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Solvent-free one-pot synthesis of iminolactone and aminofuran derivatives using three component reactions

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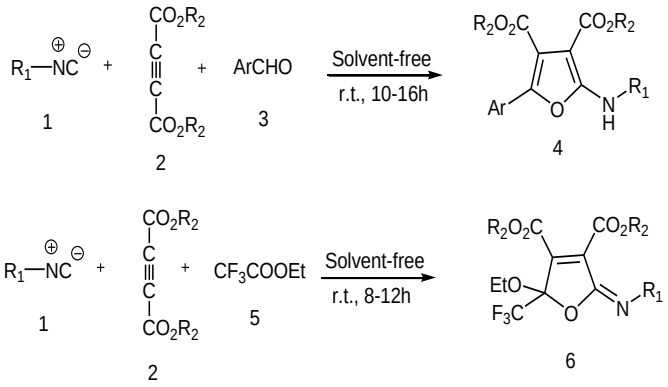
Abstract: Iminolactones and 2-aminofurans can be synthesized by three-component reaction of isocyanides, acetylenic esters, and carbonyl compounds, under solvent free conditions in good yields.

Keywords: Solvent free, Three-component reaction, Acetylenic esters, One-pot, Iminolactones.

Introduction

Heteroaromatic compounds have attracted considerable attention in the design of biologically active molecules and advanced organic materials.[1] Hence, a practical method for the preparation of such compounds is of great interest in synthetic organic chemistry.[2]

The rich and fascinating chemistry that stems from the addition of nucleophiles to activated acetylenic compounds has evoked considerable interest.[3] In previous works, the highly reactive 1:1 adduct, was trapped by carbonyl compounds to form iminolactone or 2-aminofuran derivatives in good yields, these reactions have been the subject of detailed investigation by a number of research groups [4-6]. Our investigations initiated with carbonyl compounds which on treatment with dialkyl acetylene dicarboxylates in presence of stoichiometric amount of alkyl isocyanides in solvent free conditions afforded products characterized as the aminofurans **4a-k** and iminolactones **6a-d** in good yields (Scheme **1**). Solvent free synthesis has several advantages over the classical method of synthesis.



Scheme 1. Synthesis of 2-aminofuran and iminolactone derivatives.

Green chemistry, the design of chemical products and processes that reduce or eliminate the use and generation of hazardous substances is an overarching approach that is applicable to all aspects of chemistry. Green chemistry provides "Green" paths for different synthetic routes using non-hazardous solvents and environmental-friendly chemicals [7].

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Results and discussion

The classical synthesis of aminofurans and iminolactones was carried out at high temperature using dichloromethane or benzene as a solvent and the reaction time was 24-48 hrs [8-11]. Solvent free reactions were carried out at room temperature and the reaction time was reduced for five membered rings synthesis. (Table **1** and Table **2**).

Table 1: Synthesis of 2-aminofurans under solvent-free conditions.

Entry	R_1	R_2	Ar	Product	[a]Yield%	m.p, ^oC	Lit, m.p, ^oC [Ref]
1	Cyclohexyl	Me	Phenyl	4a	80	—	— [9]
2	Cyclohexyl	Me	4-Nitrophenyl	4b	87	170-172	169-171[9]
3	Cyclohexyl	Et	4-Nitrophenyl	4c	79	148-150	150-153[12]
4	Cyclohexyl	Me	4-Chlorophenyl	4d	85	—	— [14]
5	t-Bu	Me	2-Fluoro	4e	82	—	— [15]
6	Cyclohexyl	Me	2-Nitrophenyl	4f	84	—	— [14]
7	t-Bu	Me	4-Nitrophenyl	4g	84	168-170	168-170[13]
8	t-Bu	Et	4-Nitrophenyl	4h	81	115-117	117-119[13]
9	Cyclohexyl	Me	4-Bromophenyl	4i	85	—	—
10	Cyclohexyl	Et	4-Bromophenyl	4j	83	—	—
11	t-Bu	Me	4-Chlorophenyl	4k	87	—	—

[a]Isolated yields

Table 2: Synthesis of iminolactones under solvent-free conditions.

Entry	R_1	R_2	Product	[a]Yield% [Ref]
1	Cyclohexyl	Me	6a	89 [16]
2	Cyclohexyl	Et	6b	91 [16]
3	t-Bu	Me	6c	90 [16]
4	t-Bu	Et	6d	83 [16]

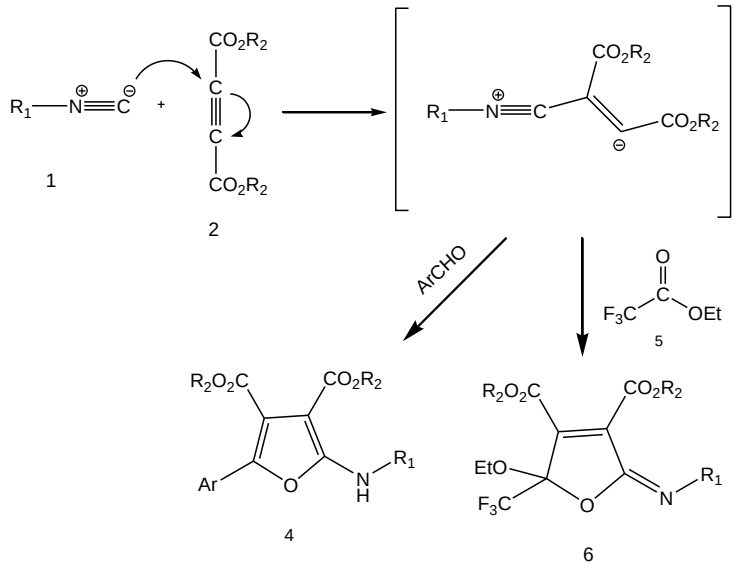
[a]Isolated yields

The structure of compounds **4i-k** was deduced from their IR, ^{1}H NMR, ^{13}C NMR, mass spectral data and elemental analysis. The ^{1}H NMR spectrum of compound **4i** exhibited two singlet sharp lines, readily recognizable as arising from two methoxy groups (at δ = 3.89 and 3.80 ppm) and NH proton resonated at δ = 6.66 ppm supporting the IR absorption at 3353 cm^{-1}.

The structure of compounds **6a-d** was deduced from their IR, ^{1}H NMR, ^{13}C NMR, and elemental analysis. The ^{1}H NMR spectrum of compound **6a** exhibited a triplet for the methyl group at δ = 1.30 ppm (^3J = 7.2 Hz), a multiplet for the cyclohexyl ring δ = 1.19-1.86

ppm, a multiplet for the N-CH cyclohexyl proton δ = 3.69 ppm, a quartet for the O-CH_2 group δ = 3.64 ppm, (^3J = 7.2 Hz) and two singlets for the methoxy groups δ = 3.76 and 3.80 ppm. The ^{13}C NMR spectrum of each compound displayed resonances in agreement with proposed structure.

A mechanistic rationale could be proposed for the formation of iminolactones or 2-aminofurans is shown (Scheme **2**) [9, 16]. The 1:1 zwitterionic intermediate which adds to the ethyl triflouroacetate leading to a dipolar species, cyclization of the latter leads to the iminolactone derivatives **6a-d**, in the presence of aromatic aldehyde, furan forms. This reaction, undergoes a [1,5]- hydrogen shift to yield the aminofuran derivatives **4a-k**. It is conceivable that these multicomponent reactions will be applicable to the synthesis of heterocyclic rings with high hindrance.



Scheme 2: Proposed mechanisms for the formation of compounds **4** and **6**.

Conclusion

In conclusion, an efficient one-pot synthesis of aminofurans and iminolactones involves the three-component reaction of alkyl isocyanides, acetylenic esters and carbonyl compounds at room temperature in solvent-free conditions. Not using hazardous solvents, good yields, and short reaction times make it a useful addition to modern synthetic methodologies.

Experimental

Cyclohexyl isocyanide, *tert*-butyl isocyanide, dialkyl acetylenedicarboxylate, ethyl trifluoroacetate and aromatic aldehydes were purchased from Fluka and Aldrich and used without further purification. Melting points and IR spectra were measured on an Electrothermal 9100 apparatus and a JASCO FT-IR spectrometer, respectively. The ^{1}H NMR and ^{13}C NMR spectra were recorded on a BRUKER 400 AVANCE instrument with $CDCl_3$ as solvent at 400.1 and 100.6 MHz, respectively. Mass spectra were recorded on a Shimadzu GC/MS QP 1100 EX mass spectrometer operating at an ionization potential of 70 eV. Elemental analyses were performed using a Heraeus CHN-O-Rapid analyser.

General procedure:

The process for the preparation of **4i** is described as an example. Cyclohexyl isocyanide (1 mmol) was slowly added dropwise, to the mixture of benzaldehyde (1 mmol) and dimethyl acetylenedicarboxylate (1 mmol) at room temperature for 3 minutes. After the addition, we began stirring the solution at suitable time. The progress of the reaction was monitored by TLC. Then, the crude product was washed with cold diethyl ether and n-hexane (1:3) to afford the pure product.

Dimethyl 2-(cyclohexylamino)-5-(4-bromophenyl) furan-3,4-dicarboxylate (**4i**):

yellow viscous liquid (0.37 g, 85%); IR (KBr) (ν_{max}, cm^{-1}): 3353 (NH), 1745 and 1681 (2C=O); ^{1}H NMR (400.1 MHz, $CDCl_3$): δ_H 1.42-1.96 (10H, m, $5CH_2$), 3.89 and 3.80 (6H, 2s, $2OCH_3$), 3.78 (1H, m, N-CH), 6.66 (1H, d, ^3J = 8.0 Hz, NH), 7.20-7.65 (4H, m, Ar-H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ_C 24.4, 25.3, 33.4 ($5CH_2$), 51.2 (N-CH), 51.6 and 53.0 ($2OCH_3$), 116.7,

124.3, 128.8, 129.6, 134.0, 137.9, 151.9, 161.6, 164.6, 164.9(2C=O); MS (*m/z*, %): 437 (M^++1, 35), 347 (M^+, 22), 318 (45), 288 (18), 155 (35), 83 (58), 55 (100). Anal. Calcd for $C_{20}H_{22}BrNO_5$ (436.30): C, 55.06; H, 5.08; N, 3.21; Found: C, 55.17; H, 5.09; N, 3.25 %.

Diethyl 2-(cyclohexylamino)-5-(4-bromophenyl)furan-3,4-dicarboxylate **(4j):**

light yellow viscous liquid, yield: 0.39 g (83%), IR (KBr) (ν_{max}, cm^{-1}): 3325 (N-H), 1735 and 1673 (2C=O). ^{1}H NMR ((400.1 MHz, $CDCl_3$): δ_H 1.33 (3H, t, CH_3), 1.41 (3H, t, CH_3), 1.43-2.08 (10H, m, cyclohexyl), 3.77 (1H, m, CH), 4.27 (2H, q, OCH_2), 4.43 (2H, q, OCH_2), 6.74 (1H, d, J = 8.1 Hz, N-H), 7.25-7.76 (4H, m, Ar-H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ_C 14.1, 14.4 ($2CH_3$), 24.4, 25.3, 33.3 ($5CH_2$), 51.6 (N-*C*H), 59.9 and 62.1 ($2OCH_2$), 117.8, 123.7, 128.2, 129.7, 135.1, 137.5, 149.7, 161.5, 164.4 and 164.9 (2C=O). Anal. Calcd. for $C_{22}H_{26}BrNO_5$ (464.35): C, 56.90; H, 5.64; N, 3.02. Found: C, 57.12; H, 5.69; N, 3.08%.

Dimethyl 2-(tert-butylamino)-5-(4-chlorophenyl)furan-3,4-dicarboxylate (**4k**):

yellow solid (0.32 g, 87%); IR (KBr) (ν_{max}, cm^{-1}): 3353 (NH), 1743 and 1685 (2C=O); ^{1}H NMR ((400.1 MHz, $CDCl_3$): δ_H 1.47 (9H, s, $C(CH_3)_3$), 3.90 and 3.77 (6H, 2s, $2OCH_3$), 6.83 (1H, br, NH), 7.31-7.46 (4H, m, Ar-H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ_C 27.9 ($C(CH_3)_3$), 52.1 and 52.6 ($2OCH_3$), 53.8 (N-*C*$(Me)_3$), 91.3, 115.7, 125.7, 127.7, 130.7, 133.8, 139.5, 160.4, 164.8, 165.5; MS (*m/z*, %): 366 (M^++1, 42), 365 (M^+, 78), 308 (85), 303 (28), 232 (38), 57 (100). Anal. Calcd for $C_{18}H_{20}ClNO_5$ (365.81): C, 59.10; H, 5.51; N, 3.83; Found: C, 59.19; H, 5.54; N, 3.89 %.

General procedure:

The process for the preparation of **6*a*** is described as an example. Cyclohexyl isocyanide (1 mmol) in was slowly added dropwise to a mixture of ethyl trifluoroacetate (1mmol) and dimethyl acetylenedicarboxylate (1 mmol) at room temperature for 3 min. After the addition, we began stirring the solution at suitable time. The progress of the reaction was monitored by TLC. Then, the crude product was washed with cold diethyl ether and n-hexane (1:3) to afford the pure product.

Dimethyl 5-(cyclohexylimino)-2-ethoxy-2-(trifluoromethyl)-2,5-dihydrofuran-3,4-dicarboxylate (**6a**):

Dark orange powder (0.35 g, 89%); m.p. 60-62 ˚C; IR (KBr) (ν_{max}, cm^{-1}): 2933, 2858, 1744 and 1697 (2C=O), 1647 (C=N); ^{1}H NMR (400.1 MHz, $CDCl_3$): δ_H 1.30 (3H, t, ^3J = 7.0 Hz, CH_3), 1.19-1.86 (10H, m, $5CH_2$), 3.64 (2H, q, ^3J = 7.0 Hz, OCH_2), 3.69 (1H, m, N-CH), 3.80 and 3.76 (6H, 2s, $2OCH_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ_C 14.7 (CH_3), 24.4, 24.5, 25.8, 33.0 and 33.2 ($5CH_2$ of cyclohexyl), 53.1 and 53.3 ($2OCH_3$), 57.7 (N-CH), 60.9 (OCH_2), 106.9 (q, ^2J = 35.2 Hz, *C*CF_3), 120.5 (q, ^1J = 286.1 Hz, CF_3), 136.6 and 142.1 (C_{olefin}), 149.6 (C_{imine}), 160.1 and 161.6 (2C=O); Anal. Calcd for $C_{17}H_{22}F_3NO_6$ (393.35): C, 51.91; H, 5.64; N, 3.56%. Found: C, 52.35; H, 5.75; N, 3.88%.

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