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Solvent-free synthesis of 1,2-disubstituted 1,2-dihydroisoquinolines

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Abstract: One-pot and efficient approach to the synthesis of dialkyl 2-[1-[(alkoxycarbonyl)anilino]-2(1H)-isoquinolinyl]-2-butenedioates is described. This method involves three component reaction between isoquinoline, dialkyl acetylenedicarboxylate and *N*-phenyl carbamates under solvent-free condition, without using any catalyst and at room temperature. The mild reaction conditions and high yields of the products exhibit the good synthetic advantage of this method.

Keywords: 1,2-Dihydroisoquinoline, Solvent-free conditions, Phenyl carbamate.

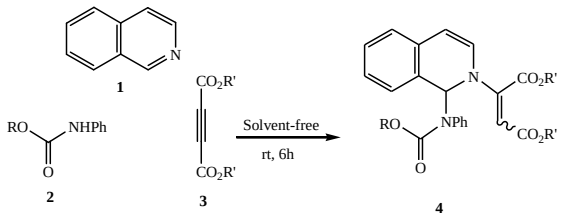
Introduction

The methods of green chemistry continue to grow in importance. Alternative processes to help conserve resources and can even reduce costs. The replacement of convention solvents with water or solvent-free conditions, which is harmless to health and is available in large quantities, is one of the most interesting basic approaches along these lines.

The isoquinoline skeleton is found in a large number of naturally occurring and synthetic biologically active heterocyclic compounds [1]. In particular, 1,2-dihydroisoquinoline derivatives act as delivery systems that transport drugs through the otherwise highlyimpermeable blood–brain barrier [2]. These compounds also exhibit sedative [3], antidepressant [4], antitumor, and antimicrobial activities [5]. In recent times, multicomponent reactions (MCRs) have been generally used for the synthesis of various and complex compounds as well as small and drug-like heterocycles [6].

Results and discussion

Here we describe a one-pot and efficient method for synthesis of 1,2-disubstituted 1,2-dihydroisoquinolines derivatives via the reaction of isoquinoline, dialkyl acetylenedicarboxylate and *N*-phenyl carbamates under solvent-free conditions, at room temperature (Scheme **1**, Table **1**).



Scheme 1: Three component reaction isoquinoline, dialkyl acetylenedicarboxylate and N-phenyl carbamates

The reaction of isoquinoline **1**, *N*-phenyl carbamates **2**, and dialkyl acetylenedicarboxylate **3** proceeded smoothly under solvent-free conditions at room temperature to produce dialkyl 2-[1-[(alkoxycarbonyl)anilino]-2(1H)-isoquinolinyl]-2-butenedioate derivatives **4** in 75–85% yields (Scheme **1**, Table **1**). The products were characterized on the basis of their elemental analyses and their IR, ^{1}H NMR and ^{13}C NMR spectra. The mass spectra of compounds **4a–4d** displayed molecular ion peaks at appropriate values, which were consistent with 1:1:1 adducts of isoquinoline, *N*-phenyl carbamates and the dialkyl acetylenedicarboxylate.

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The ^{1}H NMR spectrum of **4b** exhibited a triplet and sixtet for methyl and CH_2 (δ 3.68 and 1.73 ppm), respectively. ^{1}H NMR spectrum also showed two sharp singlet signals recognized as arising from methoxy groups (δ 3.68 and 3.83 ppm), one triplet (δ 4.16 ppm) for OCH_2 moiety and olefinic (δ 6.80 ppm) protons, along with multiplets for the isoquinoline and phenyl moieties.

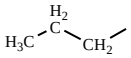
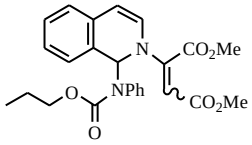
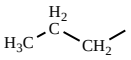
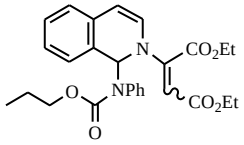
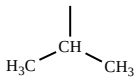
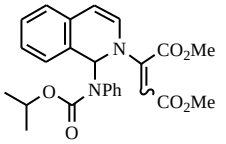
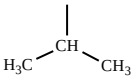
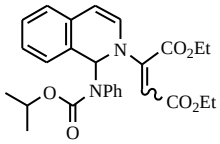
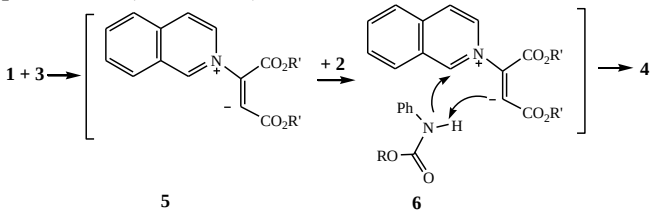
Entry	R	R'	Product	Yield (%)
1		Me		**4a** 75
2		Et		**4b** 78
3		Me		**4c** 80
4		Et		**4d** 80

Table 1: 1,2-disubstituted 1,2-dihydroisoquinoline derivatives.

The proton-decoupled ^{13}C NMR spectrum of **4b** showed 23 distinct resonances which were in agreement with the proposed structure. The spectral data of other derivatives were also in agreement with the proposed structures.

A tentative mechanism for this transformation is proposed in Scheme **2**. It is conceivable that the initial event is the formation of a 1:1 zwitterionic intermediate isoquinoline and dialkyl acetylenedicarboxylate **5** [7–10] which is subsequently protonated by the *N*-phenyl carbamates **2** and then attacked by the conjugate base of the carbamate to produce **4** (Scheme **2**).



Scheme 2: Proposed mechanism for synthesis of 1,2-disubstituted 1,2-dihydroisoquinoline Derivatives.

Conclusion

In conclusion, we have described a one-pot and convenient route for the synthesis of 1,2-disubstituted nitrogen containing heterocycles, by reaction of isoquinoline , *N*-phenyl carbamates and the dialkyl acetylenedicarboxylate under solvent-free condition and at room temperature.

Experimental

General procedure for the preparation of compounds 4a – 4d:

To a magnetically stirred mixture of a *N*-phenyl carbamate **2** (2 mmol) and dialkyl acetylenedicarboxylate **3** (2 mmol) was slowly added isoquinoline **1** (quinoline and pyridine) (2 mmol), and the reaction mixture was stirred or 6 h at rt. After completion of the reaction as indicated by TLC, the residue was purified by chromatography over silica gel

(Merck 230 –400 mesh) using an *n*-hexane-AcOEt mixture (5 : 1) as eluant, to afford the pure adducts.

*Dimethyl 2-[1-[(propoxycarbonyl)anilino]-2(1H)-isoquinolinyl]-2-butenedioates (**4a**):*

Yellow oil, yield: 0.67 g (75%), IR (KBr): ν = 1732 (C=O), 2982 (CH) cm $^{-1}$. EI-MS: 450 (2, M+), 435 (5), 407 (40), 391 (54), 363 (42), 307 (38), 77 (75), 59 (100), 43 (67). Anal. Calc. for $C_{25}H_{26}N_2O_6$ (450.48): C 66.65, H 5.82%; found: C 66.66, H 5.84%. ^{1}H NMR: 1.00 (t, $^3J_{HH}$ = 7.1, CH_3), 1.73 (sixtet, $^3J_{HH}$ = 7.2, CH_2), 3.70 (s, OCH_3), 3.83 (s, OCH_3), 4.16 (t, $^3J_{HH}$ = 7.0, CH_2), 6.80 (s, CH), 7.08 (d, $^3J_{HH}$ = 7.3, CH), 7.09 (d, $^3J_{HH}$ = 7.3, CH), 7.32–7.50 (m, 10CH). ^{13}C NMR: 11.0 (Me), 23.0 (CH_2), 51.5 (OMe), 52.0 (OMe), 67.6 (CH_2), 68.2 (CH), 93.6 (CH), 106.5 (CH), 118.6 (CH), 123.3 (CH), 123.7 (CH), 128.8 (2CH), 129.1 (2CH), 129.3 (CH), 132.4 (C), 136.3 (C), 138.1 (C), 140.5 (C), 154.8 (C=O), 163.8 (C=O), 167.8 (C=O).

*Diethyl 2-[1-[(propoxycarbonyl)anilino]-2(1H)-isoquinolinyl]-2-butenedioates (**4b**):*

Yellow oil, yield: 0.70 g (78%), IR (KBr): ν = 1732 (C=O), 2982 (CH) cm $^{-1}$. EI-MS: 478 (2, M+), 449 (34), 405 (38), 391 (45), 307 (33), 77 (87), 59 (100), 29 (78). Anal. Calc. for $C_{27}H_{30}N_2O_6$ (476.54): C 67.77, H 6.32%; found: C 66.73, H 6.34%. ^{1}H NMR: 1.02 (t, $^3J_{HH}$ = 7.2, CH_3), 1.22 (t, $^3J_{HH}$ = 7.1, CH_3), 1.24 (t, $^3J_{HH}$ = 7.1, CH_3), 1.74 (sixtet, $^3J_{HH}$ = 7.0, CH_3), 4.15 (q, $^3J_{HH}$ = 7.1, CH_2), 4.16 (q, $^3J_{HH}$ = 7.2, CH_2), 4.21 (t, $^3J_{HH}$ =7.0, CH_2), 6.81 (s, CH), 7.07 (d, $^3J_{HH}$ = 7.3, CH), 7.09 (d, $^3J_{HH}$ = 7.4, CH), 7.10–7.80 (m, 10CH). ^{13}C NMR: 10.14(Me), 14.0 (Me), 14.1 (Me), 22.3 (CH_2), 61.1 (CH_2), 62.3 (CH_2), 66.8 (CH_2), 68.3 (CH), 93.8 (CH), 105.1 (CH), 118.6 (CH), 123.3 (CH), 124.0 (CH), 128.5 (2CH), 128.9 (2CH), 129.0 (CH), 132.5 (C), 136.3 (C), 138.0 (C), 138.1 (C), 154.8 (C=O), 163.8 (C=O), 167.8 (C=O).

*Dimethyl 2-[1-[(isopropoxycarbonyl)anilino]-2(1H)-isoquinolinyl]-2-butenedioates (**4c**):*

Yellow oil, yield: 0.72 g (80%), IR (KBr): ν = 1732 (C=O), 2982 (CH) cm $^{-1}$. EI-MS: 450 (2, M+), 435 (5), 407 (40), 391 (54), 363 (42), 307 (38), 77 (75), 59 (100), 43 (67). Anal. Calc. for $C_{25}H_{26}N_2O_6$ (450.50): C 66.65, H 5.82%; found: C 66.66, H 5.81%. ^{1}H NMR: 1.23 (d, $^3J_{HH}$ = 6.2, CH_3), 1.30 (d, $^3J_{HH}$ = 6.2, CH_3), 3.70 (s, OCH_3), 3.83 (s, OCH_3), 5.03 (heptet, $^3J_{HH}$ = 6.2, CH), 6.80 (s, CH), 7.08 (d, $^3J_{HH}$ = 7.3, CH), 7.09 (d, $^3J_{HH}$ = 7.3, CH), 7.32–7.54 (m, 10CH). ^{13}C NMR: 21.8 (2Me), 52.0 (OMe), 53.1 (OMe), 68.2 (CH), 70.6 (CH), 94.0 (CH), 107.1 (CH), 118.5 (CH), 123.5 (CH), 128.8 (2CH), 129.1 (2CH), 129.2 (CH), 132.5 (C), 136.1 (C), 138.2 (C), 139.1 (C), 153.2 (C=O), 164.2 (C=O), 167.8 (C=O).

*Diethyl 2-[1-[(isopropoxycarbonyl)anilino]-2(1H)-isoquinolinyl]-2-butenedioates (**4d**):*

Yellow oil, yield: 0.77 g (80%), IR (KBr): ν = 1732 (C=O), 2982 (CH) cm $^{-1}$. EI-MS: 478 (2, M+), 449 (34), 405 (35), 391 (46), 307 (38), 87 (85), 59 (78), 29 (78). Anal. Calc. for $C_{27}H_{30}N_2O_6$ (478.54): C 67.77, H 6.32%; found: C 67.78, H 6.30%. ^{1}H NMR: 1.22 (d, $^3J_{HH}$ = 6.2, CH_3), 1.24 (d, $^3J_{HH}$ = 6.2, CH_3), 1.30 (d, $^3J_{HH}$ = 6.5, CH_3), 1.34 (d, $^3J_{HH}$ = 6.2, CH_3), 4.13 (q, $^3J_{HH}$ = 7.1, CH_2), 4.26 (t, $^3J_{HH}$ = 7.1, CH_2), 4.18 (heptet, $^3J_{HH}$ = 6.2, CH), 6.80 (s, CH), 7.07 (d, $^3J_{HH}$ = 7.3, CH), 7.09 (d, $^3J_{HH}$ = 7.3, CH), 7.20–7.42 (m, 10CH). ^{13}C NMR: 14.0 (Me), 14.1 (Me), 21.8 (2Me), 60.6 (CH_2), 61.1 (CH_2), 67.7 (CH), 70.6 (CH), 94.1 (CH), 106.2 (CH), 118.5 (CH), 123.2 (CH), 124.0 (CH), 128.5 (2CH), 129.0 (2CH), 129.2 (CH), 132.4 (C), 138.1 (C), 140.5 (C), 140.6 (C), 153.2 (C=O), 164.2 (C=O), 167.8 (C=O).

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