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A new green protocol for the synthesis of 2-substituted perimidines from hydrazones under catalyst- and solvent-free conditions

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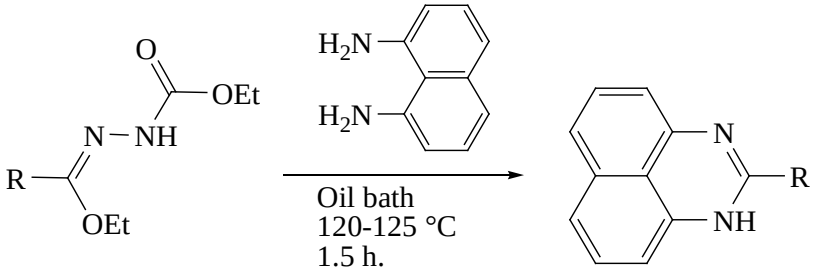

A new green protocol was developed for the synthesis of 2-substituted perimidines. The protocol involves a reaction of ethoxy carbonylhydrazone with 1,8-diaminonaphthalene under solvent- and catalyst-free conditions. Simple workup procedure, economical and environmentally benign are the most advantages of the present method.

Keywords: Perimidine, Hydrazone, Green synthesis, 1,8-Diaminonaphthalene, Catalyst-free conditions

INTRODUCTION

Perimidines, also called 1*H*-benzo[d,e] quinazolines or perinaphthimidazoles, are an interesting heterocyclic system because they include both an excess and a deficiency of π electrons [1-3] and these systems show amphoteric chemical properties [1, 2]. Their derivatives have been used in industry for dyeing of various fibres, as additives to liquid crystal displays, as sources of carbine ligands [4]. They exhibit reversible photochromic and thermochromic properties and are thus used in molecular switches, and photochemical memory devices [5-7]. Recently, the biological activity of perimidines has attracted the attention of organic chemists. Various perimidine derivatives have been found effective as neurotropic preparations

[8]. Also, some synthetic perimidine derivatives are found which have anticancer [9], cytostatic [10], antimicrobial [11] and antifungal activities [12].

Literature surveys reveal that there are many protocols for the synthesis of perimidine derivatives. Many methods provide the condensation of 1,8-diaminonaphthalene and carboxylic acids or their derivatives such as aldehydes, acylhalides, anhydrides, nitriles and imidates [12-17] (Scheme 1). However, these methods generally require a catalyst, long reaction time and difficult purification steps. Also, the yield is low due to side reactions. Therefore, there is a need for an easy and efficient method for the synthesis of perimidine derivatives.

The increasing need for environmental protection has led our researches to develop chemical processes with maximum yield and minimum cost while using nontoxic reagents, solvents and catalysts. For this propose, a new method was developed for the synthesis of perimidine derivatives, which is environmentally benign, simple and economical by condensation of 1,8-diaminonaphalene and 2-[(alkyl/aryl) (ethoxy)methylidene]hydrazinecarboxylates. This is the first synthesis of perimidine derivatives from ethoxy carbonylhydrazones and 1,8-diaminonaphthalene. This reaction requires neither solvents nor harmful reagents.

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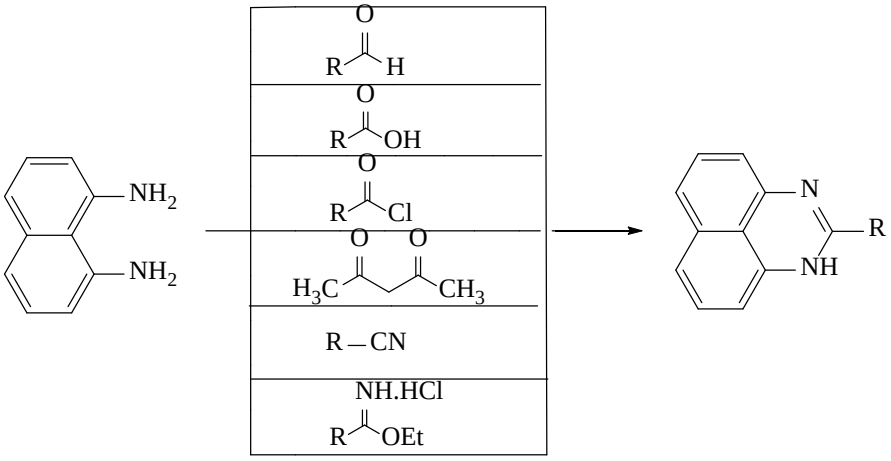


Scheme 1. The synthetic approach for perimidines

EXPERIMENTAL

All chemicals were supplied from Merck (Darmstadt, Germany), Aldrich and Fluka (Buchs SG, Switzerland). Melting points were determined in capillary tubes on a Büchi oil-heated melting point apparatus (Essen, Germany) and uncorrected. ^{1}H-NMR spectra were recorded on the Varian-Mercury 400 MHz spectrometer (Varian, Darmstadt, Germany) in DMSO-d_6 using TMS as internal standard. Mass spectra were recorded on a Thermo Scientific Quantum Access max LC-MS spectrometer. The elemental compositions were determined on a Carlo Erba 1106 CHN analyzer (Heraeus, Hanau, Germany); the experimental values were in agreement (±0.4 %) with the calculated ones. All reactions were monitored by TLC using precoated aluminum sheets (silica gel 60 F 2.54, 0.2 mm thickness).

Synthesis of compounds 3-14

The corresponding ethoxy carbonylhydrazones (**2**) (0.01 mol) and 1,8-diaminonaphthalene (0.01 mol) were heated in an oil bath at 120-125 °C for 1.5 h. The mixture was cooled to room temperature. The product was recrystallized from EtOH–H_2O /1:2 to give the pure product.

2-Methyl-1H-perimidine (**3**)

Yield: 1.33 g (%73), m.p. 215-216 °C (213-214 °C [12]). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 10.54 (s, 1H, NH), 7.30 (d, *J* = 7.6 Hz, 2H, Ar-H), 7.20 (t, *J* = 7.6 Hz, 2H, Ar-H), 7.47 (dd, *J* = 7.7 Hz & *J* = 2.0 Hz, 2H, Ar-H), 2.29 (s, 3H, CH_3); LC-MS: 183.24 $[M+H]^+$. Anal. Calcd. for $C_{12}H_{10}N_2$, C:79.10, H:5.53, N: 15.37; Found, C:79.04, H:5.47, N: 15.31.

2-Phenyl-1H-perimidine (**4**)

Yield: 1.73 g (%71), m.p. 189-190 °C (187-188 °C [18]). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 10.63 (s, 1H, NH), 8.00 (s, 2H, Ar-H), 7.55-7.48 (m, 3H, Ar-H), 7.16-7.01 (m, 4H, Ar-H), 6.67 (d,*J* = 8.0 Hz, 1H, Ar-H), 6.52 (d, *J* = 8.0 Hz, 1H, Ar-H); LC-MS: 245.34 $[M+H]^+$. Anal. Calcd. for $C_{17}H_{10}N_2$, C:83.58, H:4.95, N: 11.47; Found, C:83.50, H:4.86, N: 11.42.

2-Benzyl-1H-perimidine (**5**)

Yield: 1.75 g (%68), m.p. 196-197 °C (196-197 °C [16]). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 7.62 (d, *J* = 7.0 Hz, 2H, Ar-H), 7.47-7.27 (m, 7H, Ar-H), 6.84 (d, *J* = 2.4 Hz, 2H, Ar-H), 3.95 (s, 2H, CH_2); LC-MS: 259.09 $[M+H]^+$. Anal. Calcd. for $C_{18}H_{14}N_2$, C:83.69, H:5.46, N: 10.84; Found, C: 83.60, H:5.38, N: 10.76.

2-(4-Chlorobenzyl-1H-perimidine) (**6**)

Yield: 1.28 g (%78), m.p. 184-185 °C (183-185 °C [16]). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 10.65 (s, 1H, NH), 7.39 (t, *J* = 7.0 Hz, 2H, Ar-H), 7.10-6.97 (m, 6H, Ar-H), 6.88 (d, *J* = 7.0 Hz, 1H, Ar-H), 6.40 (d, *J* = 7.0 Hz, 1H, Ar-H), 3.57 (s, 2H, CH_2); LC-MS: 293.86 $[M+H]^+$. Anal. Calcd. for $C_{18}H_{13}ClN_2$, C:73.85, H:4.48, N: 9.57; Found, C: 73.80, H:4.42, N: 9.51.

2-(4-Methylbenzyl-1H-perimidine) (**7**)

Yield: 1.87 g (%69), m.p. 163-164 °C (159-160 °C [19]) ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 11.70 (s, 1H, NH), 7.36 (d, *J* = 7.6 Hz, 2H, Ar-H), 7.14-7.07 (m, 6H, Ar-H), 6.57 (d, *J* = 7.6 Hz, 2H, Ar-H), 3.66 (s, 2H, CH_2), 2.24 (s, 3H, CH_3); LC-MS: 273.36 $[M+H]^+$. Anal. Calcd. for $C_{19}H_{16}N_2$, C:83.79, H:5.92, N: 10.29; Found, C: 83.71, H:5.85, N: 10.24.

2-(4-Fluorobenzyl-1H-perimidine) (**8**)

Yield: 1.85 g (%67), m.p. 174-175 °C (173-175 °C [16]). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 10.61 (s, 1H, NH), 7.42 (t, *J* = 7.0 Hz, 2H, Ar-H), 7.19-6.97 (m, 6H, Ar-H), 6.51 (d, *J* = 7.0 Hz, 1H, Ar-H), 6.28 (d, *J* = 7.0 Hz, 1H, Ar-H), 3.54 (s, 2H, CH_2); LC-MS: 277.26 $[M+H]^+$. Anal. Calcd. for $C_{18}H_{13}FN_2$, C:78.24, H:4.74, N: 10.14; Found, C: 78.20, H:4.68, N: 10.08.

2-(4-Bromobenzyl-1H-perimidine) (**9**)

Yield: 2.56 g (%76), m.p. 172-173 °C (170-172 °C [16]). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 10.62 (s, 1H, NH), 7.53 (t, *J* = 8.4 Hz, 2H, Ar-H), 7.36 (d, *J* = 8.0 Hz, 2H, Ar-H), 7.09 (t, *J* = 7.6 Hz, 2H, Ar-H), 6.98 (d, *J* = 8.4 Hz, 2H, Ar-H), 6.43 (brs, 2H, Ar-H), 3.56 (s, 2H, CH_2); LC-MS: 339.23, 337.19 $[M+H]^+$. Anal. Calcd. for $C_{18}H_{13}BrN_2$, C:64.11, H:3.89, N: 8.31; Found, C: 64.06, H:3.84, N: 8.26.

2-(4-Methoxybenzyl-1H-perimidine) (**10**)

Yield: 2.04 g (%71), m.p. 205-206 °C (205 °C [19]) ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 10.30 (s, 1H, NH), 7.34 (d, *J* = 5.6 Hz, 2H, Ar-H), 7.08 (t, *J* = 5.2 Hz, 2H, Ar-H), 6.97 (t, *J* = 5.6 Hz, 2H, Ar-H), 6.89 (d, *J* = 5.2 Hz, 2H, Ar-H), 6.46 (d, *J* = 5.6 Hz, 2H, Ar-H), 3.69 (s, 3H, OCH_3), 3.53 (s, 2H, CH_2); LC-MS: 289.46 $[M+H]^+$. Anal. Calcd. for $C_{19}H_{16}N_2O$, C:79.14, H:5.59, N: 9.72; Found, C: 79.10, H:5.52, N: 9.65.

2-(3-Chlorobenzyl-1H-perimidine) (**11**)

Yield: 1.92 g (%66), m.p. 175-176 °C (175-176 °C [16]). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 10.65 (s, 1H, NH), 7.59 (s, 1H, Ar-H), 7.45-7.25 (m, 3H, Ar-H), 7.10-6.95 (m, 4H, Ar-H), 6.54 (d, *J* = 6.6 Hz, 1H,Ar-H), 6.27 (d, *J* = 7.0 Hz, 1H,Ar-H), 3.56 (s, 2H, CH_2); LC-MS: 293.79 $[M+H]^+$. Anal. Calcd. for $C_{18}H_{13}ClN_2$, C:73.85, H:4.48, N: 9.57; Found, C: 73.81, H:4.40, N: 9.49.

2-(3-Methylbenzyl-1H-perimidine) (**12**)

Yield: 2.12 g (%78), m.p. 176-177 °C (175-176 °C [16]). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 10.67 (s, 1H, NH), 7.59 (s, 1H, Ar-H), 7.48-7.27 (m, 3H, Ar-H), 7.13-6.92 (m, 4H, Ar-H), 6.52 (d, *J* = 7.0 Hz, 1H,Ar-H), 6.29 (d, *J* = 7.0 Hz, 1H,Ar-H), 3.61 (s, 2H, CH_2), 2.12 (s, 3H, CH_3); LC-MS: 273.36 $[M+H]^+$. Anal. Calcd. for $C_{19}H_{16}N_2$, C:83.79, H:5.92, N: 10.29; Found, C: 83.71, H:5.85, N: 10.24.

2-(3-Fluorobenzyl-1H-perimidine) (**13**)

Yield: 2.18 g (%79), m.p. 164-165 °C (163-164 °C [16]).^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 10.76 (s, 1H, NH), 7.88 (s, 2H, Ar-H), 7.72-7.30 (m, 2H, Ar-H), 7.10-6.95 (m, 4H, Ar-H), 6.41 (d, *J* = 6.6 Hz, 1H,Ar-H), 6.25 (d, *J* = 6.6 Hz, 1H,Ar-H), 3.72 (s, 2H, CH_2); LC-MS: 277.61 $[M+H]^+$. Anal. Calcd. for $C_{18}H_{13}FN_2$, C:78.24, H:4.74, N: 10.14; Found, C: 78.18, H:4.69, N: 10.06.

2-(3-Bromobenzyl-1H-perimidine) (**14**)

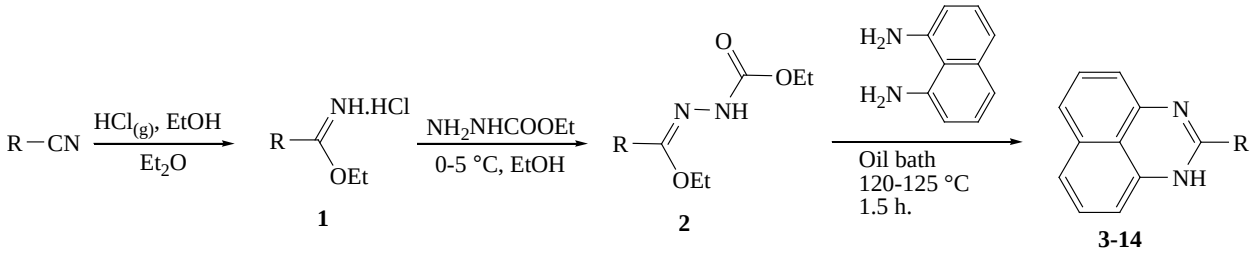
Yield: 2.76 g (%82), m.p. 162-163 °C (160-162 °C [16]). ^{1}H-NMR (400 MHz, DMSO-d_6, δ, ppm) δ 10.69 (s, 1H, NH), 7.63 (s, 1H, Ar-H), 7.54-7.20 (m, 3H, Ar-H), 7.10-6.79 (m, 4H, Ar-H), 6.55 (*dd*, *J*=6.6 Hz & *J*=1.2 Hz, 1H, Ar-H), 6.23 (*dd*, *J*=7.0 Hz & *J*=1.5 Hz, 1H, Ar-H), 3.56 (s, 2H, CH_2). LC-MS: 339.25, 337.29 $[M+H]^+$. Anal. Calcd. for $C_{18}H_{13}BrN_2$, C:64.11, H:3.89, N: 8.31; Found, C: 64.03, H:3.81, N: 8.25.

RESULTS AND DISCUSSION

The syntheses of new perimidine derivatives were carried out by reacting 1,8-diaminonaphthalene with an equimolar amount of ethoxy carbonylhydrazone. The reaction was performed in an oil bath at 120-125 °C without using solvent and catalyst. In this reaction, ethoxy carbonylhydrazones were used instead of iminoesters because hydrazones are more stable than iminoesters. The approach provides an environmentally friendly pathway to obtain good yields. Moreover, ethoxy carbonylhydrazones were used for the first time to obtain perimidine derivatives, therefore, this technique is a good alternative to other synthetic methods of perimidine derivatives.

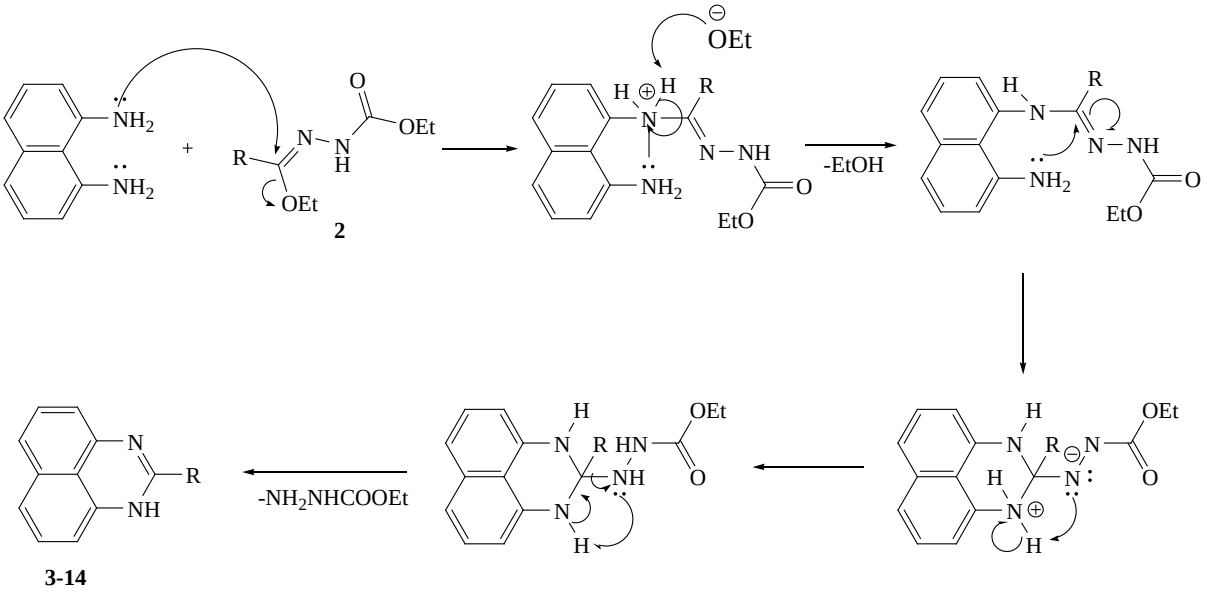
Firstly, iminoester hydrochlorides (**1**) were obtained by the Pinner method [20]. The reaction of ethyl carbazate with iminoester hydrochlorides (**1**) gave ethoxy carbonylhydrazones (**2**) which are useful intermediates for synthesis of potential bioactive heterocyclic compounds such as benzimidazole and triazole derivatives [21-27]. Then, 2-substituted perimidine derivatives (**3-14**) were synthesized by the reaction of ethoxy carbonylhydrazones with 1,8-diaminonaphthalene under solvent- and catalyst-free conditions (Scheme 2).

A mechanism of the type shown in Scheme 3 proposed for this reaction appears likely. In a former study, iminoester hydrochlorides were used by our group under solvent-free conditions to obtain perimidines, but the result was negative because of decomposition of iminoethers (**1**) at high temperatures. In this work, hydrazones (**2**) were used instead of iminoester hydrochlorides at high temperatures and the result was positive.



R: CH_3, C_6H_5, $C_6H_5CH_2$, 4-$ClC_6H_4CH_2$, 4-$BrC_6H_4CH_2$, 4-$FC_6H_4CH_2$, 4-$CH_3C_6H_4CH_2$, 4-$CH_3OC_6H_4CH_2$, 3-$ClC_6H_4CH_2$, 3-$BrC_6H_4CH_2$, 3-$FC_6H_4CH_2$, 3-$CH_3C_6H_4CH_2$

Scheme 2. Synthesis of 2-substituted perimidines



Scheme 3. Proposed mechanism for the cyclization reaction**.**

CONCLUSION

In conclusion, a green new method for the synthesis of 2-substituted perimidine derivatives was developed. In this method, 2-[(alkyl/aryl)(ethoxy)methylidene] hydrazine carboxylates were used for the first time to obtain perimidine derivatives. The present protocol was achieved under solvent- and catalyst-free conditions. Therefore, this method is more important than others in terms of green chemistry.

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НОВ "ЗЕЛЕН" ПРОТОКОЛ ЗА СИНТЕЗ НА 2-ЗАМЕСТЕНИ ПЕРИМИДИНИ ОТ ХИДРАЗОНИ В ОТСЪСТВИЕ НА КАТАЛИЗАТОР И РАЗТВОРИТЕЛ

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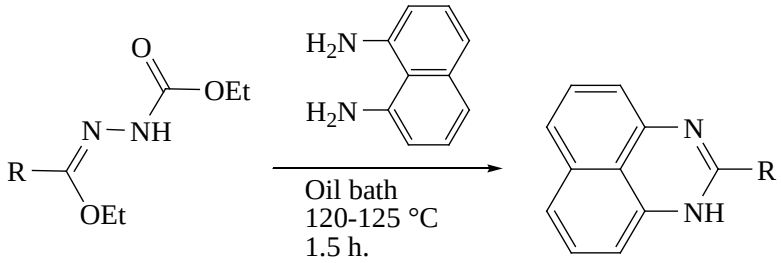
(Резюме)



Предложен е нов "зелен" протокол за синтез на 2-заместени перимидини. Протоколът включва реакция на етокси карбонилхидразон с 1,8-диаминонафталин в отсъствие на разтворител и катализатор. Процедурата е проста за изпълнение, икономична и щадяща околната среда.