# Conversion of piperidine-4-ones into [1,4]-diazepan-5-ones under microwave irradiation using a silica gel supported $NaHSO_4$ catalyst

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A rapid conversion of some 2,6-diarylpiperidin-4-ones into 2,7-diaryl-[1,4]-diazepan-5-ones in high yields has been developed involving treatment with hydroxylamine hydrochloride under microwave irradiation in the presence of a silica gel supported $NaHSO_4$ catalyst.

**Keywords:** [1,4]-diazepan-5-ones, silica gel supported $NaHSO_4$ catalyst, solvent-free conditions, microwave irradiation, environmentally friendly

During the last decade, a number of publications and reviews[1-9] have advocated the use of microwave technology in organic synthesis. With no direct contact between the chemical reactants and the energy source, microwave-assisted chemistry can be more efficient in terms of the energy used, provide faster heating rates and enable rapid optimisation of synthetic procedures, often with an increase in reaction rate and efficiency.

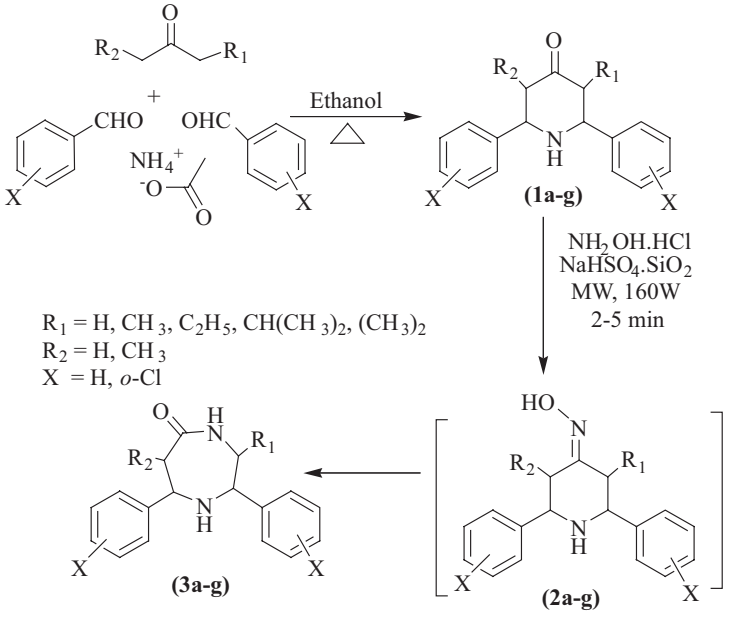
The conversion of ketones into the corresponding amides is an important transformation that has been utilised for the synthesis of various bioactive natural compounds[10] as well as for the industrial production of polyamides, such as nylon-6.[11] The ketones can be converted into oximes, which undergo Beckmann rearrangement to produce amides.[12] One-pot conversion of ketones into amides (*e.g.*, Schmidt rearrangement) has also been reported,[13] though numbers are limited. However, these methods suffer from certain drawbacks, which include the use of corrosive reagents (*e.g.*, nitroparaffin and concentrated $H_2SO_4$, $NaN_3$ and concentrated $H_2SO_4$, hydroxylamine-*o*-sulfonic acid, *etc.*), low yields and several steps involved in the experimental procedure. The process using concentrated $H_2SO_4$ may affect systems that are sensitive to acids.[14a-c] Moreover, these methods, which have not utilised microwave irradiation require long reaction times.[13,14]

## Results and discussion

3-Alkyl-2,7-diaryl-[1,4]-diazepan-5-ones (3), seven membered lactams, which are intermediates in 1,2-diamines synthesis[15] have been formed by Beckmann and Schmidt[16] rearrangements from piperidin-4-ones (**1**). However, these two methods suffer from some drawbacks like longer reaction periods, low yields, tiresome workup procedure and use of corrosive concentrated $H_2SO_4$ and polyphosphoric acid. Das *et al.*[17] reported the conversion of ketones to amides using $NaHSO_4.SiO_2$ catalyst under microwave irradiation. We have now adopted this method for the formation of 3-alkyl-2,7-diaryl-[1,4]-diazepan-5-ones (**3a–g**) from 2,6-diphenylpiperidin-4-ones (**1a–g**) (Scheme 1).

The oximes are believed to be intermediates in this reaction, but we are unable to isolate the respective oximes. To confirm the formation of oximes as intermediates, we ran the reaction with respective oximes and the $NaHSO_4.SiO_2$ catalyst under microwave irradiation at $P$ = 160W. As we expected, the oximes gave the 3-alkyl-2,7-diaryl-[1,4]-diazepan-5-ones quantitatively. In all cases, $^1$H NMR spectroscopic studies revealed that the migration is preferentially a*nti*.

In summary, microwave-assisted solvent-free (under conditions of so-called 'green chemistry') reactions were employed to synthesise 3-alkyl-2,7-diaryl-[1,4]-diazepan-5-ones in good to excellent yields. The method not only offers a substantial improvement in yield over conventional heating




**Scheme 1** A convenient synthesis of some novel [1,4]-diazepan-5-ones (**3a–g**).

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**Table 1** Synthesis of [1,4]-diazepan-5-ones under microwave irradiation

| Entry | $R_1$ | $R_2$ | X | Reaction time/min | Yield /% | M.p./°C | Elemental analysis (%) | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | Carbon found (calculated) | Hydrogen found (calculated) | Nitrogen found (calculated) |
| **3a** | H | H | H | 2 | 90 | 168–170 (170) | 76.5 (76.66) | 6.8 (6.81) | 10.6 (10.52) |
| **3b** | $CH_3$ | H | H | 2 | 95 | 183–185 (183) | 77.0 (77.11) | 7.1 (7.19) | 9.9 (9.99) |
| **3c** | $C_2H_5$ | H | H | 2 | 85 | 187–189 (188) | 77.5 (77.52) | 7.5 (7.53) | 9.5 (9.52) |
| **3d** | *i*-Pr | H | H | 2 | 90 | 186–188 (188) | 77.8 (77.89) | 7.8 (7.84) | 9.1 (9.08) |
| **3e** | $H_3C$ | $H_3C$ | H | 2 | 95 | 177–179 (180) | 77.5 (77.52) | 7.5 (7.53) | 9.5 (9.52) |
| **3f** | H | H | *o*-Cl | 3 | 85 | 209–211 | 60.9 (60.91) | 4.8 (4.81) | 8.3 (8.36) |
| **3g** | $H_3C$ | H | *o*-Cl | 5 | 85 | 201–203 | 61.9 (61.90) | 5.1 (5.19) | 8.0 (8.02) |

*Melting points given in parentheses are from ref. 16.

methods but also eliminates the use of hazardous solvents and an excess of expensive acidic catalyst. Advantages of this method include the fact that it is environmentally friendly, is an economical procedure, has a short reaction time and has simplicity of performance with non-aqueous work-up.

## Experimental

*General remarks*

Extent of reaction and the purity of the products was assessed by TLC. All the reported melting points were taken in open capillaries and are uncorrected. IR spectra were recorded in KBr (pellets) on a Nicolet-Avatar–360 FT-IR spectrophotometer and noteworthy absorption values (reciprocal centimetre) alone are listed. $^1$H NMR spectra were recorded at 300 MHz on a Bruker AV 300 spectrometer using $CDCl_3$ as solvent and TMS as internal standard. The APCI +ve mass spectra were recorded on a Shimazdu LCMS-QP8000α LC MS spectrometer. Elemental analysis was carried out using a PERKIN ELMER-240 CHN analyser. A conventional (*unmodified*) domestic microwave oven equipped with a turntable (LG, MG-395 WA, 230V~50 Hz, 760 W) was used for the irradiation. 2,6-Diarylpiperidin-4-ones were prepared by a literature method.[18] $NaHSO_4.SiO_2$ catalyst was prepared by the literature method.[19]

*Experimental method for the preparation of 2,7-diphenyl-[1,4]-diazepan-5-one* (**3a)**

In a 100 ml borosil beaker, 2,6-diphenylpiperidin-4-one (0.1 mol) and $NH_2OH.HCl$ (0.3 mmol) were mixed thoroughly with $NaHSO_4.SiO_2$ catalyst (100 mg), and the mixture was placed inside a microwave oven and irradiated for 2 min. The mixture was removed from the oven, cooled and shaken with ethyl acetate (40 ml). The catalyst was removed by filtration. The filtrate was concentrated and the residue was subjected to column chromatography over silica gel using ethylacetate: petroleum ether (40 : 60) (0.2 : 0.8) as eluent to afford the corresponding product (**3a**) as a crystalline solid. IR (KBr) ($cm^{-1}$): 3447, 3311, 3082, 2927, 2792, 1671; MS (*m/z*): 267 ($M^{+\cdot}$) (M.F. $C_{17}H_{18}N_2O$); $^1$H NMR (δ ppm): 2.11 (s, 1H, $H_1$), 2.67 (d, 1H, $H_{6e}$), 3.17 (m, 2H, $H_{3e}$ and $H_{6a}$), 3.70 (m, 1H, $H_{3a}$), 4.03 (d, 2H, $H_2$), 4.14 (d, 2H, $H_7$), 6.16 (s, 1H, $H_4$), 7.26–7.45 (m, 10H, aryl protons).

Compounds **3b–g** were synthesised similarly and further details for **3a–g** are given in the Table.

*3-Methyl-2,7-diaryl-[1,4]-diazepan-5-one* (**3b**): IR (KBr) ($cm^{-1}$): 3302, 3207, 3082, 2925, 2880, 2852, 1667; MS (*m/z*): 281 $M^{+\cdot}$ (M.F. $C_{18}H_{20}N_2O$); $^1$H NMR (δ ppm): 0.75 (d, 3H, $CH_3$), 2.07 (s, 1H, $H_1$), 2.65 (d, 1H, $H_{6e}$), 3.15 (t, 1H, $H_{6a}$), 3.82 (m, 1H, $H_{3a}$), 3.70 (d, 2H, $H_2$), 4.13 (d, 2H, $H_7$), 5.82 (s, 1H, $H_4$), 7.26–7.38 (m, 10H, aryl protons).

*3-Ethyl-2,7-diaryl-[1,4]-diazepan-5-one* (**3c**): IR (KBr) ($cm^{-1}$): 3308, 3224, 3061, 2978, 2929, 2881, 2852, 1663; MS (*m/z*): 295 $M^{+\cdot}$ (M.F. $C_{19}H_{22}N_2O$); $^1$H NMR (δ ppm): 0.85 (t, 3H, $CH_3$), 1.11 (m, 2H, $CH_2$), 2.03 (s, 1H, $H_1$), 2.65 (d, 1H, $H_{6e}$), 3.14 (t, 1H, $H_{6a}$), 3.65 (m, 1H, $H_{3a}$), 3.77 (d, 2H, $H_2$), 4.13 (d, 2H, $H_7$), 5.76 (s, 1H, $H_4$), 7.21–7.42 (m, 10H, aryl protons).

*3-Isopropyl-2,7-diaryl-[1,4]-diazepan-5-one* (**3d**): IR (KBr) ($cm^{-1}$): 3590, 3399, 3060, 2972, 2847, 2840, 2837, 1650; MS (*m/z*): 309 $M^{+\cdot}$ (M.F. $C_{20}H_{24}N_2O$); $^1$H NMR (δ ppm): 0.95 (d, 6H, $CH_3$), 1.60 (m, 1H, CH), 2.07 (s, 1H, $H_1$), 2.64 (d, 1H, $H_{6e}$), 3.16 (t, 1H, $H_{6a}$), 3.61 (m, 1H, $H_{3a}$), 3.95 (d, 2H, $H_2$), 4.10 (d, 2H, $H_7$), 5.74 (s, 1H, $H_4$), 7.28–7.45 (m, 10H, aryl protons).

*3,6-Dimethyl-2,7-diaryl-[1,4]-diazepan-5-one*(**3e**):IR(KBr)($cm^{-1}$): 3446, 3333, 3081, 2979, 2934, 2821, 1661; MS (*m/z*): 295 $M^{+\cdot}$ (M.F. $C_{19}H_{22}N_2O$); $^1$H NMR (δ ppm): 0.72–0.82 (d, 6H, $CH_3$), 2.08 (s, 1H, $H_1$), 3.10 (m, 1H, $H_{6e}$), 3.89 (m, 1H, $H_{3a}$), 3.66 (d, 2H, $H_2$), 3.80 (d, 2H, $H_7$), 5.69 (s, 1H, $H_4$), 7.21–7.38 (m, 10H, aryl protons).

*2,7-Bis(2-chloro-phenyl)-[1,4]-diazepan-5-one*(**3f**):IR(KBr)($cm^{-1}$): 3449, 3316, 3089, 2932, 2798, 1675; MS (*m/z*): 336 ($M^{+\cdot}$) (M.F. $C_{17}H_{16}Cl_2N_2O$); $^1$H NMR (δ ppm): 2.18 (s, 1H, $H_1$), 2.70 (d, 1H, $H_{6e}$), 3.28 (m, 2H, $H_{3e}$ and $H_{6a}$), 3.81 (m, 1H, $H_{3a}$), 4.59 (d, 2H, $H_2$), 4.70 (d, 2H, $H_7$), 6.21 (s, 1H, $H_4$), 7.40–7.81 (m, 8H, aryl protons).

*2,7-Bis(2-chloro-phenyl)-3-methyl[1,4]-diazepan-5-one* (**3g**): IR (KBr) ($cm^{-1}$): 3308, 3212, 3087, 2928, 2885, 2857, 1669; MS (*m/z*): 350 $M^{+\cdot}$ (M.F. $C_{18}H_{18}Cl_2N_2O$); $^1$H NMR (δ ppm): 0.95 (d, 3H, $CH_3$), 2.17 (s, 1H, $H_1$), 2.71 (d, 1H, $H_{6e}$), 3.22 (t, 1H, $H_{6a}$), 3.92 (m, 1H, $H_{3a}$), 4.51 (d, 2H, $H_2$), 4.72 (d, 2H, $H_7$), 5.89 (s, 1H, $H_4$), 7.41–7.70 (m, 8H, aryl protons).

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