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Tetrahedron Letters
Tetrahedron Letters 46 (2005) 6011–6014

# Microwave-assisted cyclocondensation of hydrazine derivatives with alkyl dihalides or ditosylates in aqueous media: syntheses of pyrazole, pyrazolidine and phthalazine derivatives

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Received 17 May 2005; revised 5 July 2005; accepted 6 July 2005
Available online 25 July 2005

**Abstract**—Direct syntheses of 4,5-dihydro-pyrazole, pyrazolidine, and 1,2-dihydro-phthalazine derivatives via double-alkylation of hydrazines by alkyl dihalides or ditosylates were accomplished in aqueous media under microwave irradiation conditions; the environmentally friendlier chemical transformation occurred in a single step and eliminated the use of expensive metal catalysts in building two C–N bonds.


Heterocyclic compounds occur very widely in nature and are essential to life. Nitrogen-containing heterocyclic molecules constitute the largest portion of chemical entities, which are part of many natural products, fine chemicals, and biologically active pharmaceuticals vital for enhancing the quality of life.[1] 4,5-Dihydro-pyrazoles,[2] pyrazolidines,[3] and 1,2-dihydro-phthalazines[4] are important classes of heterocycles useful as pesticides, anticonvulsants, and potent vasorelaxing agents. The standard preparation of 4,5-dihydro-pyrazoles involves the cyclocondensation of hydrazine derivatives with α,β-unsaturated carbonyl compounds,[5] or the reaction of hydrazine with substituted cyclopropanes[6] often requiring the use of a crown ether as a phase transfer catalyst.[7] Pyrazolidines are usually prepared by the condensation reaction of hydrazines with β-diketones or β-keto esters or alternatively by reacting a protected hydrazine, di-*tert*-butyldihydrazodiformate, with 1,3-dibromopropane in the presence of a phase transfer catalyst ultimately requiring a sequential deprotection of Boc group in 4 M HCl.[8] Syntheses of 4,5-dihydro-pyrazole, pyrazolidine, and 1,2-dihydro-phthalazine via direct heterocyclization of hydrazine derivatives and alkyldihalides or ditosylates have never been fully explored.

Microwave (MW) irradiation has gained popularity in the past decade as a powerful tool for rapid and efficient synthesis of a variety of organic compounds because of the selective absorption of microwave energy by polar molecules.[9] The application of MW irradiation to provide enhanced reaction rate and improved product yield in chemical synthesis has been extended to modern drug discovery[10] in complex multi-step synthesis,[11] and it is proving quite successful in the formation of a variety of carbon–heteroatom and carbon–carbon bonds.[12] During our ongoing efforts to explore organic syntheses in aqueous reaction media using MW irradiation,[13] we discovered that the cyclocondensation of phenyl hydrazines with 1,3-dihalopropanes or 1,3-glycol disulfonate in aqueous alkaline medium surprisingly afforded 4,5-dihydro-pyrazole as major product instead of the anticipated pyrazolidine (Scheme 1). We wish to report herein a 'cleaner' synthesis of nitrogen-containing heterocycles in mildly alkaline water under microwave irradiation conditions.

The microwave-assisted reaction was also examined under solventless conditions and using various reaction media such as water, polyethylene glycol (PEG 300), toluene, and *N*,*N*-dimethylformamide. Reactions under solventless condition afforded very low yield (less than 20%) because the reactants were immiscible with the base, potassium carbonate. PEG 300 is a promising medium to replace volatile organic solvents for

*Keywords*: Cyclocondensation; Microwave irradiation; Heterocycles; 4,5-Dihydro-pyrazole; 1,2-Dihydro-phthalazine.
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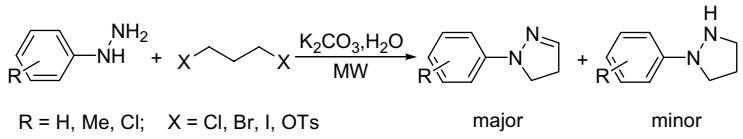
doi:10.1016/j.tetlet.2005.07.018




**Scheme 1.** MW-assisted synthesis of 4,5-dihydro-pyrazole.

green chemical synthesis under microwave irradiation[14] but relatively more expensive than water, and it broke down to ethylene glycol upon exposure to microwaves under basic condition. The reaction in toluene was a failure as the yield was less than 25%. *N*,*N*-Dimethylformamide as a reaction medium gave rise to side reactions and therefore low products yields (~40%). Water is a good absorber for microwave energy[15] and has been successfully employed as solvent for various organic syntheses.[16] Utilization of water as a safer reaction medium in conjunction with the use of microwave irradiation as the heating source is gaining widespread acceptance[17] even though water is not an ideal solvent for most organic compounds according to the traditional belief '*like dissolves like*'. We find that water is one of the best choices in view of its relatively environmental-friendly nature and abundance. Further, superheating of water above its boiling point by microwave irradiation in an heterogeneous system could substitute as a phase transfer catalyst without using any phase transfer reagent, thus providing the observed acceleration similar to ultrasound irradiation.[18]

This general reaction is applicable to a variety of hydrazine derivatives such as substituted phenyl hydrazines, 1,2-dialkylhydrazines, hydrazine hydrochlorides, and sulfates and for aliphatic dihalides and ditosylates (Table 1).

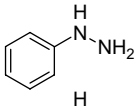
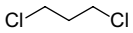
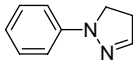
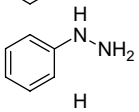
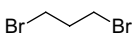
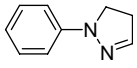
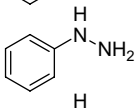
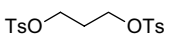
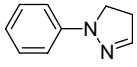
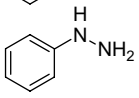
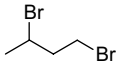
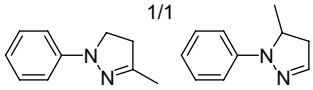
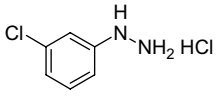
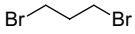
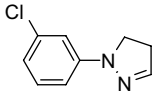
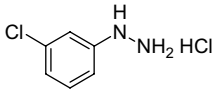
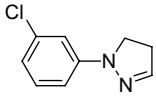
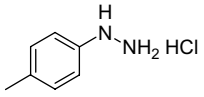
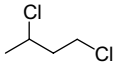
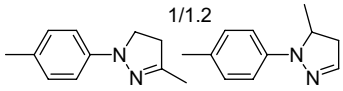
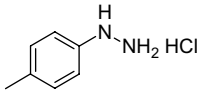
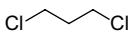
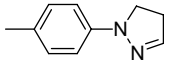
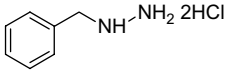
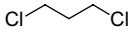
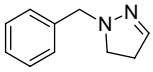
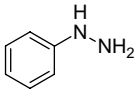
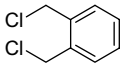
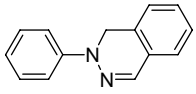
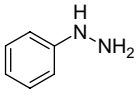
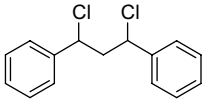
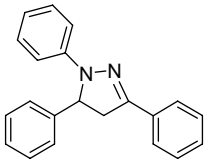
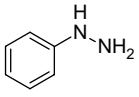
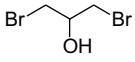
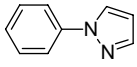
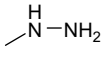
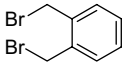
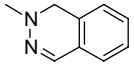
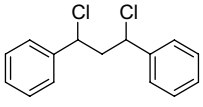
As can be seen from Table 1, a variety of heterocycles were synthesized by the cyclocondensation of hydrazine derivatives with alkyl dihalides and ditosylates. Hydrazine and mono-substituted hydrazines afforded 4,5-dihydro-pyrazole instead of pyrazolidine (entries 1–9, 11, and 14) or 1,2-dihydro-phthalazine (entries 10 and 13); disubstituted hydrazines furnished the expected pyrazolidine (entry 15) and 1,2,3,4-tetrahydro-phthalazine (entry 16). Interestingly, the reaction of phenylhydrazine with 1,3-dibromo-2-propanol gave rise to 1-phenyl-1*H*-pyrazole (entry 12), which was the result of further elimination of 1 equiv water from 1-phenyl-4,5-dihydro-1*H*-pyrazol-4-ol in an alkaline medium. The anticipated formation of two pairs of structural isomers occurred (entries 4 and 7) as ascertained by $^1$H NMR. The ease of generation of carbon–nitrogen double bond in these reactions (Table 1) was explored in two control experiments by introducing oxygen into the system or alternatively, using activated palladium on carbon as a dehydrogenation catalyst. We found that oxygen in the air played a critical role in promoting the formation of C–N double bond via dehydrogenation mechanism as was the case observed for palladium-catalyzed dehydrogenation process.

In conclusion, direct syntheses of 4,5-dihydro-pyrazole, pyrazolidine, and 1,2-dihydro-phthalazine derivatives via double-alkylation of hydrazine derivatives by alkyl dihalides or ditosylates in aqueous media under microwave irradiation were demonstrated. The general microwave protocol enabled the synthesis of a wide variety of useful precursors for pharmacologically active heterocycles using water as reaction medium in the absence of a phase transfer agent. This advantageous methodology shortened the reaction time significantly and utilized unprotected hydrazine derivatives and alkyl dihalides or ditosylates to construct heterocycles in a single step, which has never been fully realized under conventional heating conditions. Further, it eliminated the need for a phase transfer catalyst and provided water as an ideal substitute for hazardous organic solvents. Efforts to define the reaction mechanism, the scope of the reaction, and the application of this method to synthesize complex heterocycles are currently underway.

All the starting hydrazines and hydrazine hydrochlorides and alkyl dihalides were obtained from Aldrich Chemical Co. and were used as such; 1,3-propane-diol-ditosylates were prepared from 1,3-propanediol according to literature.[19] 1,3-Dichloro-1,3-diphenylpropane was synthesized by the reaction of benzaldehyde and styrene using boron trichloride.[20] The synthesized products were identified by GC/MS qualitative analysis based on Wiley library database using an HP 6890 GC system with an HP 5872 mass selective detector. The identities were further confirmed by $^1$H and $^{13}$C NMR spectra that were recorded for the pure products in chloroform-*d* ($CDCl_3$) with TMS as internal reference using a Bruker Biospin 300 MHz NMR spectrometer.

The representative experimental procedure is as follows: 1,2-diethylhydrazine dihydrochloride (1 mmol, 0.161 g), 1,2-bis-chloromethyl-benzene (1 mmol, 0.175 g), 2 M sodium hydroxide (1 mL), and potassium carbonate (1 mmol, 0.138 g) in water (1 mL) were placed in a 10 mL crimp-sealed thick-walled glass tube equipped with a pressure sensor and a magnetic stirrer. The reaction tube was placed inside the cavity of a CEM Discover Focused Microwave Synthesis System, operated at 120±5 °C (temperature monitored by a built-in infrared sensor), power 70–100 Watt and pressure 40–80 psi for 20 min. After completion of the reaction, the biphasic system was allowed to stir in the air for 6 h, and the product was extracted into ethyl acetate. The removal of the solvent under reduced pressure (rotary evaporator) and flash column chromatography using hexane/ethyl acetate (9/1) as eluent afforded the product, 2,3-diethyl-1,2,3,4-tetrahydro-phthalazine 0.114 g (60% yield).

**Table 1.** Aqueous cyclocondensation of hydrazines with dihalides using MW irradiation[a]

| Entry | Hydrazine derivatives | Dihalides or ditosylates | Main products | Yields (%) |
|---|---|---|---|---|
| 1 |  |  |  | 68[b] |
| 2 |  |  |  | 65[b] |
| 3 |  |  |  | 70[b] |
| 4 |  |  |  1/1 | 65[b,c] |
| 5 |  |  |  | 64[b] |
| 6 |  |  |  | 66[b] |
| 7 |  |  |  1/1.2 | 63[b,c] |
| 8 |  |  |  | 70[b] |
| 9 |  |  |  | 60[b] |
| 10 |  |  |  | 89[d] |
| 11 |  |  |  | 60[b] |
| 12 |  |  |  | 81[b] |
| 13 |  |  |  | 85[d] |
| 14 | $H_2N–NH_2\ H_2SO_4$ |  |  | 74[b] |
| 15 |  |  |  | 80[d] |
| 16 |  |  |  | 60[b] |

[a] Reaction of 1 mmol scale, MW power 80–100 Watt, 120 °C, pressure 40–80 psi for 20 min.
[b] Isolated yields based on starting hydrazines.
[c] Structure isomer ratio determined by NMR.
[d] Yields based on quantitative GC–MS analysis of starting dihalides.

$^1$H NMR (300 MHz, $CDCl_3$/TMS) $\delta$ ppm 7.16 (dd, 2H, $J = 3.3$, 5.7 Hz), 7.05 (t, 2H, $J = 3.3$ Hz), 3.88 (s, 4H), 2.63 (q, 4H, $J = 7.2$ Hz), 1.13 (t, 4H, $J = 7.2$ Hz); $^{13}$C NMR (75.5 MHz, $CDCl_3$/TMS) $\delta$ ppm 133.0, 117.9, 126.7, 126.1, 49.2, 43.0, 13.1; MS (EI) $m/z$ (relative intensity, %) 190 (M, 41), 161 (100), 105 (33), 104 (29), 91 (14).

In the alternative protocols, reactions in the presence of oxygen or using palladium on carbon as dehydrogenating catalyst, the work-up in either case was a simple extraction immediately after the completion of the reaction.

## Acknowledgements

This research was supported, in part, by Postgraduate Research Program at the National Risk Management Research Laboratory administered by the Oak Ridge Institute for Science and Education through an interagency agreement between the US Department of Energy and the US Environmental Protection Agency.

## References and notes

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