arylpiperazinediones

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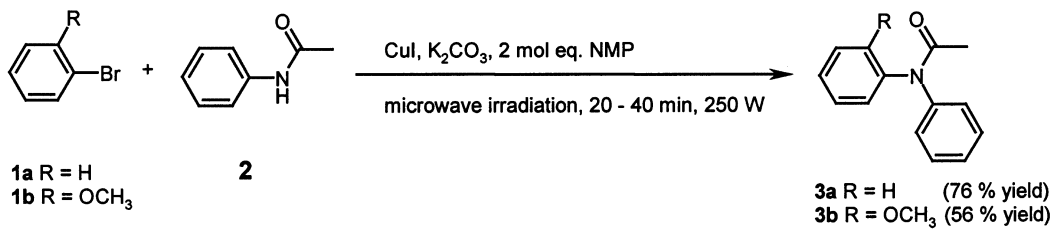
Abstract—An unprecedented microwave-enhanced Goldberg reaction constitutes the key strategic step in the synthesis of *N*-arylpiperazinones, *N*-arylpiperazinediones and *N*-aryl-3,4-dihydroquinolinones. Microwave irradiation greatly accelerates the Goldberg reaction using NMP as solvent. Alkylation at the 3-position of the formed *N*-aryl-2-piperazinones furnishes new *N*-aryl-3-alkyl-2-piperazinones.

Microwave irradiation of organic reactions has rapidly gained in popularity as it accelerates a variety of synthetic transformations[1,2] via time- and energy-saving protocols. Herein, we report the microwave-enhanced formation of *N*-aryl-2-piperazinones and *N*-aryl-2,5-piperazinediones from aryl bromides and protected 2-piperazinones or 2,5-piperazinediones, respectively.

N-Aryl-2-piperazinones are of great interest as farnesyltransferase inhibitors.[3] In addition, both *N*-aryl-2-piperazinones and *N*-aryl-2,5-piperazinediones are synthetic precursors for *N*-arylpiperazines which constitute key elements in current medicinal chemistry, especially in the area of monoamine receptor active drugs.

The Goldberg reaction,[4] the copper-catalysed amidation of aryl halides, usually requires drastic reaction conditions. Due to this drawback which limits its scope, the Goldberg reaction has not been recognised as a powerful synthetic methodology in organic synthesis,[5] albeit the nucleophilic replacement of a leaving group on an aryl ring by nitrogen is now being studied intensively.[6] Although a number of newer Goldberg variations[7–9] has been reported there is still a need for a simple and fast procedure.

Although the use of ultrasound in the Goldberg reaction has been reported for the synthesis of *N*-arylanthranilic acids,[10] the application of microwave irradiation is still unprecedented. In general, Goldberg reactions are carried out either under solvent-free conditions by refluxing the mixed reactants for a prolonged period or in polar solvents such as DMF,[11] DMSO[12] or nitrobenzene.[13] Our preliminary studies wherein bromobenzene **1a** and acetanilide **2** (Scheme 1) were reacted under solvent-free conditions using microwave irradiation gave unsatisfactory conversion rates. It is obvious that in the absence of solvent both the reflux temperature and the polarity of the reaction mixture



Scheme 1.

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will strongly depend on the particular Goldberg reaction that is being carried out. As the absorption rate of microwave energy is very dependent[2] on the polarity and dielectric properties of the reaction mixture our investigations continued with seeking the optimal organic solvent for performing microwave-enhanced Goldberg reactions in order to improve their reproducibility and scope.

Starting from the Goldberg reaction conditions that Freeman[5] used (10 mol% CuI, solvent-free, reflux temperature, 72 h) we added different polar solvents (DMF, DMSO, NMP, HMPA, nitrobenzene) and determined the respective reaction rates and chemical yields of the reaction of bromobenzene **1a** and acetanilide **2** (Scheme 1) with and without applying microwave irradiation, respectively. The optimal solvent for both reaction types turned out to be *N*-methyl-2-pyrrolidinone (NMP). The addition of a relatively small amount (2 molar equivalents) of NMP without the use of microwave irradiation induced a complete conversion, according to HPLC analysis in 17 h, to the *N*-acetyldiphenylamide **3a**, which was isolated in 71% yield. Furthermore, we established that the optimal amount of CuI catalyst (2.5 mol%) for both the reaction in NMP and the solvent-free process is considerably lower than the amount that Freeman[5] used. In general, the reaction rates of the Goldberg reactions in NMP are approximately three to four times higher in comparison with the solvent-free procedure.

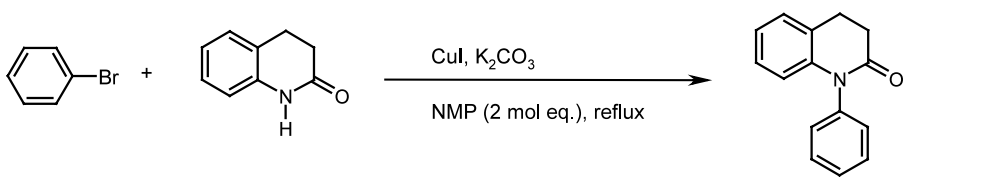
Microwave irradiation conditions (40 min, 250 W) were applied and gave a complete conversion according to HPLC analysis from **1a** and **2** in NMP into the *N*-arylated product **3a**, which was isolated in 76% yield. The corresponding reaction of 2-bromoanisole **1b** with **2** proceeded even more quickly (20 min, 250 W) and gave *N*-acetyl-2-methoxyphenyl-phenylamide[13] **3b** in 56% isolated yield. A somewhat higher yield of **3a** (80%) could be obtained by keeping a constant temperature (190°C, 40 min) during the microwave irradiation process. These findings clearly demonstrate the time- and energy-saving effect of microwave irradiation in both Goldberg reactions.

It was established that 10 mol% of CuI catalyst is the optimal amount for microwave enhanced Goldberg reactions. The synthesis of **3a** is representative. A stirred mixture of bromobenzene **1a** (3.95 mL, 37.5 mmol) and acetanilide **2** (3.38 g, 25.0 mmol), NMP (5 mL, 52 mmol), CuI (0.5 g, 2.5 mmol) and dried powdered K_2CO_3 (3.45 g, 25 mmol) in a three necked round-bottomed flask equipped with a reflux condenser was irradiated in a microwave oven (type: Milestone Ethos 900) for 40 min at 250 W power under a gentle stream of nitrogen. The mixture was allowed to attain rt and diluted with diethyl ether (200 mL). After filtration over hyflo, the diethyl ether layer was successively washed with three portions (10 mL each) of NH_4OH aq. solution and three portions of $NaHCO_3$ (5% aq. solution). The aqueous layers were extracted with diethyl ether and the combined diethyl ether fractions were dried over $MgSO_4$, filtered and concentrated in vacuo to produce a brown oil (6.2 g). This oil was purified by flash chromatography (silica gel, petroleum ether/EtOAc = 3/1 (v/v)) to furnish **3a** (4.0 g, 76% yield as a white solid, mp 101–103°C (lit.[14] mp 99°C; lit.[15] mp 102–103°C)). **CAUTION** These microwave-enhanced Goldberg reactions should be performed in an open reaction system in order to enable gaseous products to escape, thus avoiding the risk of explosion.

The scope of our microwave-enhanced Goldberg reaction was further explored by reacting the bicyclic amide 3,4-dihydro-*1H*-quinolin-2-one **4** (which can be viewed as a cyclised derivative of **2**) with bromobenzene **1a** (Scheme 2). It is interesting to note that reaction of the cyclic amide **4** proceeded relatively fast (4 h) under thermal conditions to produce 1-phenyl-3,4-dihydro-*1H*-quinolin-2-one[16] **5** (isolated yield: 77%). Microwave irradiation induced an even faster reaction (30 min at 200°C, followed by 1 h at 190°C) but the time-saving was less pronounced in comparison with the reaction in Scheme 1. In this case, microwave irradiation offers no substantial benefit.

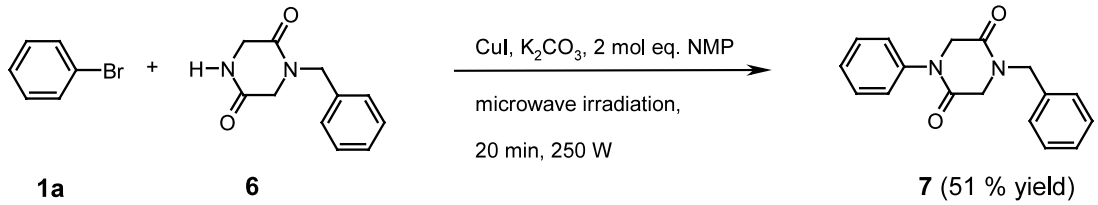
The Goldberg reaction of 4-benzylpiperazin-2,5-dione[17] **6** with bromobenzene **1a** requires 20 h heating at reflux temperature under thermal conditions in NMP. This conversion was tremendously accelerated by microwave irradiation to furnish 4-benzyl-1-phenylpiperazin-2,5-dione[18] **7** within 20 min in an isolated yield of 51% (Scheme 3). To our knowledge this is the fastest Goldberg reaction that has been reported.

The Goldberg reaction of 4-benzylpiperazin-2-one[19] **8** with bromobenzene **1a** (Scheme 4) also proceeded slowly in NMP (20 h) at 200°C under thermal conditions. This particular reaction without microwave irradiation was optimised earlier under solvent-free conditions (2.5 mol% CuI, 140°C) and was shown to be completed in 72 h. To our satisfaction this reaction was completed within 1 h using microwave irradiation by maintaining the reaction temperature between 190 and

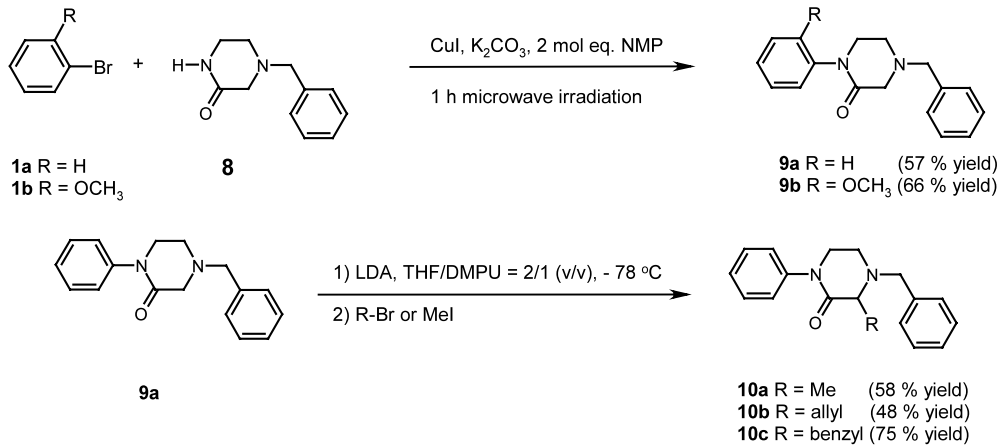


1a **4** **5** (77 % yield)

Scheme 2.



Scheme 3.



Scheme 4.

200°C, to produce 4-benzyl-1-phenylpiperazin-2-one[20] **9a** in an isolated yield of 57%. The reaction of the corresponding methoxy derivative **1b** with **8** furnished 4-benzyl-1-(2-methoxyphenyl)piperazin-2-one[21,22] **9b** in an isolated yield of 66% within 1 h.

N-Arylpiperazinones are key synthetic precursors for the pharmaceutically important class of *N*-arylpiperazines. Further functionalisation of **9a** would enable a straightforward synthetic entry into a variety of novel 3-substituted 1-arylpiperazines. This consideration prompted us to perform alkylation reactions at the 3-position of **9a**. Deprotonation of **9a** at its C_3-position with LDA in THF/DMPU (1,3-dimethyl-3,4,5,6-tetrahydro-2(*1H*)-pyrimidinone), followed by reaction with an alkyl halide gave the 3-alkylated phenylpiperazinones **10a**,[23] **10b**[24] and **10c**,[25] respectively. It should be noted that the presence of DMPU is essential in these *C*-alkylation reactions.

In conclusion, rapid and practical procedures for the *N*-arylation of piperazinediones, piperazinones and 3,4-dihydroquinolinones were developed which demonstrate the time- and energy-saving effect of microwave irradiation in the applied Goldberg reactions.

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18. Analytical data for 4-benzyl-1-phenylpiperazin-2,5-dione **7**: mp 157–158°C; ^{1}H NMR (200 MHz, $CDCl_3$): δ 4.04 (s, 2H), 4.42 (s, 2H), 4.66 (s, 2H), 7.23–7.48 (m, 10H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 48.8, 50.5, 53.0, 126.1, 127.4, 128.2, 128.7, 129.3, 129.5, 136.8, 141.0, 164.6, 164.7; MS (ESI+): $(MH)^+$ m/z 281; MS (EI): m/z (rel. intensity) 280 (72), (189 (5), 161 (29), 105 (35), 104 (39), 91 (100); HRMS (EI): calcd for $C_{17}H_{16}N_2O_2$ (M^+) 280.1212; found 280.1213.
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20. Analytical data for 4-benzyl-1-phenylpiperazin-2-one **9a**: mp 104–105°C; ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.76–2.85 (m, 2H), 3.34 (s, 2H), 3.62 (s, 2H), 3.63–3.72 (m, 2H), 7.20–7.45 (m, 10H); MS (ESI+): $(MH)^+$ m/z 267.
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22. Analytical data for 4-benzyl-1-(2-methoxyphenyl)-piperazin-2-one **9b**: mp 113–114°C (lit.[20] mp 109–111°C); ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.80 (t, $J=6$ Hz, 2H), 3.34 (s, 2H), 3.52–3.62 (m, 2H), 3.64 (s, 2H), 3.83 (s, 3H), 6.93–7.02 (m, 2H), 7.16–7.40 (m, 7H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 49.6, 56.3, 57.8, 61.3, 113.1, 121.3, 127.9, 129.0, 129.5, 129.7, 129.8, 131.1, 137.9, 155.4, 166.5; MS (ESI+): $(MH)^+$ m/z 297; MS (EI): m/z (rel. intensity) 296 (28), 267 (80), 205 (91), 91 (100); HRMS (EI): calcd for $C_{18}H_{20}N_2O_2$ (M^+) 296.1525; found 296.1533.
23. Analytical data for 4-benzyl-3-methyl-1-phenylpiperazin-2-one hydrochloride **10a**: mp 206–207°C; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.56 (d, $J=7$ Hz, 3H), 2.55–2.68 (m, 1H), 2.96–3.10 (m, 1H), 3.33–3.75 (m, 4H), 4.00 (d, $J=13$ Hz, 1H), 7.20–7.53 (m, 10H); MS (ESI+): $(MH)^+$ m/z 281; MS (EI): m/z (rel. intensity) 280 (4), 237 (65), 189 (29), 91 (100); HRMS (EI): calcd for $C_{18}H_{20}N_2O$ (M^+ free base) 280.1576; found 280.1579.
24. Analytical data for 3-allyl-4-benzyl-1-phenylpiperazin-2-one **10b**: mp 118–119°C; ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.50–2.81 (m, 2H), 2.85–3.08 (m, 2H), 3.32–3.53 (m, 3H), 3.65–3.81 (m, 1H), 4.10 (d, $J=13$ Hz, 1H), 5.08–5.26 (m, 2H), 5.91–6.14 (m, 1H), 7.18–7.43 (m, 10H); ^{13}C NMR (100 MHz, DMSO-d_6): 35.0, 46.7, 49.1, 58.1, 65.2, 117.3, 126.5, 126.9, 127.8, 128.9, 129.4, 129.5, 135.9, 138.8, 143.4, 169.0; MS (ESI+): $(MH)^+$ m/z 307; MS (EI): m/z (rel. intensity) 265 (30), 91 (100); HRMS (EI): calcd for $C_{17}H_{17}N_2O$ (M^+–$CH_2CH{=}CH_2$) 265.1341; found 265.1355.
25. Analytical data for 3,4-dibenzyl-1-phenylpiperazin-2-one **10c**: mp 109–111°C; ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.50–2.63 (m, 1H), 2.93–3.05 (m, 1H), 3.15–3.42 (m, 4H), 3.49 (d, $J=13$ Hz, 1H), 3.59–3.65 (m, 1H), 4.15 (d, $J=13$ Hz, 1H), 6.98–7.07 (m, 2H), 7.17–7.40 (m, 13H); ^{13}C NMR (100 MHz, DMSO-d_6): 36.7, 46.2, 48.7, 58.3, 66.5, 126.5, 126.7, 127.0, 127.7, 128.4, 128.9, 129.4, 129.5, 130.5, 138.6, 139.4, 143.3, 169.1; MS (ESI+): $(MH)^+$ m/z 357; MS (EI): m/z (rel. intensity) 265 (34), 91 (100); HRMS (EI): calcd for $C_{17}H_{17}N_2O$ (M^+–$CH_2C_6H_5$) 265.1341; found 265.1352. **Synthesis of 3,4-dibenzyl-1-phenylpiperazin-2-one 10c**: 4-Benzyl-1-phenylpiperazin-2-one (3.50 g, 13.2 mmol) was dissolved in a mixture of dry THF (35 mL) and DMPU (17.5 mL) under a nitrogen atmosphere. The resulting solution was cooled to –78°C and LDA (6.59 mL, 2 M solution in THF, 13.2 mmol) was added. After stirring for 35 min benzyl bromide (1.8 mL, 15.2 mmol) was added and the resulting solution was allowed to attain room temperature and stirred overnight. A solution of $NaHCO_3$ (5% aq., 175 mL) and diethyl ether were added. The organic layer was twice washed with water, dried over $MgSO_4$, filtered and concentrated in vacuo. The resulting oil was crystallised from diethyl ether to furnish 3,4-dibenzyl-1-phenylpiperazin-2-one (3.53 g, 75% yield) as a white solid.