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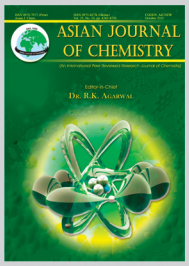

Microwave Assisted Synthesis of 1,2,4-Triazolo[4,3-*a*]perimidines

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Microwave assisted synthesis of some 1,2,4-triazolo[4,3-*a*]perimidines through cyclocondensation reaction of 2-hydrazino-1*H*-perimidine with triethylorthoesters or aryl nitriles in solvent-free conditions is described. The present methodology offers several advantages, such as a simple procedure with an easy work-up, short reaction times, high yields and the absence of any volatile and hazardous organic solvents.

Key Words: 1,2,4-Triazolo[4,3-a]perimidines, Cyclocondensation, Microwave irradiation, Triethylorthoesters.

INTRODUCTION

Perimidines are of interest because they constitute an important class of natural and non-natural products, many of which exhibit useful biological activity[1,2]. Antibacterial, antifungal and cytotoxic activities have been reported for certain of the derivatives[3,4].

On the other hand, 1,2,4-triazoles are also very important organic compounds with wide-ranging biological activities. These compounds are reported to possess significant antiviral[5], antibacterial[6-9], antifungal[5,7,10,11], antiasthmatic[12], antidepressant[13] and antiinflammatory[14-16] activities. Also a number of these compounds have been considered as being tuberculotherapeutics[17], hypoglycemics[18] and diuretics[19]. Furthermore, 1,2,4-triazol-3-ones have special antitumor[20,21] and antibacterial[22] activities.

In light of these findings, we decided to synthesize some derivatives of 1,2,4-triazolo[4,3-*a*]perimidines that might be of pharmacological interest. To the best of our knowledge, microwave assisted synthesis of 1,2,4-triazolo[4,3-*a*]-perimidines has not been reported in the literature.

In recent years, the use of microwave irradiation technique under solvent-free conditions has become popular among chemists both as a means to improve classical organic reactions and promote new reactions[23-26]. The reaction times are often dramatically reduced from hours to minutes or even seconds. These microwave assisted, solvent-free reactions also involve minimal waste, increased yield and easier work-up procedures as compared to the classical synthetic methods.

Due to our interest in the synthesis of new heterocyclic compounds[27-37] and in continuation of our previous works using microwave irradiation in organic reactions[38-44] in this paper we wish to report the synthesis of some 1,2,4-triazolo[4,3-*a*]-perimidines (**5a-f**) through cyclocondensation reaction of 2-hydrazino-1*H*-perimidine **4** with triethylorthoesters or aryl nitriles under microwave irradiation in solvent-free conditions (**Scheme-I**).

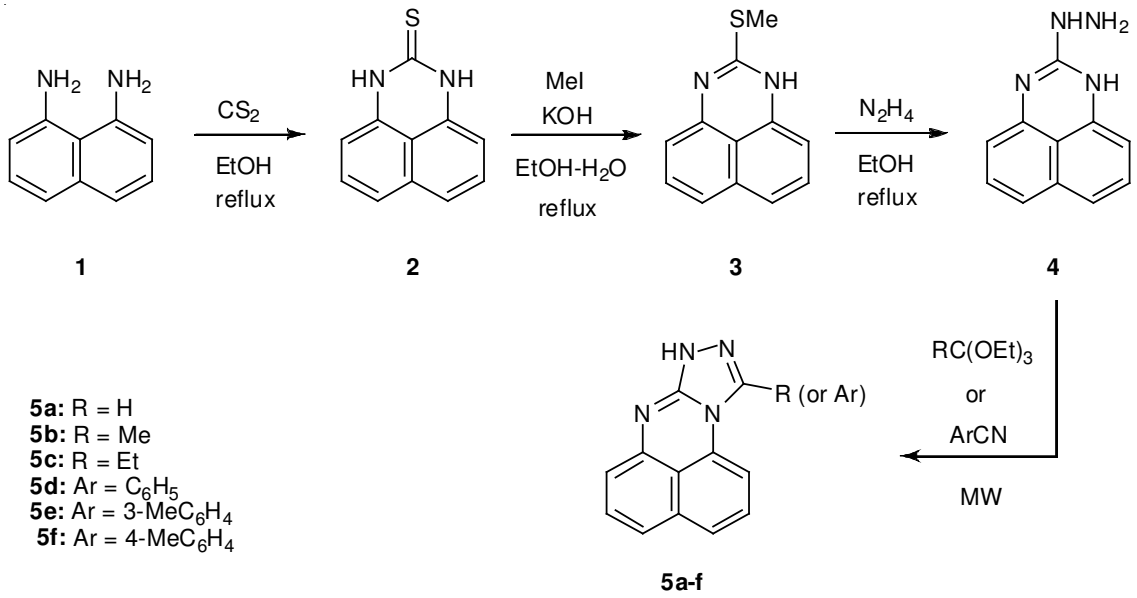
EXPERIMENTAL

Melting points were recorded on a Stuart SMP3 melting point apparatus. The IR spectra were obtained using a Tensor 27 Bruker spectrophotometer as KBr disks. The ^{1}H NMR (100 MHz) spectra were recorded on a Bruker AC 100 spectrometer. The mass spectra were determined on a Shimadzu GCMS 17A instrument.

Synthesis of 1*H*-perimidine-2(3*H*)-thione (2): A mixture of 1,8-diaminonaphthalene (**1**) (10 mmol) and carbon disulfide (20 mmol) in ethanol (10 mL) was heated under reflux for 15 min. The progress of the reaction was monitored by TLC. Upon completion, the reaction mixture was cooled to room temperature, the precipitate was filtered and recrystallized from ethanol to give compound **2**, yield 90 %; m.p. 272 ºC (Lit.[45] 265 ºC).

Synthesis of 2-methylthio-1*H*-perimidine (3): 1*H*-Perimidine-2(3*H*)-thione (**2**) (5 mmol) and methyl iodide (5 mmol) were dissolved in EtOH (10 mL) and H_2O (5 mL) containing KOH (5 mmol). The reaction mixture was stirred at room temperature for 2 h. After this time, the crude product was collected and recrystallized from ethanol to give compound **3**, yield 84 %; m.p. 298-300 ºC (Lit.[45] > 300 ºC).

Synthesis of 2-hydrazino-1*H*-perimidine (4): A mixture of 2-methylthio-1*H*-perimidine (**3**) (5 mmol) and hydrazine hydrate (2.0 mL) in ethanol (10 mL) was heated under reflux for 6 h. The reaction mixture was cooled to room temperature,



Scheme-I: Microwave assisted synthesis of 1,2,4-triazolo[4,3-*a*]perimidines

the precipitate was filtered and recrystallized from ethanol to give compound **4**, yield 82 %; m.p. 188-190 ºC (Lit.[45] 188-191 ºC).

General procedure for the synthesis of 1,2,4-triazolo-[4,3-*a*]perimidines (5a-f): A mixture of 2-hydrazino-1*H*-perimidine (**4**) (3 mmol) and a triethylorthoester or aryl nitrile (4 mmol) was subjected to microwave irradiation at 1000 W for the indicated time. After the completion of the reaction, the crude product was washed with *n*-hexane and recrystallized from ethanol to give compounds **5a-f** in 71-83 % yields (Table-1).

Spectral data for compounds 5a-f

8*H*-1,2,4-Triazolo[4,3-a]perimidine (5a): FTIR (KBr, ν_{max}, cm^{-1}, disc): 3051 (NH); ^1H NMR (DMSO-d_6): δ 6.70-7.60 (m, 6H, arom-H), 9.08 (s, 1H, CH of triazole ring), 11.33 (s br, 1H, NH); MS: m/z 208 (M^+).

10-Methyl-8*H*-1,2,4-triazolo[4,3-*a*]perimidine (5b): FTIR (KBr, ν_{max}, cm^{-1}, disc): 3065 (NH); ^1H NMR (DMSO-d_6): δ 2.78 (s, 3H, CH_3), 6.65-7.60 (m, 6H, arom-H), 11.08 (s. br., 1H, NH); MS: m/z 222 (M^+).

10-Ethyl-8*H*-1,2,4-triazolo[4,3-*a*]perimidine (5c): FTIR (KBr, ν_{max}, cm^{-1}, disc): 3070 (NH); ^1H NMR (DMSO-d_6): δ 1.34 (t, J = 7.4 Hz, 3H, CH_3), 3.18 (q, J = 7.4 Hz, 2H, CH_2), 6.60-7.60 (m, 6H, arom-H), 11.09 (s, br, 1H, NH); MS: m/z 236 (M^+).

10-Phenyl-8*H*-1,2,4-triazolo[4,3-*a*]perimidine (5d): FTIR (KBr, ν_{max}, cm^{-1}, disc): 3084 (NH); ^1H NMR ($CDCl_3$): δ 6.45 (s. br., 1H, NH), 6.90-7.70 (m, 11H, arom-H); MS: m/z 284 (M^+).

10-(3-Methylphenyl)-8*H*-1,2,4-triazolo[4,3-*a*]-perimidine (5e): FTIR (KBr, ν_{max}, cm^{-1}, disc): 3072 (NH); ^1H NMR ($CDCl_3$): δ 2.39 (s, 3H, CH_3), 6.48 (s. br., 1H, NH), 7.00-7.70 (m, 10H, arom-H); MS: m/z 298 (M^+).

10-(4-Methylphenyl)-8*H*-1,2,4-triazolo[4,3-*a*]-perimidine (5f): FTIR (KBr, ν_{max}, cm^{-1}, disc): 3068 (NH); ^1H NMR ($CDCl_3$): δ 2.47 (s, 3H, CH_3), 6.46 (s. br., 1H, NH), 7.00-7.90 (m, 10H, arom-H); MS: m/z 298 (M^+).

RESULTS AND DISCUSSION

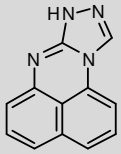
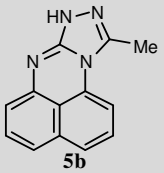
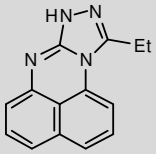
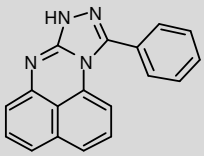
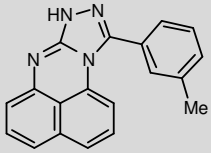
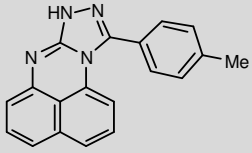
Our synthesis started from 1,8-diaminonaphthalene (**1**) which was converted directly to 1*H*-perimidine-2(3*H*)-thione (**2**) when heated at reflux temperature with carbon disulfide in ethanol. Compound **2** was transformed smoothly to its methylthio derivative (**3**) using methyl iodide in the presence of potassium hydroxide at room temperature. Displacement of the methylthio group with hydrazine hydrate furnished the hydrazino derivative (**4**). Then, treatment of the latter compound with triethylorthoesters or aryl nitriles using microwave irradiation in solvent-free conditions was explored. Thus, the reactants were mixed together and then irradiated at 1000 W for the indicated time, using a domestic microwave oven Model LG MS-543XD, to give the desired tetracyclic products, 1,2,4-triazolo[4,3-*a*]perimidines (**5a-f**) in high yields. The results are summarized in Table-1.

The structure of the products **5a-f** were established from their spectral data. For example, the IR spectrum of **5b** did not exhibit the stretching vibration bands at 3340, 3260 and 3050 cm^{-1} due to NH_2 and NH groups of precursor **4**[45] but showed a sharp band at 3065 cm^{-1} for NH vibration. The ^1H NMR spectrum in DMSO-d_6 showed the disappearance of two broad signals belonging to NH_2 and NH moieties of compound **4** and the appearance of a singlet broad 1H (NH) signal at δ 11.08 ppm which was removed on deuteration along with a multiplet at 6.65-7.60 ppm due to 6 aromatic protons as well as one singlet at 2.78 ppm for methyl group. Also, the molecular ion of compound **5b** was observed at m/z 222 (M^+), corresponding to the molecular formula $C_{13}H_{10}N_4$ (experimental section).

Conclusion

A microwave assisted synthesis of 1,2,4-triazolo[4,3-*a*]-perimidines in solvent-free conditions is reported. This method offers several advantages, such as a simple procedure with an easy work-up, short reaction time, high yields and the absence of any volatile and hazardous organic solvents.

TABLE-1
SYNTHESIS OF 1,2,4-TRIAZOLO[4,3-a]PERIMIDINES **5a-f** USING MICROWAVE IRRADIATION IN SOLVENT-FREE CONDITIONS*

Entry	R	Ar	Products	Time (min)	Yields (%)**	m.p. (ºC)
1	H	–	 **5a**	6	76	320-322
2	Me	–	 **5b**	9	71	308-310
3	Et	–	 **5c**	9	73	294-296
4	–	C_6H_5	 **5d**	12	83	170-172
5	–	3-MeC_6H_4	 **5e**	12	78	153-155
6	–	4-MeC_6H_4	 **5f**	9	79	147-149

*2-Hydrazino-1*H*-perimidine (**4**) (3 mmol) and a triethylorthoester or aryl nitrile (4 mmol) under microwave irradiation at 1000 W. **Isolated yields.

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REFERENCES

1. K. Undheim and T. Benneche, In eds.: A.R. Katritzky, C.W. Rees and E.F.V. Scriven, In Comprehensive Heterocyclic Chemistry, Pergamon, Oxford, Vol. 6, pp. 93-231 (1996).
2. A.F. Pozharskii and V.V. Dalnikovskaya, *Russ. Chem. Rev. (Engl. Trans.)*, **50**, 816 (1981).
3. D.R. Panchasara and S. Pande, *E. J. Chem*., **6**, S91 (2009).
4. X.Y. Bu, J.J. Chen, L.W. Deady, C.L. Smith, B.C. Baguley, D. Greenhalgh, S.J. Yang and W.A. Denny, *Bioorg. Med. Chem*., **13**, 3657 (2005).
5. S. Papakonstantinou-Garoufalias, E. Filippatos, O. Todoulou, A. Tsantili-Kakolidou and A. Papadaki-Valikari, *Farmaco*, **52**, 707 (1997).
6. A.A. Ikizler, C.B. Johansson, O. Bekircan and C. Celik, *Acta. Pol. Pharm*., **56**, 283 (1999).
7. N. Ulusoy, A. Gursoy and G. Otuk, *Farmaco*, **56**, 947 (2001).
8. B.N. Goswami, J.C.S. Kataky and J.N. Baruah, *J. Heterocycl. Chem*., **21**, 1225 (1984).
9. H.N. Dogan, S. Rolla and H. Erdeniz, *IL Farmaco*, **53**, 462 (1998).
10. T. Konosu, Y. Tajima, N. Takeda, T. Miyaoka and M. Kasahara, *Chem. Pharm. Bull*., **39**, 2581 (1991).
11. N.N. Gulerman, H.N. Dogan, S. Rollas, C. Johonsson and C. Celike, *IL Farmaco*, **56**, 953 (2001).
12. Y. Naito, F. Akahoshi, S.. Takeda, T. Okada, M. Kajii, H. Nishimura, M. Sugiura, C. Fukaya and Y. Kagitani, *J. Med. Chem*., **39**, 3019 (1996).
13. J.M. Kane, MW. Dudley, S.M. Sorensen and F.P. Miller, *J. Med. Chem*., **31**, 1253 (1988).
14. S. Schenone, O. Bruno, A. Ranise, F. Bondavalli, W. Filippeli, F. Rossi and G. Falcone, *IL Farmaco*, **53**, 590 (1998).
15. M. Tandon, J.P. Bathhwal, T.N. Bhatia and K.P. Bhargava, *Indian J. Chem., B*, **20B**, 1017 (1981).
16. M.B. Talawar, S.C. Bennur, S.K. Kankanwadi and P.A. Patil, *Indian J. Pharm. Sci*., **57**, 194 (1995).
17. I. Mir and M.T. Siddiqui, *Tetrahedron*, **26**, 5235 (1970).
18. M.Y. Mhasalkar, M.H. Shah, S.T. Nikam, K.G. Anantanarayanan and C.V. Deliwala, *J. Med. Chem*., **13**, 672 (1970).

19. M.H. Shah, M.Y. Mhasalkar, V.M. Patki, C.V. Deliwala and U.K. Sheth, *J. Pharm. Sci*., **58**, 1399 (1969).
20. N. Demirbas, R. Ugurluoglu and A. Demirbas, *Bioorg. Med. Chem*., **10**, 3717 (2002).
21. A.A. Ikizler, A. Ikizler, M. Serdar and N. Yildirim, *Acta Pol. Pharm*., **54**, 363 (1997).
22. R. Milcent, P. Vicart and A.M. Bure, *Eur. J. Med. Chem. Chim. Ther*., **18**, 215 (1983).
23. P. Lidstrom, J. Tierney, B. Wathey and J. Westman, *Tetrahedron*, **57**, 9225 (2001).
24. J.S. Yadav and B.V.S. Reddy, *Tetrahedron Lett*., **43**, 1905 (2002).
25. A. Davoodnia, M. Bakavoli, N. Zareei and N. Tavakoli-Hoseini, *Bulg. Chem. Commun*., **41**, 226 (2009).
26. A. Davoodnia, M. Rahimizadeh, H. Atapour-Mashhad and N. Tavakoli-Hoseini, *Heteroatom Chem*., **20**, 346 (2009).
27. M. Bakavoli, A. Davoodnia, M. Rahimizadeh, M.M. Heravi and M. Ghassemzadeh, *J. Chem. Res*., **1**, 178 (2002).
28. M. Bakavoli, A. Davoodnia, M. Rahimizadeh and M. M. Heravi, *Phosphorus, Sulfur Silicon Rel. Elem.*, **177**, 2303 (2002).
29. M. Roshani, A. Davoodnia, M.Sh. Hedayat and M. Bakavoli, *Phosphorus, Sulfur Silicon Rel. Elem.*, **179**, 1153 (2004).
30. M. Bakavoli, A. Davoodnia, M. Rahimizadeh and M.M. Heravi, *Mendeleev Commun.*, **16**, 29 (2006).
31. A. Davoodnia, M. Bakavoli, A. Vahedinia, M. Rahimizadeh and M. Roshani, *Heterocycles*, **68**, 801 (2006).
32. A. Davoodnia, R. Zhiani, M. Roshani, M. Bakavoli and M. Bashash, *Phosphorus, Sulfur Silicon Rel. Elem.*, **182**, 1219 (2007).
33. A. Davoodnia, H. Behmadi, A. Zare-Bidaki, M. Bakavoli and N. Tavakoli-Hoseini, *Chin. Chem. Lett*., **18**, 1163 (2007).
34. A. Davoodnia, M. Bakavoli, N. Pooryaghoobi and M. Roshani, *Heterocycl. Commun*., **13**, 323 (2007).
35. A. Davoodnia, M. Bakavoli, M. Bashash, M. Roshani and R. Zhiani, *Turk. J. Chem*., **31**, 599 (2007).
36. A. Davoodnia, M. Bakavoli, Sh. Mohseni and N. Tavakoli-Hoseini, *Monatsh. Chem*., **139**, 963 (2008).
37. A. Davoodnia, R. Zhiani and N. Tavakoli-Hoseini, *Monatsh. Chem*., **139**, 1405 (2008).
38. A. Davoodnia, M. Bakavoli, F. Khorramdelan and M. Roshani, *Indian J. Heterocyl. Chem*., **16**, 147 (2006).
39. A. Davoodnia, M. Rahimizadeh, Sh. Rivadeh, M. Bakavoli and M. Roshani, *Indian J. Heterocyl. Chem*., **16**, 151 (2006).
40. A. Davoodnia, M. Roshani, S.H. Malaeke and M. Bakavoli, *Chin. Chem. Lett*., **19**, 525 (2008).
41. A. Davoodnia, S. Allameh, A.R. Fakhari and N. Tavakoli-Hoseini, *Chin. Chem. Lett*., **21**, 550 (2010).
42. A. Davoodnia, *Asian J. Chem*., **22**, 1591 (2010).
43. A. Davoodnia, L. Anvari and N. Tavakoli-Hoseini, *Asian J. Chem*., **23**, 3683 (2011).
44. A. Davoodnia, M. Kosari and N. Tavakoli-Hoseini, *Asian J. Chem*., **23**, 3654 (2011).
45. K.C. Liu and H.H. Chen, *J. Heterocycl. Chem*., **21**, 911 (1984).