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Microwave assisted efficient synthesis of (Pyrimido[4, 5- *e*][1,3,4]thiadiazin-7-yl) hydrazine derivatives

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ABSTRACT

An efficient and mild technology for the synthesis of (pyrimido[4, 5- e][1, 3, 4]thiadiazin-7-yl)hydrazine compounds was described via the microwave assisted cyclocondensation of alkyl-2-phenylhydrazinecarbodithioates as bidentate nucleophiles with 5-bromo-2,4-dichloro-6-methylpyrimidine and further replacement of chlorine atom of pyrimido[4, 5- e][1, 3, 4]thiadiazin by hydrazine under microwave irradiation. These compounds are prepared under microwave irradiation versus conventional heating in high yields and short reaction times.

KEYWORDS

Heterocyclization;
5- bromo- 2,4- dichloro-6-methylpyrimidine;
Pyrimido[4, 5- *e*][1, 3, 4]thiadiazine;
microwave.

INTRODUCTION

Microwave-assisted organic synthesis (MAOS) is a new and quickly developing area in synthetic organic chemistry, which is based on the empirical observation that some organic reactions proceed much faster and with higher yields under microwave irradiation than conventional heating. In many cases, the reactions that normally required many hours at refluxing temperature under classical conditions, could be completed within several minutes or even seconds in a microwave oven, even at comparable reaction temperatures. While different hypotheses were proposed to account for the effect of microwaves on organic reactions, the reason for such dramatic acceleration effects remains largely unknown. Regardless of the exact origin of the microwave effect, it is extremely efficient and applicable to a very broad range of practical synthesis.

The biological activities of pyrimido[4, 5- *e*][1, 3, 4]thiadiazines, persuaded us to search for efficient synthetic methods for this class of heterocyclic compounds, which are described as nucleoside analogues[1,2], anti-inflammatory, hypotensive, diuretic[3,4], and phosphodiesterase inhibitor agents[2] Previous routes to such a system involved the heterocyclization of 6-hydrazino-substituted uracils with isothiocyanates and *N*-bromosuccinimide[1–5], condensation of 2,4- dichloro-5- nitro- 6- methylpyrimidine with dithizone[6] via the Smiles rearrangement, reaction of thiosemicarbazide with 4,5-dihalopyrimidines[7], cyclocondensation of thiosemicarbazide with 5- bromobarbituric acid[8] and condensation of 5-bromo-2-chloro-6-methyl-4-(1-methylhydrazino) pyrimidine with carbon disulfide and alkyl halides[9] or isothiocyanates[10] Previously, we described the formation of fused[1,3,4] thiadiazines by the condensation of alkyl-2-phenylhydrazinecarbodithioates with heterocyclic polyhalides[11,12]. A more efficient method for achieving such a transformation, would be the reaction of hydrazine with 4,6- dichloropyrimidine-5- carbaldehyde allowing formation of the desired ring system in a single step. Such a similar transformation was known for chloroformylpyridines[13], and conden-

sations of hydrazine itself with such pyrimidinylaldehydes and pyrimidinylketones were reported[14,15], and related transformations were carried out on solid support to yield pyrimidone products[16].

Such a transformation of 4,6-dichloro-2-phenylpyrimidine-5-carbaldehyde and phenylhydrazine proceeding with concomitant displacement of a second hydrazine molecule to form N-[(1,6-diphenyl-7-H-pyrazolo[4,5-e]pyrimidin-4-ylidene)amino]- aniline was reported[17,18].

MATERIAL AND METHODS

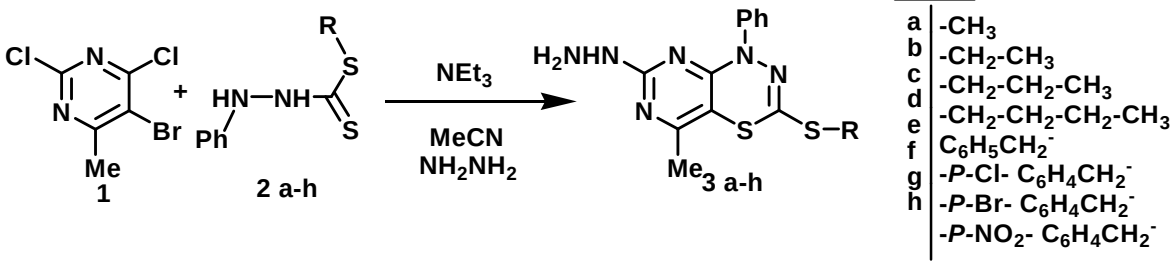
The melting points were recorded on an Electrothermal type 9100 melting point apparatus. 5- Bromo-2, 4- dichloro- 6- methylpyrimidine was prepared according to the published procedure[19]. Experiments were carried out in closed vessels of a multimode Microsynth Milstone laboratory 900 W Westpointe microwave operating at 3.67 GHz with an internal volume of 0.9 m^3. All experiments had good reproducibility by repeating the experiments in the same conditions.

General procedure for the preparation of pyrimido[4,5-e][1,3,4]thia- diazines 3f–h in microwave irradiation

A mixture of compound 1 (2.5 mmol, 0.61 g), alkyl-2-phenylhydrazinecarbodithioate 2 (2.5 mmol) and triethylamine (1mL) in acetonitrile (5mL) was irradiated under an microwave irradiation (3.67 GHz, 300 W). After the reaction was completed, the mixture was cooled to room temperature and then evaporated under reduced pressure. The residue was washed with water and crystallized from ethanol prior to washing with light petroleum 40–60 to give products 3f–h.

General procedure for the reaction of 3 a-h with hydrazine

A mixture of each compound 3a-h (5 mmol) in ethanol (20 ml) was irradiated under microwave irradiation (3.67 GHz, 300 W) with hydrazine (excess) until complication of the reaction that monitored with TLC. After this step, The solvent was removed and the residue was washed with water and then crystallized from ethanol to give products (4a–h) Scheme-1, TABLE 1.



Scheme 1 : General procedure for the reaction of pyrimido[4,5-e][1,3,4]thia diazines with hydrazine

TABLE 1 : Pyrimido[4, 5- *e*][1, 3, 4]thiadiazin-7-yl) hydrazine derivatives

Entry	R	Time (min)	Yield (%)
3a	CH_3	4	88
3b	$-CH_2-CH_3$	3	90
3c	$-CH_2-CH_2-CH_3$	5	85
3d	$-CH_2-CH_2-CH_2-CH_3$	5	87
3e	$CH_2-C_6H_5$	2	90
3f	$CH_2-C_6H_5$-*P*-Cl	4	85
3g	$CH_2-C_6H_5$-*P*-Br	6	82
3h	$CH_2-C_6H_5$-*P*-NO_2	5	80

All the compounds were characterized with the comparison with our published manuscript[19,20].

RESULTS AND DISCUSSION

Our strategy for the synthesis of (pyrimido[4, 5-*e*][1, 3, 4]thiadiazin-7-yl)hydrazines 4a-h, which are potential precursors for further heterocyclic systems is a hydrazine substitution of the chlorine atom of 3-alkylsulfanyl- 7-Chloro-5-methyl-1-phenyl-1H-pyrimido[4,5-e]- [1,3,4]thiadiazines 3a-h. Compounds 3a-e was recently prepared[11] and new compounds 3f-h were prepared by the same procedure. The struc-

tures assigned to compounds 3f-h were substantiated by spectral data. The ^{1}HNMR spectra were devoid of the signals at 6.0 and 9.0 ppm (δ) for NH groups of precursor's 2f-h and showed further downfield shifts for aromatic protons and a signal at 2.35 ppm for the methyl group of precursor 1 indicating the construction of a thiadiazine ring around the 4- and 5-positions of the pyrimidine ring. Further proofs came from their IR spectra, which lacked the N–H stretching frequencies of their precursor's 2f-h and confirm the presence of the methyl group and the chlorine atom in compounds 3f-h by two stretching frequencies at about 2900 and 850 cm^{-1}, respectively. Mass spectra showed the expected molecular ion peak and the fragmentation pattern indicated the loss of alkylthio groups from compounds 3f–h and 4a-h, which is in line with the proposed structure as shown in Scheme1.

Hence, the condensation of 5-bromo-2,4-dichloro-6-methylpyrimidine 1 with alkyl-2-phenylhydrazinecarbodithioates (2f-h) in alkaline acetonitrile afforded a group of pyrimido[4, 5- e][1, 3, 4]thiadiazine derivatives. Orientation of this reaction was recently determined[11,21].

CONCLUSION

In conclusion, we described a highly efficient microwave induced modification of conventional heating procedure for the preparation of (pyrimido[4, 5- *e*][1, 3, 4]thiadiazin-7-yl)hydrazine that allows for the rapid synthesis of biologically important pyrimidine rings. The advantages of this environmentally benign and safe protocol, included a simple reaction set-up, high product yields, short reaction time as well as the elimination of side products.

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REFERENCES

[1] O.Haruo, T.Hiroshi, S.Masakazu; Nucleic Acids Res.Spec.Publ.5(Symp.Nucleic Acids Chem,6th), 251 **(1978)**.
[2] O.Haruo, T.Hiroshi, K.Emi; J.Carbohydr. Nucleosides., **5**, 329 **(1978)**.
[3] N.Tatehiko, F.Sumiyasu; Japan, Kokai, (Cl.C07D513/ 04), (Chem.Abstr, 59905, 89), March 1978, **78(28)**, 192 **(1978)**.
[4] N.Tatehiko, F.Sumiyasu, Japan, Kokai, (Cl. C07D487/04), March 1978 (Chem. Abstr, 109596, 89), **78(31)**, 694 **(1978)**.
[5] N.Tatehiko; F.Sumiyasu; Chem.Pharm.Bull., **27**, 1965 **(1979)**.
[6] M.Rahimizadeh, M.M.Heravi, A.Malekan; Indian.J.Heterocycl.Chem., **6**, 223 **(1997)**.
[7] A.J.Elliott; J.Heterocycl.Chem., **18**, 799 **(1981)**.
[8] C.S.Madhukar, J.D.Rajesh; Indian J.Chem.Sect.B., **35B**, 251 **(1996)**.
[9] M.Bakavoli, M.Nikpour, M.Rahimizadeh; J.Heterocycl.Chem., **44**, 463 **(2007)**.
[10] M.Bakavoli, M.Rahimizadeh, A.Shiri, H.Eshghi, M.Nikpour; Heterocycles., **75**, 1745 **(2008)**.
[11] M.Nikpour, M.Bakavoli, M.Rahimizadeh, A.Javid, M.R.Bigdeli; Mendeleev Commun., **18**, 284 **(2008)**.
[12] M.Bakavoli, M.Nikpour, M.Rahimizadeh; Phosphorus Sulfur Silicon Relat.Elem., **180**, 2265 **(2005)**.
[13] B.Lynch, M.M.Khan, H.C.A.Teo, F.Pedrotti; Can.J.Chem., **66**, 420 **(1988)**.
[14] F.Seela, H.Steker; Helv.Chim.Acta., **69**, 1602 **(1986)**.
[15] A.Gomtsyan, S.Didomenico, L.A.Chih-Hung, O.Stewart, S.S.Bhagwat, E.A.Kowaluk, M.F.Jarvis; Bioorg.Med.Chem.Lett., **14**, 4165 **(2004)**.
[16] Y.Zhang, G.Jin, B.Illarionov, A.Bacher, M.Fischer, M.Cushman; J.Org.Chem., **72**, 7176 **(2007)**.
[17] T.M.C.Tan, F.Fu, H.Yang, M.S.Raghavendra, Y.J.Lam; Comb.Chem., **9**, 210 **(2007)**.
[18] D.Briel, R.Aurich, U.Egerland, K.Unverferth; Pharmazie., **60**, 732 **(2005)**.
[19] M.Bakavoli, M.Nikpour, M.Rahimizadeh; J.Heterocycl.Chem., **43**, 1327 **(2006)**.
[20] J.Azizian, R.Miri, M.K.Mohammadi, F.Sheikholeslami Farahani, J.Hosseini, M.Nikpour; Phosphorus, Sulfur, and Silicon, **185**, 1782-1787 **(2010)**.
[21] M.Nikpour, M.Bakavoli, M.Rahimizadeh, M.R.Bigdeli, M.Mirzaei; Acta Crystallogr., **E64**, o1491 **(2008)**.