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A Green and Efficient One-pot Synthesis of Propanamides by a Three-component Reaction of 2-(2-oxopropyl) isoindoline-1,3-dione, Alkyl isocyanide and an *E*-cinnamic acid under Catalyst-free Conditions in Water

Ali Ramazani[1,*], Ali Jafari[1], Sang Woo Joo[2,*], Yavar Ahmadi3, Fariba Sadri[4], Pegah Azimzadeh Asiabi[1]

[1]Department of Chemistry, University of Zanjan, Zanjan, Iran
[2]School of Mechanical Engineering, Yeungnam University, Gyeongsan, Republic of Korea
[3]North West Reseach Complex, Nuclear Science and Technology Research Institute, Bonab, Iran
[4]Department of Chemistry, Payame Noor University, Tehran, Iran
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Abstract

A green and convenient protocol is described for the preparation of *E*-1-(alkylamino)-3-(1,3-dioxoisoindolin-2-yl)-2-methyl-1-oxopropan-2-yl viaone-pot three-component reaction between 2-(2-oxopropyl)isoindoline-1,3-dione, an alkyl isocyanide and an E-cinnamic acid in water at room temperature. The methods used to follow the reactions are TLC and NMR, which indicated that there is no side product and the products were obtained without any purification. The structures of the products were deduced from their ^{1}H NMR, ^{13}C NMR and IR spectra. The present methodology offers several advantages such as a simple procedure, catalyst-free, mild reaction conditions, high yields, and the absence of any volatile and hazardous organic solvents.

***Keywords**: 2-(2-oxopropyl)isoindoline-1,3-dione, Alkyl isocyanide, E-cinnamic acid.*

Introduction

For the synthetic chemist, water is an ideal solvent for chemical synthesis because it is safe, non-toxic, not inflammable, environmentally friendly, readily available, and cheap compared to organic solvents [1]. In the past years, water was not used as a solvent for synthetic organic chemistry due to the poor

***Corresponding author:** Dr. Ali Ramazani, Department of Chemistry, University of Zanjan, P.O. BOX 45195-313, Zanjan, Iran. E-mail:aliramazani@gmail.com.*
Dr. Sang Woo Joo, School of Mechanical Engineering, Yeungnam University, Gyeongsan 712-749, Republic of Korea. E-mail: swjoo@yu.ac.kr.

solubility and, in some cases, the instability of organic reagents in aqueous solutions. But nowadays, It is well known that chemical reactions in mixed aqueous solutions or two-phase systems often give better results than in organic solvents and often the insolubility of the final products facilitates their isolation [2,3]. Organic reactions in water exhibit unique reactivity and selectivity that are different from reactions in organic solvent. In particular, reactions with negative activation volume are reported to occur faster in water than in organic solvents [4]. In 1980, Rideout and Breslow [5] discovered a rate increase by a factor of more than 700 when the Diels-Alder reaction is performed in water instead of hydrocarbons. Breslow explained his results on the basis of hydrophobic interactions that induce a favorable association of the apolar components in the polar water.

In recent years, multicomponent reactions (MCRs) have become an important tool in novel primary synthetic chemistry as these reactions expand the efficiency by combining several operational steps without any isolation of intermediates or changes in the conditions [6−16]. Hence, this principle is very efficient in terms of time as nice as resources [17]. Amongst the known MCRs, the most valuable reactions are those based on isocyanides. Isocyanide-based multicomponent reactions (abbreviated to IMCRs by Ugiand Dömling) [18−21] due to their synthetic potential, their inherent atom efficiency, convergent nature, ease of implementation, and molecular diversity have attracted much attention. Therefore, because of these advantages they offer a valuable tool in the field of combinatorial chemistry [22−24].

Catalyst-free organic reactions in water are very important based on green chemistry protocols [25]. Herein a catalyst-free and an efficient green protocol for the synthesis of *E*-1-(alkylamino)-3-(1,3-dioxoisoindolin-2-yl)-2-methyl-1-oxopropan-2-yl derivatives (**4**) *via* one-pot three-component reaction between 2-(2-oxopropyl)isoindoline-1,3-dione (**1**), an alkyl isocyanide (**2**) and an E-cinnamic acid (**3**) in water at room temperature is reported (Scheme 1).

Experimental

Material and methods

Starting materials and solvents were purchased from Merck (Germany) and Fluka (Switzerland) and were used without further purification. The methods used to follow the reactions are TLC and NMR, which indicated that there is no side product. Melting points were measured on an Electrothermal 9100 apparatus and are uncorrected. The IR spectra were measured on a Jasco 6300 FTIR spectrometer. ^{1}H- and ^{13}C-NMR spectra were measured ($CDCl_3$) with a BRUKER DRX-250 AVANCE spectrometer at 250.0 and 62.89 MHz, respectively.2-(2-oxopropyl)

isoindoline-1,3-dione (**1**) were prepared based on known procedure [26].

*General procedure for the preparation of **4a-j***

A mixture of 2-(2-oxopropyl)isoindoline-1,3-dione (**1**) (1 mmol, 0.203 g), an alkyl isocyanide(**2**) (1mmol, cyclohexylisocyanide, t-butyl isocyanide and n-butylisocyanide) and an *E*-cinnamic acid(**3**) (1 mmol; 0.162 g, α-methyl *E*-cinnamic acid; 0.182 g, 3-Chloro *E*-cinnamic acid; 0.166 g, 4-Fluoro *E*-cinnamic acid; 0.162g, 4-Methyl *E*-cinnamic acid) in H_2O (5 mL) was stirred at room temperature for 24h. After the completion of the reaction, the solvent was removed under reduced pressure, and the products were obtained without any purification. The products were dried at room temperature during two days.

Table1. Preparation of *E*-1-(alkylamino)-3-(1,3-dioxoisoindolin-2-yl)-2-methyl-1-oxopropan-2-yl derivatives.

4	R	R′	R″	Yield%
a	Cyclohexyl	Me	H	95
b	Cyclohexyl	H	4-F	92
c	Cyclohexyl	H	3-Cl	93
d	Cyclohexyl	H	4-Me	95
e	*tert*-Buthyl	Me	H	95
f	*tert*-Buthyl	H	4-F	94
g	*tert*-Buthyl	H	4-Me	88
h	*n*-Buthyl	Me	H	95
i	*n*-Buthyl	H	4-F	86
j	*n*-Buthyl	H	4-Me	87

The characterization data of the compounds (**4a-j**) are given below:

*(E)-1-(Cyclohexylamino)-3-(1,3-dioxoisoindolin-2-yl)-2-methyl-1-oxopropan-2-yl 2-methyl-3-phenylacrylate (**4a**)*

Pale Yellow oil,yield :95%,IR (KBr): ν=3342 ,3057,2925,2854,1777,1732,1670,1537cm^{-1}. ^{1}H NMR (250MHz,$CDCl_3$): 1.00-1.86 (10H, $5CH_2$), 1.72 (3H,s , CH_3), 2.10 (3H, s, CH_3), 3.79 (1H ,d, $^3J_{HH}$=7.75 Hz, CH), 4.29 and 4.36 (2H ,AB quartet, $^2J_{HH}$=16.0 Hz, CH_2), 5.89 (1H,d, $^3J_{HH}$= 7.75 Hz, NH), 7.35-7.83 (m, 10H, 9CH, arom, 1CH, alkene)ppm. ^{13}C NMR (62.59MHz, $CDCl_3$): 14.10 (CH_3), 20.97 (CH_2), 24.62 (CH_3), 25.45($2CH_2$), 32.66 ($2CH_2$), 43.35 (CH), 48.14 (CH2), 82.31 (C), 123.42 و 128.36 و128.17 و 139.94 ,135.74 ,134.13 ,131.88 ,129.80 ,128.50 12)C, arom, 2C, alken), 166.99 (C=O), 168.05 (2C=O), 169.19 (C=O)ppm.

*(E)-1-(Cyclohexylamino)-3-(1,3-dioxoisoindolin-2-yl)-2-methyl-1-oxopropan-2-yl 3-(4-fluorophenyl)acrylate (**4b**)*

Pale Yellow oil,yield :92%,IR (KBr): ν =3325, 3068, 2930, 2854, 1776, 1723, 1638, 1509,

721cm^{-1}.^{1}H NMR (250MHz, $CDCl_3$): 0.84-1.92(10H, 5CH_2), 1.69 (3H , s, CH_3), 3.76 (1H , d, $^{3}J_{HH}$=7.75 Hz, CH), 4.36 (2H, CH_2), , 5.88 (1H, d, $^{3}J_{HH}$= 8.0 Hz, NH), 6.32 (1H,d, $^{3}J_{HH}$=16.0 Hz, CH), 7.07-7.83 (m, 9H, 4CH, Arom, 1CH, alkene) ppm. ^{13}C NMR (62.89MHz, $CDCl_3$): 21.24 (CH_2), 24.71 (CH_3), 25.45(2CH_2), 32.72 (2CH_2), 43.10 (CH), 48.26 (CH_2), 82.33 (C), 116.02 (d, $^{2}J_{CF}$=22.0 Hz), 117.63 (CH), 123.45 (2CH,arom), 130.39(d, $^{3}J_{CF}$=8.5 Hz, 2CH, orto), 130.54 (C), 131.88 (2C,arom), 134.12 (2CH,arom), 144.57(CH), 164.23 (d, $^{1}J_{CF}$= 251 Hz, C) 165.08 (C=O), 168.13 (C=O), 169.10 (C=O)ppm.

*(E)-1-(Cyclohexylamino)-3-(1,3-dioxoisoindolin-2-yl)-2-methyl-1-oxopropan-2-yl 3-(3-chlorophenyl)acrylate (***4c***)*

Pale Yellow oil, yield:93%,IR (KBr): ν =3323, 3062, 2931, 2854, 1776, 1719, 1659, 1534, 715cm^{-1}.^{1}H NMR (250MHz, $CDCl_3$): 1.08-1.91 (10H, 5CH_2), 1.68 (3H, s, CH_3), 3.76 (1H,d, $^{3}J_{HH}$=7.75 Hz, CH), 4.36 (2H, CH_2), 5.88 (1H,d, $^{3}J_{HH}$=8.0 Hz, NH), 6.39 (1H,d, $^{3}J_{HH}$=16.0 Hz, CH), 7.34-8.09 (m, 9H, 6CH, Arom, 1CH, alkene)ppm.^{13}C NMR (62.89MHz, $CDCl_3$): 21.28 (CH_2), 24.71 (CH_3), 25.44(2CH_2), 32.72 (2CH_2), 42.95 (CH), 48.28 (CH_2), 82.45 (C), 119.39 (CH), 123.47, 126.51, 127.88, 130.10, 130.30, 131.86, 134.88, 136.07 , 144.19 (12C, arom, 2C, alken), 164.80 (C=O), 168.13 (2C=O),169.01 (C=O)ppm.

*(E)-1-(Cyclohexylamino)-3-(1,3-dioxoisoindolin-2-yl)-2-methyl-1-oxopropan-2-yl 3-p-tolylacrylate (***4d***)*

Pale Yellow oil, yield:95%,IR (KBr): ν =3323, 2929, 2854, 1776, 1719, 1661, 1539, 720cm^{-1}. ^{1}H nmr (250MHz, $CDCl_3$): 1.08-1.91 (10H, 5CH_2), 1.68 (3H,s, CH_3), 2.35 (3H,s, CH_3), 3.75 (1H,d, $^{3}J_{HH}$=8.0 Hz, CH), 4.35 (2H, CH_2), , 5.90 (1H,d, $^{3}J_{HH}$= 8.0 Hz, NH), 6.34 (1H,d, $^{3}J_{HH}$=16.0 Hz, CH), 7.17-7.83 (m, 9H, 4CH, arom, 1H, 1CH, alkene)ppm. ^{13}C nmr (62.89MHz, $CDCl_3$): 21.27 (CH_2), 24.70 (CH_3), 25.45(2CH_2), 32.68 (CH_3), 32.80 (2CH_2), 43.11 (CH), 48.21 (CH_2), 82.20 (C), 116.73, 123.47, 128.26, 129.58, 131.89, 134.09, 140.97, 145.90 (12C, arom, 2C, alken), 165.38 (C=O), 168.09 (2C=O), 169.23 (C=O)ppm.

*(E)-1-(tert-Butylamino)-3-(1,3-dioxoisoindolin-2-yl)-2-methyl-1-oxopropan-2-yl 2-methyl-3-phenylacrylate (***4e***)*

White Powder, yield:95%,m.p. 120-122ºC.IR (KBr): ν =3436, 3059, 2966, 1776, 1716 ,1670, 1519, 715cm^{-1}. ^{1}H NMR (250MHz, $CDCl_3$): 1.30(9H,s, 3CH_3), 1.71 (3H,s, CH3), 2.11 (3H,s, CH_3), 4.32 and 4.34 (2H,AB quartet, $^{1}J_{HH}$=14.75 Hz, CH_2), 5.84 (1H, s, NH), 7.34-7.85 (m, 10H, 9CH, arom, 1CH, alkene) ppm.^{13}C NMR (62.89MHz, $CDCl_3$): 14.10 (CH_3), 21.00 (CH_3), 28.50 (3CH_3), 43.21 (CH_2), 51.37 (C), 82.62 (C), 123.42, 128.23, 128.36, 128.47, 129.79, 131.91, 134.11, 135.76, 139.94 (12C,arom, 2C, alken), 166.96 (C=O), 168.04

(2C=O), 169.29 (C=O) ppm.

*(E)-1-(tert-Butylamino)-3-(1,3-dioxoisoindolin-2-yl)-2-methyl-1-oxopropan-2-yl 3-(4-fluorophenyl)acrylate (***4f***)*

White Powder, yield :94%, m.p. 116-118ºC.IR (KBr): ν =3385, 2964, 2853, 1773, 1716, 1670, 1509, 713cm^{-1}.^{1}H NMR (250MHz, $CDCl_3$): 1.31(9H, s, $3CH_3$), 1.67 (3H, s, CH_3), 4.34 and 4.36 (2H, AB quartet, $^{2}J_{HH}$=14.75 Hz, CH_2), 5.80 (1H, s, NH), 6.32 (1H, d, $^{3}J_{HH}$=16.0 Hz, CH), 7.07-7.83 (m, 9H, 4CH, arom, 1CH, alkene)ppm.^{13}C NMR (62.89MHz, $CDCl_3$): 21.27 (CH_3), 28.48 ($3CH_3$), 43.21 (CH_2), 51.37 (C), 82.57 (C), 116.01 (d, $^{2}J_{CF}$=22.0 Hz), 117.65 (CH), 123.41 (2CH), 130.16 (d, $^{3}J_{CF}$=8.5 Hz, 2CH), 131.91 (2C), 132.04 (C), 134.13 (2CH), 144.49(CH), 167.13 (d, $^{1}J_{CF}$= 261.5 Hz, C) 165.05 (C=O), 168.13 (C=O), 169.21 (C=O) ppm.

*(E)-1-(tert-Butylamino)-3-(1,3-dioxoisoindolin-2-yl)-2-methyl-1-oxopropan-2-yl 3-p-tolylacrylate (***4g***)*

White Powder, yield :88%,m.p.118-119 ºC. IR (KBr): ν =3431, 2923, 2853, 1770, 1634, 1514, 724cm^{-1}.^{1}H nmr (250MHz, $CDCl_3$): 1.30(9H, s, $3CH_3$), 1.67 (3H, s, CH_3), 2.36 (3H, s, CH_3), 3.75 (1H, d, $^{3}J_{HH}$=8.0Hz, CH), 4.34,4.36 (2H, CH_2), 5.82 (1H, s, NH), 6.34 (1H, d, $^{3}J_{HH}$=15.75, CH), 7.18-7.84(m, 9H, 4CH, arom, 1CH, alkene) ppm.13C nmr (62.89MHz, $CDCl_3$): 21.29 (CH_3), 28.48 ($3CH_3$), 32.78(CH_3), 43.00 (CH_2), 51.37 (C), 82.50 (C), 116.09 (CH), 123.39 (2CH), 128.26(2CH), 129.63 (2CH), 131.90 (C), 132.04 (2C), 134.05 (2CH), 140.81(C), 146.70 (CH), 165.38 (C=O), 168.09 (C=O), 169.23 (C=O)ppm.

*(E)-1-(Butylamino)-3-(1,3-dioxoisoindolin-2-yl)-2-methyl-1-oxopropan-2-yl 2-methyl-3-phenylacrylate (***4h***)*

White Powder, yield: 95%, m.p. 124ºC. IR (KBr)υ=3352, 2929, 2871, 1777, 1716, 1667, 1538, 715cm^{-1}. ^{1}H nmr (250MHz, $CDCl_3$): 0.869 (3H, t, $^{3}J_{HH}$=7.0Hz, CH3), 1.24-1.48 (4H, $2CH_2$), 1.72 (3H, s, CH_3), 2.10 (3H, s, CH_3), 3.26 (2H, q, $^{3}J_{HH}$=6.0, CH_2), 4.29, 4.37 (2H, AB quartet, ^{2}J=14.75Hz, CH_2), 6.06 (1H, NH), 7.35-7.84 (m, 9H, 8CH, arom, 1CH, alkene)ppm.

^{13}C nmr (62.89MHz, $CDCl_3$): 13.67 (CH_3), 14.07 (CH_3), 19.97 (CH_2), 20.99 (CH_3), 31.36 (CH_2), 39.43 (CH_2), 43.40 (CH_2), 82.25 (C), 123.43 (2CH), 128.10 (C), 128.37 (2CH,), 128.51 (CH), 129.80 (2CH) 131.89 (2C), 134.14 (2CH), 135.73 (C), 140.06 (CH), 167.04 (C=O), 168.07 (C=O), 170.12 (C=O)ppm.

*(E)-1-(Butylamino)-3-(1,3-dioxoisoindolin-2-yl)-2-methyl-1-oxopropan-2-yl 3-(4-fluorophenyl) acrylate (***4i***)*

White Powder, yield: 86%, m.p.130 ºC. IR (KBr)υ=3416, 2923, 2852, 1775, 1717, 1652, 1540, 718cm^{-1}. ^{1}H nmr (250MHz, $CDCl_3$): 0.875 (3H, t, $^{3}J_{HH}$=7.25Hz, CH_3), 1.25-1.45

(4H, 2CH2), 1.71 (3H, s, CH_3), 3.26 (2H, q, $^3J_{HH}$=6.75Hz, CH2), 4.30, 4.38 (2H, AB quartet, ^2J=14.75Hz, CH2), 6.08 (1H, d, $^3J_{HH}$=6.75Hz, NH), 6.35 (1H, d, $^3J_{HH}$:16.0Hz, CH), 7.09-7.86 (m, 9H, 8CH, arom, 1CH, alkene)ppm. ^{13}C nmr (62.89MHz, $CDCl_3$): 13.67 (CH_3), 19.21 (CH_2), 21.44 (CH_3), 31.37 (CH_2), 39.41 (CH_2), 43.00 (CH2), 82.48 (C),116.02(2CH, d, $^2J_{CF}$= 22.0Hz), 123.39 (2CH), 129.63 (C), 131.52 (C),131.94 (2CH, d, $^3J_{CF}$= 7.5Hz), 134.05 (2CH), 143.81 (CH),164.13 (1C, d, $^1J_{CF}$= 255.5Hz) 165.32 (C=O), 167.59 (C=O), 168.09 (C=O)ppm.

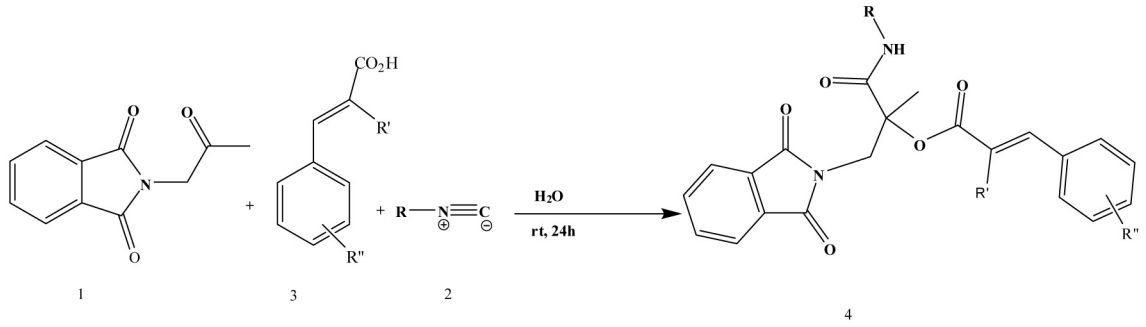
*(E)-1-(Butylamino)-3-(1,3-dioxoisoindolin-2-yl)-2-methyl-1-oxopropan-2-yl 3-p-tolylacrylate (***4j***)*

White Powder, yield: 87%, m.p. 138 ºC. IR (KBr)υ=3423, 2923, 2853, 1775, 1653, 1540, 720cm^{-1}. ^{1}H nmr (250MHz, $CDCl_3$): 0.876 (3H, t,$^3J_{HH}$=7.25Hz, CH_3), 1.25-1.59 (4H, 2CH_2), 1.72 (3H, s, CH_3), 2.39 (3H, s, CH_3), 3.26 (2H, q, $^3J_{HH}$=6.75Hz, CH_2), 4.30, 4.38 (2H,AB quartet, ^2J=14.75Hz, CH_2), 6.05(1H, d, 3JHH=6.75Hz, NH), 6.36 (1H, d, $^3J_{HH}$:16.25Hz, CH), 7.18-7.85(m, 9H, 8CH, arom, 1CH, alkene)ppm.^{13}C nmr (62.89MHz, $CDCl_3$): 13.68 (CH_3), 19.24 (CH_2), 21.42 (CH_3), 31.36 (CH_2), 39.40 (CH_2), 43.02 (CH2), 82.56 (C),116.02 (CH), 123.45 (2CH), 128.28(2CH), 129.90 (2CH), 131.58 (C), 132.04 (2C), 134.11 (2CH), 140.95(C), 146.03 (CH), 165.19 (C=O), 167.83 (C=O), 168.14 (C=O)ppm.

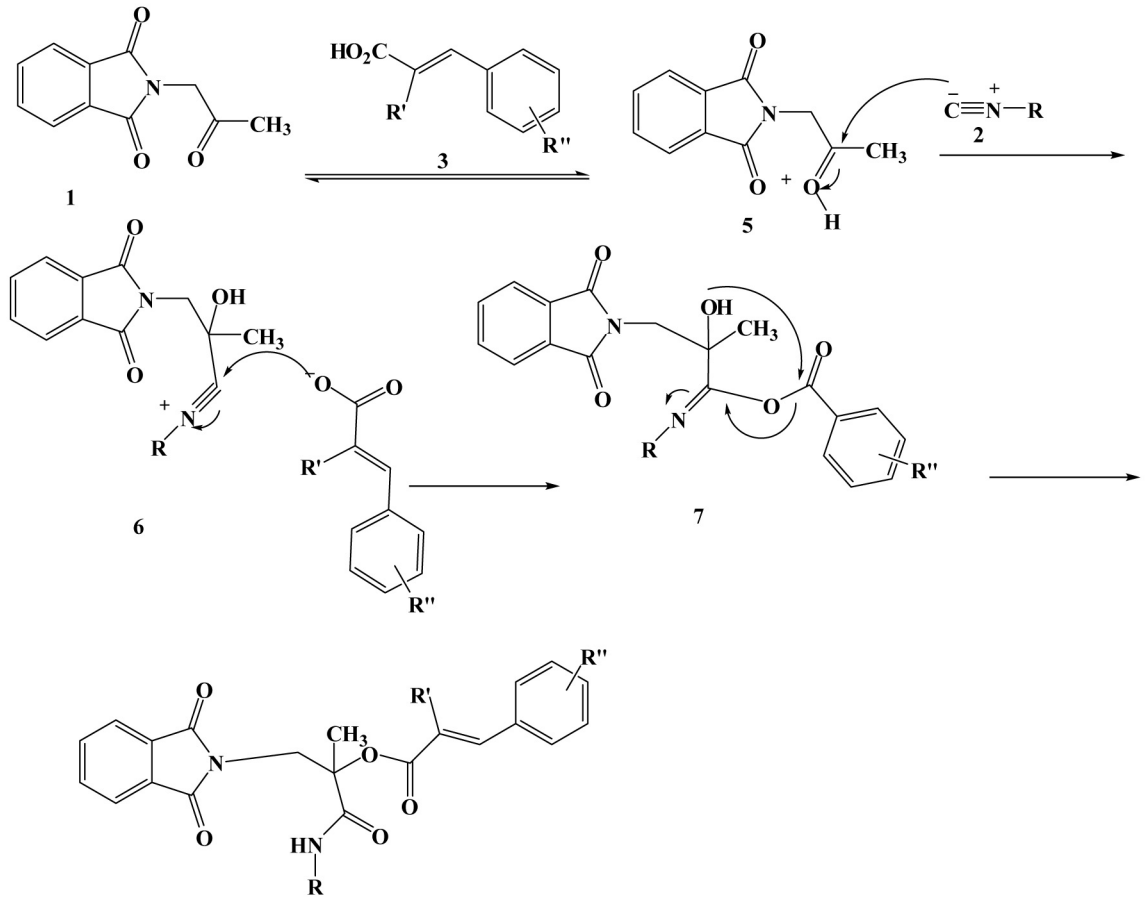
Results and discussion

The *E*-cinnamic acid derivative **3** was reacted with 2-(2-oxopropyl)isoindoline-1,3-dione **1** and an alkylisocyanide **2** in H_2O in a 1:1:1 ratio at room temperature to produce *E*-1-(alkylamino)-3-(1,3-dioxoisoindolin-2-yl)-2-methyl-1-oxopropan-2-yl derivative **4**. The reaction proceeded smoothly and cleanly under mild conditions and no side reactions were observed. Structures of compounds **4a–j** were determined on the basis of their IR, ^{1}H NMR, ^{13}C NMR spectra. In the ^{1}H NMR spectrum of **4a** are displayed one multiplet at 1.00-1.86 (10H, 5CH_2) for cyclohexyl group, two singlet at 1.72 and 2.10 for two methyl group, one doublet at 3.79 (d, $^3J_{HH}$=7.75 Hz, CH) for cyclohexyl group, two doublet at 4.29 and 4.36(AB quartet, $^1J_{HH}$=16.0 Hz) for CH_2, one doublet at 5.89(d, $^3J_{HH}$= 7.75 Hz) for NH and one multiplet at 7.35-7.83 (m, 10 H; 9 CH arom and 1CH alkene) ppm. In ^{13}C NMR spectrum of 4a showed 17 differentresonances in agreement with the proposed structure. The carbonyl groups resonances in the ^{13}C NMRspectra of **4a** are appeared at 166.99(C=O), 168.05 (C=O) and169.19 (C=O) ppm.The ^{1}H and ^{13}C NMR spectra of compounds **4b–j** were similar to those of **4a**, except for the aromatic and aliphatic moieties, which exhibited characteristic signals with appropriate chemical shifts.A proposed mechanism for this reaction toachievement of compound 4is shown in Scheme2. On the basis of the chemistry of isocyanides, it is reasonable

to assume that the first step may involve protonation of 2-(2-oxopropyl)isoindoline-1,3-dione **1** by the E-cinnamic acid **3** to form an intermediate, which is then attacked by the alkyl isocyanide **2**, leading to the formation of 4 [25].



Scheme 1. Synthesis of *E*-1-(alkylamino)-3-(1,3-dioxoisoindolin-2-yl)-2-methyl-1-oxopropan-2-yl derivatives in water.



Scheme 2. Aproposed mechanism for the formation of compound **4**.

Conclusion

We believe that the reported protocol offers a mild, simple, and efficient route for the preparation of *E*-1-(alkylamino)-3-(1,3-dioxoisoindolin-2-yl)-2-methyl-1-oxopropan-2-yl derivatives **4** from 2-(2-oxopropyl) isoindoline-1,3-dione **1**, alkyl isocyanides **2** and E-cinnamic acids **3** in H_2O at room temprature. This procedure offers significant advantages such as operational simplicity, mild reaction conditions, high yields, ease of isolation of products, cleaner reaction profiles, and H2O as medium, rendering it a useful protocol for the synthesis of these compounds.

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