ICC
Iranian Chemical Communication
Original Research Article
Payame Noor University http://icc.journals.pnu.ac.ir

The three-component reaction of 2-(2-oxopropyl)isoindoline-1,3-dione with alkyl isocyanides and aromatic carboxylic acids under catalyst-free conditions in water

Ali Jafari[a], Ali Ramazani[a,*], Sang Woo Joo[b,*], Yavar Ahmadi[c], Fariba Sadri[d] , Pegah Azimzadeh Asiabi[a]

[a]*Department of Chemistry, University of Zanjan, P.O. BOX 45195-313, Zanjan, Iran*

[b]*School of Mechanical Engineering, Yeungnam University, Gyeongsan 712-749, Republic of Korea*

[c]*Young Researchers and Elite Clube, Marand Branch, Islamic Azad University, Marand , Iran*

[d]*Department of Chemistry, Payame Noor University, P.O. BOX 19395-4697 Tehran, Iran*

Received: 24 April 2015, Accepted: 14 August 2015, Published: 15 August 2015

Abstract

A green and convenient protocol is described for the preparation of 1-(alkylamino)-3-(1,3-dioxoisoindolin-2-yl)-2-methyl-1-oxopropan-2-yl benzoates *via* one-pot three-component reaction between 2-(2-oxopropyl)isoindoline-1,3-dione, an alkyl isocyanide and an aromatic carboxylic 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; aromatic carboxylic acid.

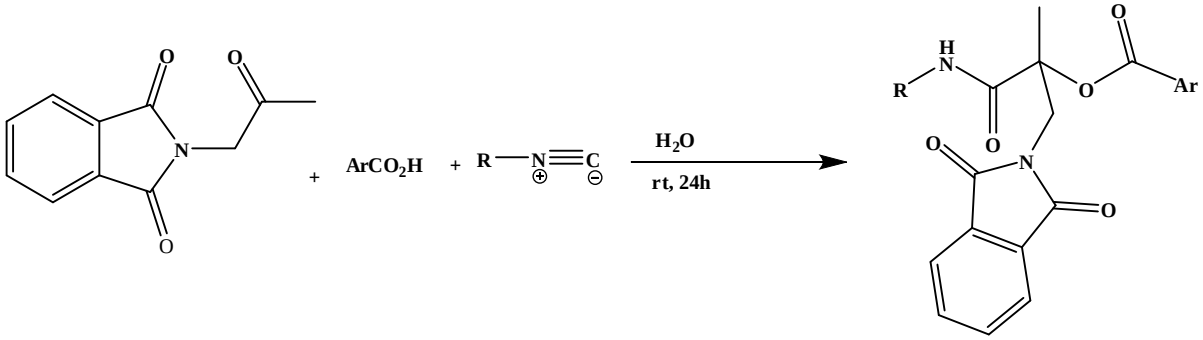
*Corresponding author: Ali Ramazani, Sang Woo Joo
Tel: +98 (24) 33052572, Fax: +98 (24) 33052477
E-mail: aliramazani@gmail.com, swjoo@yu.ac.kr

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 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 the 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 Ugi and 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 1-(alkylamino)-3-(1,3-dioxoisoindolin-2-yl)-2-methyl-1-oxopropan-2-yl benzoate *via* one-pot three-component reaction between 2-(2-oxopropyl)isoindoline-1,3-dione, an alkyl isocyanide and an aromatic carboxylic acid in water at room temperature is reported (Scheme 1).



Scheme 1. Synthesis of 1-(alkylamino)-3-(1,3-dioxoisoindolin-2-yl)-2-methyl-1-oxopropan-2-yl benzoate derivatives

Experimental

General

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-l

A mixture of 2-(2-oxopropyl)isoindoline-1,3-dione (1) (1 mmol, 0.203 g), an alkyl isocyanide (1 mmol, cyclohexyl isocyanide, *t*-butyl isocyanide and *n*-butyl isocyanide) and a carboxylic acid (1 mmol; 0.156 g, Ar=3-ClC_6H_4), 0.136 g (Ar=3-MeC_6H_4), 0.140 g (Ar=4-FC_6H_4), 0.136 g (Ar=4-MeC_6H_4), 0.178 g (Ar=4-*t*-BuC_6H_4) in H_2O (5 mL) was stirred at room temperature for 24 h. 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. The characterization data of the compounds (4a-l) are given below:

1-(Cyclohexylamino)-3-(1,3-dioxoisoindolin-2-yl)-2-methyl-1-oxopropan-2-yl 3-chlorobenzoate (4a)

Yellow oil, yield: 398 mg (85%), IR (neat) (υ_{max}, cm^{-1}): 714, 1260, 1292, 1667, 1721,

1777, 2854, 2931, 3377. ^{1}H NMR ($CDCl_3$): δ= 0.95-1.78 (10H,5CH_2); 1.74 (s, 3H, CH_3); 3.78 (d, $^{3}J_{HH}$=8.5 Hz, 1H, CH); 4.34 and 4.42 (AB quartet, $^{2}J_{HH}$=14.5 Hz, 2H, CH_2); 5.81 (d, $^{3}J_{HH}$=8.5 Hz, 1H, NH); 7.39-8.01 (8H, arom). ^{13}C NMR ($CDCl_3$): δ_C=21.02(CH_2); 24.66(CH_3); 25.41(2CH_2); 32.76(2CH_2); 43.22(CH); 48.34(CH_2); 82.93(C); 123.52; 127.98; 129.79; 129.95; 131.83; 133.23; 134.20; 134.61 and 138.58(9C, 12CH, arom); 163.86(C=O); 168.12(2C=O); 168.70(C=O).

1-(Cyclohexylamino)-3-(1,3-dioxoisoindolin-2-yl)-2-methyl-1-oxopropan-2-yl 3-methylbenzoate (4b)

Yellow oil, yield: 367 mg (82%), IR (neat) (υmax, cm-1): 715, 1281, 1673, 1720, 1776, 2854, 2930, 3378. ^{1}H NMR ($CDCl_3$): δ=0.98-2.02 (10H,5CH_2); 1.75 (s, 3H, CH_3); 2.40 (s, 3H, CH_3); 3.79 (d, $^{3}J_{HH}$=8.5 Hz, 1H, CH); 4.34 and 4.42 (AB quartet, $^{2}J_{HH}$=14.25 Hz, 2H, CH_2); 5.86 (d, $^{3}J_{HH}$=8.5 Hz, 1H, NH); 7.33-7.84 (8H, arom). ^{13}C NMR ($CDCl_3$): δ_C= 21.01 (CH_2); 24.65(CH_3); 25.43(CH_2); 32.64(CH_3); 32.71(CH_2); 43.41(CH); 48.22(CH_2); 82.57(C); 123.44; 126.94; 128.36; 129.99; 130.44; 131.90; 134.00; 134.11 and 138.25 (9C, 12CH, arom); 165.12(C=O); 168.04(2C=O); 169.07(C=O).

1-(Cyclohexylamino)-3-(1,3-dioxoisoindolin-2-yl)-2-methyl-1-oxopropan-2-yl 4-fluorobenzoate (4c)

Yellow oil, yield: 384 mg (85%), IR (neat) (υ_{max} , cm^{-1}): 714, 1279, 1673, 1720, 1776, 2854, 2929. ^{1}H NMR ($CDCl_3$): δ=1.05-1.92 (10H,5CH_2); 1.74 (s, 3H, CH_3); 3.78 (d, $^{3}J_{HH}$=8.25 Hz, 1H, CH); 4.31 and 4.40 (AB quartet, $^{2}J_{HH}$=14.5 Hz, 2H, CH_2); 5.79 (d, $^{3}J_{HH}$=8.25 Hz, 1H, NH); 7.12-7.84 (8H, arom). ^{13}C NMR ($CDCl_3$): δ_C=20.90(CH_2); 24.68(CH_3); 25.42 (2CH_2); 32.80(2CH_2); 43.51(CH); 48.33(CH_2); 82.66(C); 123.50; 131.85; 134.15 and 134.18 (7C, arom); 115.63(d, $^{2}J_{HH}$=22 Hz, 2CH, meta); 132.50(d, $^{3}J_{HH}$=10 Hz, 2CH, orto); 164.50(d, $^{2}J_{HH}$=221.50 Hz, C, para); 165.50(C=O); 168.11(2C=O); 168.82(C=O).

1-(Cyclohexylamino)-3-(1,3-dioxoisoindolin-2-yl)-2-methyl-1-oxopropan-2-yl 4-methylbenzoate (4d)

Pale yellow oil, yield: 394 mg (88%), IR (neat) (υ_{max} , cm^{-1}): 713, 1281, 1678, 1721, 1776.31, 2871, 2959, 3391. ^{1}H NMR ($CDCl_3$): δ=0.87-1.85 (10H,5CH_2); 1.74 (s, 3H, CH_3); 2.40 (s, 3H, CH_3); 3.77 (d, $^{3}J_{HH}$=7.75 Hz, 1H, CH); 4.33 and 4.41 (AB quartet, $^{2}J_{HH}$=14.75 Hz, 2H, CH_2); 5.83 (d, $^{3}J_{HH}$=7.75 Hz, 1H, NH); 7.24-7.92 (8H, arom).^{13}C NMR ($CDCl_3$): δ_C= 21.02(CH_2); 24.67(CH_3); 25.43(2CH_2); 32.65(CH_3); 32.78 (2CH_2); 43.41(CH); 48.21(CH_2); 82.48(C); 123.45; 127.36; 129.19; 129.87; 131.89;

134.10 and 143.99 (7C, 12CH, arom); 165.04(C=O); 168.04(2C=O); 169.13(C=O).

1-(Cyclohexylamino)-3-(1,3-dioxoisoindolin-2-yl)-2-methyl-1-oxopropan-2-yl 4-tert-butylbenzoate (4e)

Yellow oil, yield: 426 mg (87%), IR (neat) (υ_{max} , cm^{-1}): 713, 1280, 1680, 1720, 1775, 2854, 2925, 3387. ^{1}HNMR ($CDCl_3$): δ=0.87-1.88 (10H, $5CH_2$); 1.34 (s, 9H, $3CH_3$); 1.74 (s, 3H, CH_3); 3.78 (d, $^{3}J_{HH}$= 7.75 Hz, 1H, CH); 4.33 and 4.41 (AB quartet, $^{2}J_{HH}$=14.75 Hz, 2H, CH_2), 5.80 (d, $^{3}J_{HH}$=7.75 Hz, 1H, NH); 7.48-7.97 (8H, arom). ^{13}C NMR ($CDCl_3$): δ_C=20.92(CH_2); 24.72(CH_3); 25.4($2CH_2$); 31.08($3CH_3$); 32.82(C); 32.83($2CH_2$); 43.54(CH); 48.26(CH_2); 82.50(C); 123.49; 127.45; 129.57; 129.75; 131.90; 134.10 and 144.00(9C, 12CH, arom); 165.04(C=O); 168.04(2C=O); 169.13(C=O).

1-(Butylamino)-3-(1,3-dioxoisoindolin-2-yl)-2-methyl-1-oxopropan-2-yl 3-chlorobenzoate (4f)

Pale yellow oil, yield: 398 mg (92%), IR (neat) (υ_{max} , cm^{-1}): 714, 1279, 1674, 1724, 1776, 2854, 2930, 3375. ^{1}H NMR ($CDCl_3$): δ=0.865 (t, $^{3}J_{HH}$=7 Hz, 3H, CH_3); 1.24-1.47 (4H, $2CH_2$); 1.74 (s, 3H, CH_3); 3.26 (q, $^{3}J_{HH}$=7 Hz, 2H, CH_2); 4.33 and 4.42 (AB quartet, $^{2}J_{HH}$=14.75 Hz, 2H, CH_2); 6.02 (1H, NH); 7.38-8.00 (8H, arom). ^{13}C NMR ($CDCl_3$): δ_C= 13.65(CH_3); 19.69(CH_2); 21.04(CH_3); 31.34(CH_2); 39.51(CH_2); 43.23 (CH_2); 82.91(C); 123.53; 128.02; 129.78; 129.97; 131.75; 131.82; 133,25; 134.21 and 138.68(9C, 12CH, arom); 163.90 (C=O); 168.13 (C=O); 169.62 (C=O).

1-(Cyclohexylamino)-3-(1,3-dioxoisoindolin-2-yl)-2-methyl-1-oxopropan-2-yl 4-chlorobenzoate (4g)

Yellow oil, yield: 389 mg (83%), IR (neat) (υ_{max}, cm^{-1}): 712, 1275, 1680, 1720, 1771, 2854, 2928, 3389. ^{1}H NMR($CDCl_3$): δ=0.87-1.88 ($5CH_2$, 10H); 1.74 (s, 3H, CH_3); 3.78 (1H, CH) ; 4.33 and 4.40 (AB quartet, $^{2}J_{HH}$=14.75 Hz, 2H, CH_2); 5.81 (1H, NH); 7.42-8.01 (8H, arom). ^{13}C NMR ($CDCl_3$): δ_C=20.94(CH_2); 24.68(CH_3); 25.40($2CH_2$); 32.78(2CH2); 43.38(CH); 48.35(CH_2); 82.93(C); 123.54; 128.82; 131.28; 131.47; 132.04; 134.14 and 138.60(7C, 12CH, arom); 165.04(C=O); 168.04(2C=O); 169.13(C=O).

1-(Tert-butylamino)-3-(1,3-dioxoisoindolin-2-yl)-2-methyl-1-oxopropan-2-yl 4-tert-butylbenzoate (4h)

White powder, m.p. 126-128°C, yield: 418 mg (90%), IR (neat) (υ_{max} , cm^{-1}): 713, 1279, 1674, 1720, 1775, 2964, 3388. ^{1}H NMR ($CDCl_3$): δ=1.29 (s, 9H, $3CH_3$); 1.33 (s, 9H, $3CH_3$); 1.74 (s, 3H, CH_3); 4.35 and 4.38 (AB quartet, $^{2}J_{HH}$=14.75 Hz, 2H, CH_2); 5.81 (s, 1H, NH); 7.46-7.96 (8H, arom). ^{13}C NMR ($CDCl_3$): δ_C=20.93(CH_3);

28.49($3CH_3$); 31.07($3CH_3$); 35.09(C); 43.43(CH_2); 51.36(C); 82.87(C); 123.44; 125.48; 129.69; 130.00; 131.92; 134.09 and 134.24(7C, 12CH); 165.00(C=O); 168.05(2C=O); 169.23(C=O).

1-(Tert-butylamino)-3-(1,3-dioxoisoindolin-2-yl)-2-methyl-1-oxopropan-2-yl 4-fluorobenzoate (4i)

White powder, m.p. 102-103 °C, yield: 366 mg (86%), IR (neat) (υ_{max} , cm^{-1}): 713, 1278, 1674, 1727, 1774, 2968, 3382. ^{1}H NMR ($CDCl_3$): δ=1.30 (s, 9H, $3CH_3$); 1.72 (s, 3H, CH_3); 4.33 and 4.37 (AB quartet, $^2J_{HH}$=14.75 Hz, 2H, CH_2); 5.74 (s, 1H, NH); 7.12 (t, $^2J_{HH,HF}$=7.5 Hz, 2H, CH, meta); 7.74 (2H, CH); 7.85(2H, CH); 8.07(dd, $^2J_{HH}$=7.75 Hz, $^4J_{HF}$=5 Hz, 2H, CH, orto). ^{13}C NMR ($CDCl_3$): δ_C=20.92(CH_3); 28.48($3CH_3$); 43.37(CH_2); 51.49(C); 82.90(C); 123.44; 125.48; 129.69; 130.00; 131.92; 134.09 and 134.24 (7C,12CH, arom); 165.00(C=O); 168.05(2C=O); 169.23(C=O).

1-(Tert-butylamino)-3-(1,3-dioxoisoindolin-2-yl)-2-methyl-1-oxopropan-2-yl 3-chlorobenzoate (4j)

White powder, m.p. 86-87°C, yield: 372 mg (84%), IR (neat) (υ_{max} , cm^{-1}): 713, 1260, 1674, 1715, 1773, 2924, 3390. ^{1}HNMR ($CDCl_3$): δ=1.30 (s, 9H, $3CH_3$); 1.71 (s, 3H, CH_3); 4.35 and 4.38 (AB quartet, $^2J_{HH}$=14.75 Hz, 2H, CH_2); 5.76 (s, 1H, NH); 7.38-8.00 (8H, arom). ^{13}C NMR ($CDCl_3$): δ_C=21.04(CH_3); 28.47($3CH_3$); 43.08(CH_2); 51.52(C); 82.90(C); 123.52; 127.95; 129.78; 129.91; 131.86; 132.04; 133.19; 134.14 and 138.35 (9C, 12CH, Arom), 165.20(C=O); 168.25(2C=O); 169.30(C=O).

1-(Tert-butylamino)-3-(1,3-dioxoisoindolin-2-yl)-2-methyl-1-oxopropan-2-yl 4-methylbenzoate (4k)

White powder, m.p. 110-112°C, yield: 363 mg (86%), IR (neat) (υ_{max} , cm^{-1}): 713, 1278, 1611, 1732, 1774, 2925, 2968, 3388. ^{1}H NMR ($CDCl_3$): δ=1.28 (s, 9H, $3CH_3$); 1.72 (s, 3H, CH_3); 4.34 and 4.37 (AB quartet, $^2J_{HH}$=14.75 Hz, 2H, CH_2); 5.80 (s, 1H, NH); 7.23-7.90 (8H, arom). ^{13}C NMR ($CDCl_3$): δ_C=21.04(CH_3); 28.47 ($3CH_3$); 32.78(CH_3); 43.26(CH_2); 51.33(C); 82.75(C); 123.40; 127.43; 129.17; 129.81; 131.90; 134.08 and 143.92 (7C, 12CH, Arom); 165.01(C=O); 168.03(2C=O); 169.25(C=O).

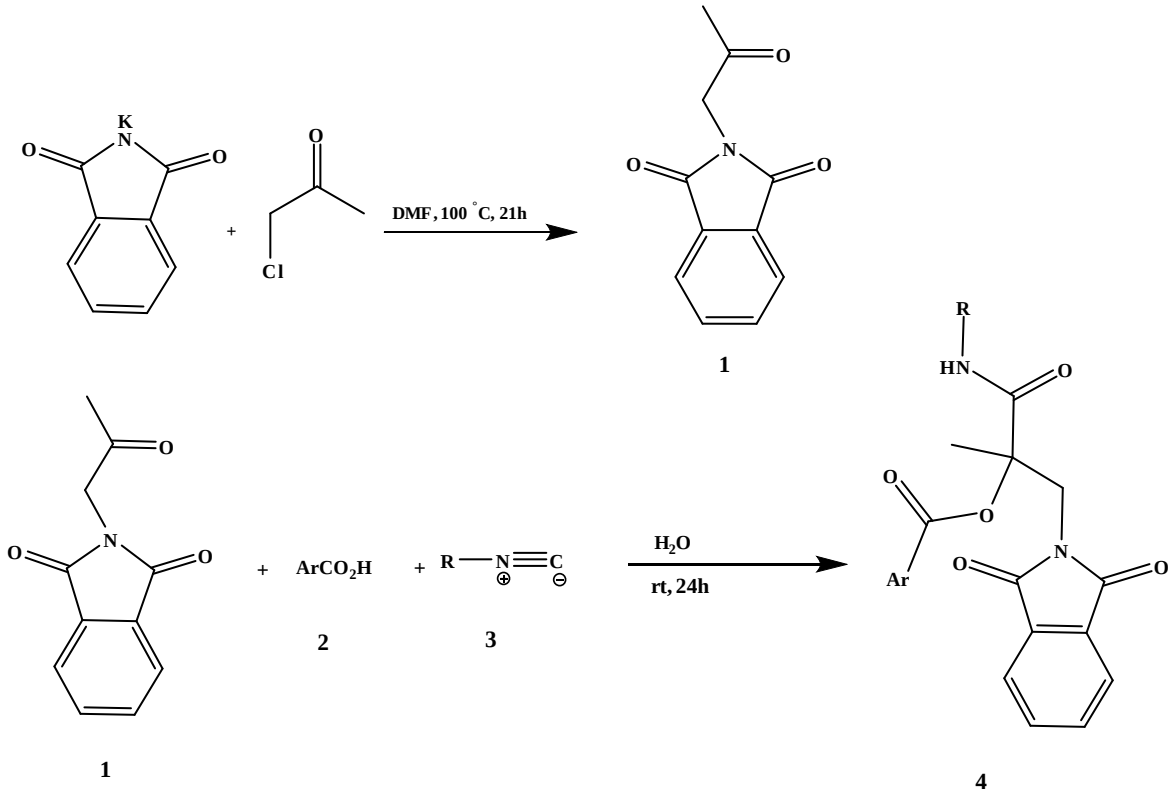
1-(Butylamino)-3-(1,3-dioxoisoindolin-2-yl)-2-methyl-1-oxopropan-2-yl 4-tert-butylbenzoate (4l)

Pale yellow oil, yield: 408 mg (88%), IR (neat) (υ_{max} , cm^{-1}): 713, 1281, 1678, 1721, 1776, 2871, 2959, 3391. ^{1}H NMR ($CDCl_3$): δ=0.856 (t, $^3J_{HH}$=7 Hz, 3H, CH_3); 1.24-1.42 (4H, $2CH_2$); 1.33 (s, 9H, $3CH_3$); 1.76 (s, 3H, CH_3); 3.26 (q, $^3J_{HH}$=6.25 Hz, 2H, CH_2); 4.36 and 4.38 (AB quartet, $^2J_{HH}$=14.75 Hz, 2H,

CH_2); 6.01 (1H, NH); 7.47-7.97 (8H, arom). ^{13}C NMR ($CDCl_3$): δ_C=13.65(CH_3); 19.95(CH_2); 20.94(CH_3); 31.07(3CH_3); 31.37 (CH_2); 35.11 (C); 39.47(CH_2); 43.61(CH_2); 82.56(C); 123.48; 125.48; 127.21; 129.79; 131.90; 134.11 and 144.22(7C, 12CH, arom); 165.90 (C=O); 168.06 (C=O); 170.00 (C=O).

Results and discussion

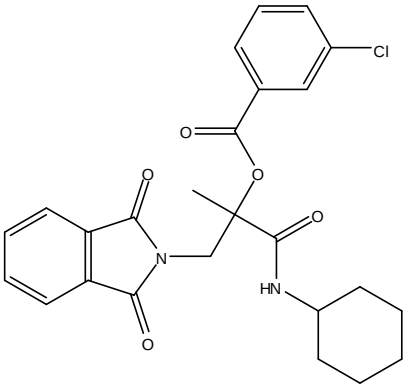
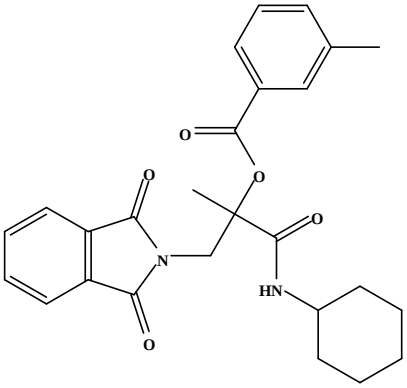
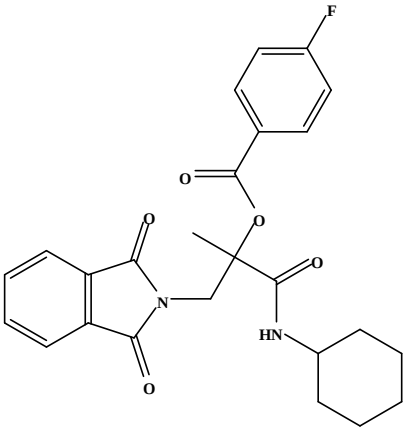
The carboxylic acid derivative was reacted with 2-(2-oxopropyl)isoindoline-1,3-dione (1) and alkylisocyanides in H_2O in a 1:1:1 ratio at room temperature to produce 1-(alkylamino)-3-(1,3-dioxoisoindolin-2-yl)-2-methyl-1-oxopropan-2-yl benzoate derivatives (Scheme 2 and Table 1). The reaction proceeded smoothly and cleanly under mild conditions and no side reactions were observed.

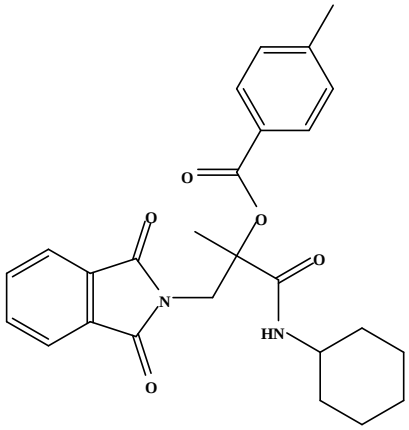
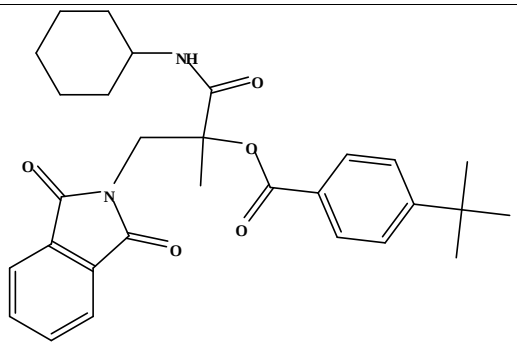
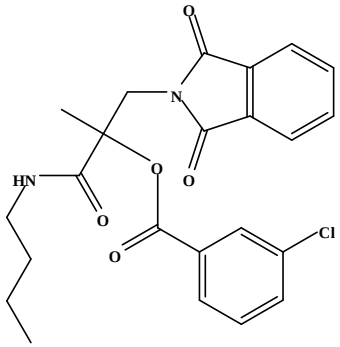


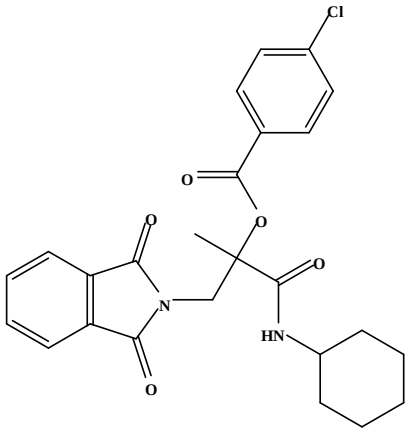
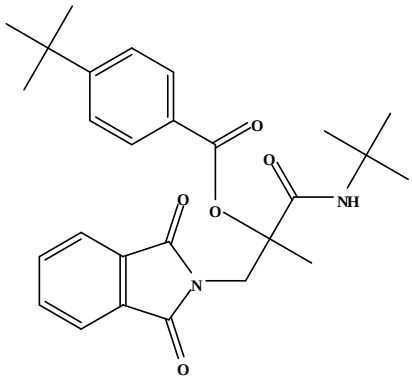
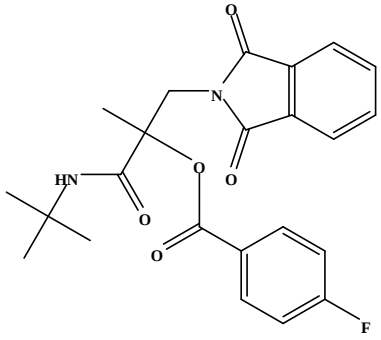
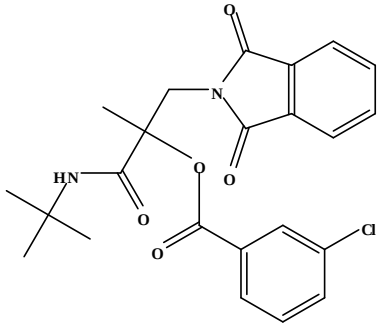
4a. R=cyclohexyl,, Ar=3-ClC_6H_4; 4b: R=cyclohexyl, Ar=3-MeC_6H_4; 4c: R= cyclohexyl, Ar=4-FC_6H_4; 4d: R= cyclohexyl, Ar=4-MeC_6H_4; 4e: R=cyclohexyl, Ar=4-*t*-butylC_6H_4; 4f: R=*n*-butyl, Ar=3-ClC_6H_4; 4g: R= cyclohexyl, Ar=4-ClC_6H_4; 4h: R=*t*-butyl, Ar=4-*t*-butyl C_6H_4; 4i: R= *t*-butyl, Ar=4-FC_6H_4; 4j: R= *t*-butyl, Ar=3-ClC_6H_4; 4k: R= *t*-butyl, Ar=4-MeC_6H_4; 4l: R=*n*-butyl, Ar=4-*t*-butyl C_6H_4.

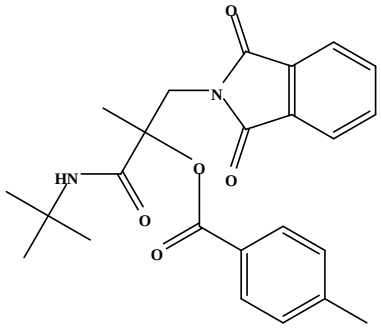
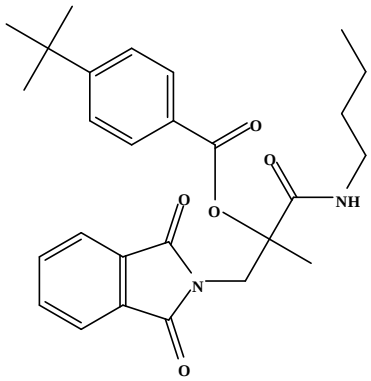
Scheme 2. Synthesis of 2-(2-oxopropyl)isoindoline-1,3-dione 3 and three-component synthesis of 1-(alkylamino)-3-(1,3-dioxoisoindolin-2-yl)-2-methyl-1-oxopropan-2-yl benzoate derivatives 4a-l (See Experimental part)

Table 1. Structures of synthesized isoindoline-1,3-dione derivatives in water

4	product	Yield%	M.P. ◦C
a		85	_____
b		82	_____
c		85	_____

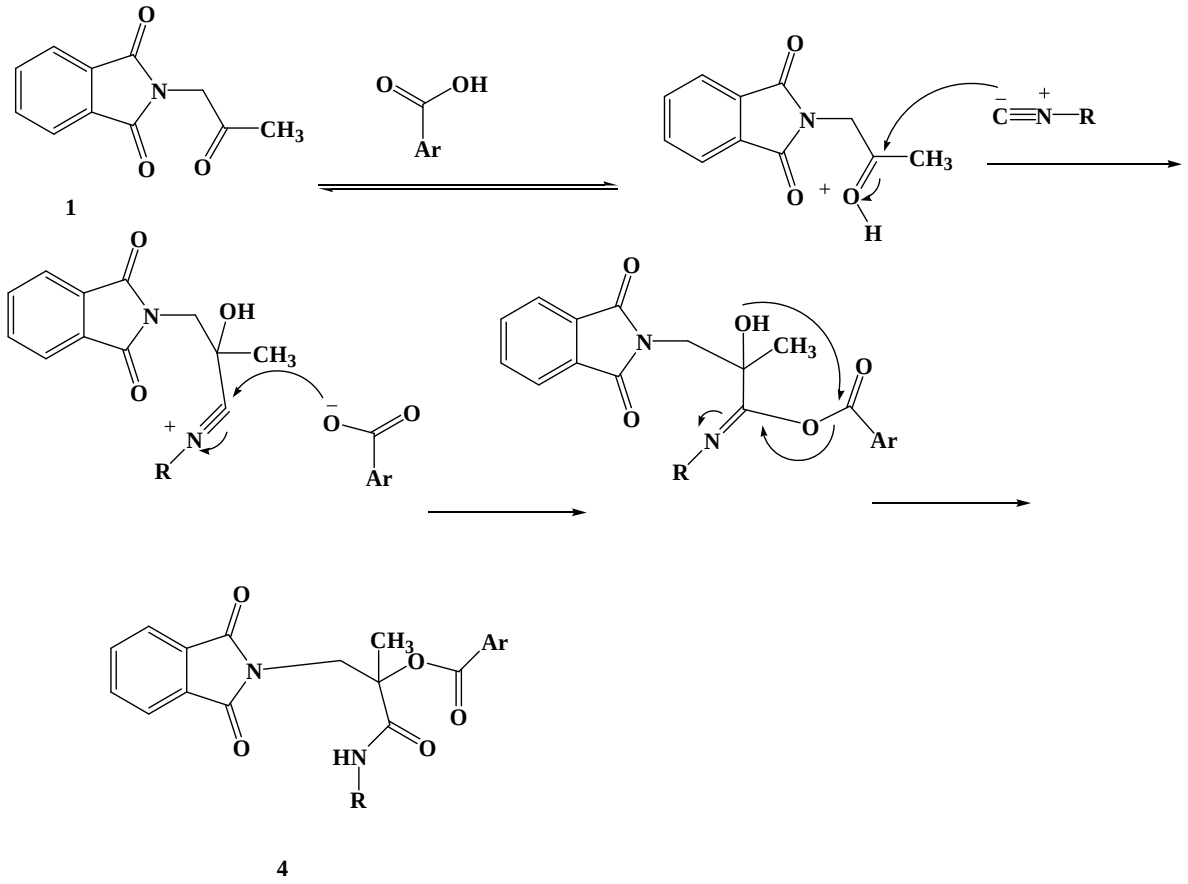
d		88	_____
e		87	_____
f		92	_____

g		83	———
h		90	126-128
i		86	102-103
j		84	86-87

k		86	110-112
l		88	———————

The structures of the products were deduced from their ^{1}H NMR, ^{13}C NMR and IR spectra. For example, the ^{1}H NMR spectrum of **4a** consisted δ 0.95-1.78 (10H,5CH_2); 1.74 (s, 3H, CH_3); 3.78 (d, $^{3}J_{HH}$=8.5 Hz ,1H, CH); 4.34 and 4.42 (AB quartet, $^{2}J_{HH}$=14.5 Hz, 2H, CH_2); 5.81 (d, $^{3}J_{HH}$=8.5,1H, NH); 7.39-8.01 (8H, 8CH) ppm for H-aromatic. The aryl groups exhibited characteristic signals in the aromatic region of the spectrum. The ^{1}H decoupled ^{13}C NMR spectrum of **4a** showed 19 distinct resonances, partial assignment of these resonances is given in the experimental section. The ^{1}H and ^{13}C NMR spectra of compounds **4b–l** were similar to those of **4a**, except for the aromatic and aliphatic moieties, which exhibited characteristic signals with appropriate chemical shifts.

The suggested mechanism for the formation of products **4a-l** is illustrated in Scheme 3. 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 carboxylic acid **2** to form an intermediate, which is then attacked by the alkyl isocyanide **3**, leading to the formation of **4** [25].



Scheme 3. Proposed mechanism for the formation of produce 1-(alkylamino)-3-(1,3-dioxoisoindolin-2-yl)-2-methyl-1-oxopropan-2-yl benzoate derivatives **4a-l**

Conclusion

We believe that the reported protocol offers a mild, simple, and efficient route for the preparation of 1-(alkylamino)-3-(1,3-dioxoisoindolin-2-yl)-2-methyl-1-oxopropan-2-yl benzoate derivatives 4 from 2-(2-oxopropyl)isoindoline-1,3-dione 3, alkyl isocyanides and aromatic carboxylic acids 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 H_2O as medium, rendering it a useful protocol for the synthesis of these compounds.

Acknowledgements

This research was supported by the University of Zanjan.

Reference

[1] a) C.J. Li, T.H. Chan, *Organic Reactions in Aqueous Media*, Wiley: New York, 1997. b) C.J. Li, *Chem. Rev.*, **2005**, *105*, 3095–3165.

[2] P.A. Grieco, *Organic Synthesis in Water*, Ed, Thomson Science: Glasgow:Scotland, **1998**.

[3] P. Anastas, T.C. Williamson, *Green Chemistry Frontiers in Benign Chemical Synthesis and Processes*, Oxford University Press: New York, **1998**.

[4] P.T Anastas, J.C. Warner, *Green Chemistry: Theory and Practice*, Oxford University Press, UK, **1998**.

[5] R. Breslow, *Acc. Chem. Res*. **1991**, 24, 159–164; Breslow, *R. Acc. Chem. Res*., **2004**, *37*, 471–478.

[6] J. Zhu, H. Bienayme, *Multicomponent Reactions*. Wiley, Weinheim, **2005**.

[7] B. Henkel, M. Sax, A. Dömling, *Tetrahedron Lett*., **2003**, *44*, 3679–3682.

[8] R.W. Waller, L.J. Diorazio, B.A. Taylor, W.B. Motherwell, T.D. Sheppard, *Tetrahedron*, **2010**, *66*, 6496–6507.

[9] I. Yavari, Z. Hossaini, M. Sabbaghan, *Mol. Divers*., **2006**, *10*, 479–482.

[10] S.R.C. Venkata, V.R. Rao, *J. Sulfur Chem.*, **2010**, *31*, 545–550.

[11] I. Yavari, M.J. Bayat, M. Sirouspour, S. Souri, *Tetrahedron*, **2010**, *66*, 7995–7999.

[12] M. Bayat, H. Imanieh, N. Zabarjad Shiraz, M. Shah Qavidel, *Monatsh. Chem*., **2010**, *141*, 333–338.

[13] A.Ramazani, F.Z Nasrabadi, F. Z.; Ahmadi, Y. *Helv. Chim. Acta.*, **2011**, *94*, 1024–1029.

[14] A. Ramazani, N. Shajari, A. Mahyari, Y. Ahmadi, *Mol. Divers.*, **2011**, *15*, 521–527.

[15] a) M. Rouhani, A. Ramazani, S.W. Joo, Y. Hanifehpour, *Bull. Korean Chem. Soc.*, **2012**, *33*, 4127–4130. b) M. Khoobi, A. Ramazani, A. Foroumad, S. Emami, F. Jafarpour, A. Mahyari, K. Slepokura, T. Lis, A. Shafiee, *Helv. Chim. Acta.*, 2012, *95*, 660–671. c) M.R. Ganjali, S. Aghabalazadeh, M. Khoobi, A. Ramazani, A. Foroumadi, A. Shafiee, P. Norozi, *Int. J. Electrochem. Sci.*, 2011, *6*, 52–62. d) M. Khoobi, S. Emami, G. Dehghan, A. Foroumadi, A. Ramazani, A. Shafiee, *Arch. Pharm.* 2011, *344*, 588–594. e) M. Khoobi, L. Mamani, F. Rezazadeh, Z. Zareie, A. Foroumad, A. Ramazani, A. Shafiee, A. *J. Mol. Cat.* A., 2012, *359*, 74–80. f) A. Ramazani, F. Zeinali Nasrabadi, B. Abdian, M. Rouhani, *Bull. Korean Chem. Soc.*, 2012, *33*, 453–458. g) F. Zeinali Nasrabadi, A. Ramazani, Y. Ahmadi, *Mol. Divers.* 2011, *15*, 791–798. h) A. Ramazani, A. Tofangchi Mahyari, M. Rouhani, A. Rezaei, *Tetrahedron Lett.*, 2009, *50*, 5625–5627. i) Z.

Zareie, M. Khoobi, A. Ramazani, A. Foroumad, A. Souldozi, K. Slepokura, T. Lis, A. Shafiee, *Tetrahedron* 2012, *68*, 6721–6726. j) A. Ramazani, A.R. Kazemizadeh, *Curr. Org. Chem.*, 2011, *15*, 3986–4020. k) A.R. Kazemizadeh, A. Ramazani, *Curr. Org. Chem.*, 2012, *16*, 418–450. l) M. Khoobi, A. Ramazani, A. Foroumadi, H. Hamadi, Z. Hojjati, A. Shafiee, A. *J. Iran. Chem. Soc.*, 2011, *8*, 1036–1042. m) M. Khoobi, A. Foroumadi, S. Emami, M. Safavi, G.H. Dehghan, B.H. Alizadeh, A. Ramazani, S.K. Ardestani, A. Shafiee,. *Chem. Biol. Drug Des.*, 2011, *78*, 580–586. n) A. Ramazani, A. Souldozi, A. Morsali, A.R. Jalilian, *Kristallogr. NCS*, 2004, *219*, 247–248. o) R. Moosavi, A.R. Abbasi, M. Yousefi, A. Ramazani, A. Morsali, A. *Ultrason. Sonochem.*, 2012, *19*, 1221–1226. p) A. Ramazani, B. Abdian, F. Zeinali Nasrabadi, N. Shajari, Z. Ranjdoost, *Bull. Korean Chem. Soc.*, 2012, *33*, 3701–3705. q) M.Valizadeh Holagh, A. M. Maharramov, M.A. Allahverdiyev, A. Ramazani, Y. Ahmadi, F. Zeinali Nasrabadi, A. Souldozi, *Turk. J. Chem.*, 2012, *36*, 671–681; r) A. Ramazani, R. Kalhor, A. Rezaei, Z. Karimi, *Heteroat. Chem.*, 2012, *23*, 315–321. s) I. Yavari, A. Ramazani, A.Yahya–Zadeh, *Synth. Commun.*, 1996, *26*, 4495–4499. t) I. Yavari, A. Ramazani, *Phosphorus Sulfur Silicon Relat. Elem.*, 1997, *130*, 73–77. u) A.Ramazani, K. Dastanra, F. Zeinali Nasrabadi, Z. Karimi, M. Rouhani, M. Hosseini, *Turk. J. Chem.*, 2012, *36*, 467–476. v) A.Ramazani, A. Azizian, M. Bandpey, N. Noshiranzadeh, *Phosphorus Sulfur Silicon Relat. Elem.*, 2006, *181*, 2731–2734. w) A. Ramazani, A. Souldozi, *Phosphorus Sulfur Silicon Relat. Elem.*, 2004, *179*, 529–534. x) A. Ramazani, A. Mahyari, A. Farshadi, M. Rouhani, *Helv. Chim. Acta.*, 2011, *94*, 1831–1837. y) A. Massoudi, I. Amini, A. Ramazani, F. Zeinali Nasrabadi, Y. Ahmadi, *Bull. Korean Chem. Soc.*, 2012, *33*, 39– 42. z) A.Ramazani, A. Rezaei, Y. Ahmadi, *Phosphorus Sulfur Silicon Relat. Elem.*, 2012, *187*, 22–31.

[16] A.Dömling,. *Chem. Rev.*, **2006**, *106*, 17–89.

[17] A. Dömling, I. Ugi, *Angew. Chem. Int. Ed. Engl*., **2000**, *39*, 3168–3210.

[18] I. Ugi, B. Werner, A. Dömling, *Molecules*, **2003**, *8*, 53–66.

[19] A. Dömling, E. Herdtweck, S. Heck, *Tetrahedron Lett*., **2006**, *47*, 1745–1747.

[20] X. Wu, X. Li, S.J. Danishefsky, *Tetrahedron Lett*., **2009**, *50*, 1523–1525.

[21] B.M. Ebert, I.K. Ugi, M. Grosche, E. Herdtweck, W.A. Herrmann, *Tetrahedron*, **1998**, *54*, 1887–11898.

[22] A. Shaabani, E. Soleimani, A.H. Rezayan, *Tetrahedron Lett*., **2007**, *48*, 6137–6140.

[23] H. Prokopcova, C.O. Kappe, *J. Org. Chem*., **2007**, *72*, 4440–4448.

[24] B. Kaboudin, D. Elhamifar, *Synthesis*, **2006**, 224–226.

[25] E. Vessally, A. Ramazani, E. Yaaghubi, *Monatsh Chem.*, **2011**, *142*, 1143.

[26] I. Kasumi, O. Kuniaki, K. Masahiro, *J. Label Compd Radiopharm.*, **2007**, *50*, 251.