Synthesis of functionalised 2,5-diaminofurans by reaction of isocyanides, acetylenic esters and acid anhydrides

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The reaction between two equivalents of an isocyanide, a dialkyl acetylenedicarboxylates and an acid anhydride at room temperature provides a simple and efficient one-pot route for the synthesis of 2,5-diaminofuran derivatives in high yields. The reaction is characterised by mild conditions, short reaction time and tolerance to various functional groups.

Keywords: multicomponent reactions, isocyanides, diaminofurans, dialkyl acetylenedicarboxylates, acid anhydrides

Isocyanides, as the only class of stable organic compounds with a two-valence carbon atom, are very reactive species and react with many functional groups by different mechanisms. On the basis of valence-bond theory, the isocyanide functionality can be shown as two resonance forms **I** and **II** (Scheme 1). Isocyanides have carbenic character on the basis of resonance form **I** and nucleophilic character on the basis of form **II**. In most addition reactions of isocyanides both the nucleophile and electrophile add to the α-carbon atom, and no species is added to the nitrogen.

The Ugi four-component reaction (U-4CR)[1–3] and Passerini three component reaction (P-3CR)[4] are among the most important isocyanide-based multi-component reactions (IMCRs). U-4CR and P-3CR describe the reaction of isocyanides with carboxylic acids in the presence of imines or aldehydes, respectively.

Recently, a wide variety of electrophiles have been applied to trap isocyanide-dimethyl acetylenedicarboxylates (DMAD) intermediates, among them are carbon electrophiles such as aldehydes, imines, quinonids,[5] 1,2-diketones,[6] 1,2,3-tricarbonyl compounds,[7] isocyanates,[8] and hydrogen electrophiles such as pyrrole,[9] amides,[10] hydroxy coumarine,[11] phenols,[12] phthalic anhydride[13] and isatoic anhydride.[14] Treatment of an isocyanide-DMAD zwitterion with aromatic carboxylic acids has been reported to produce unsaturated amides.[15] The reaction of an isocyanide-DMAD adduct with aromatic-substituted acetic acids has been reported to afford 2,5-diaminofuran derivatives in the presence of two equivalents of an isocyanide.[16] The reaction between two equivalents of an isocyanides, aliphatic carboxylic acids and dialkyl acetylenedicarboxylates has been reported to afford 2,5-diaminofuran derivatives.[17] In the context of our previous work on IMCRs,[9–11,17–21] we nowreport the results of our investigations on the reaction of isocyanides and dialkyl acetylenedicarboxylates (DAADs) in the presence of acid anhydrides.

I **II**

Scheme 1 Two resonance forms.

Results and discussion

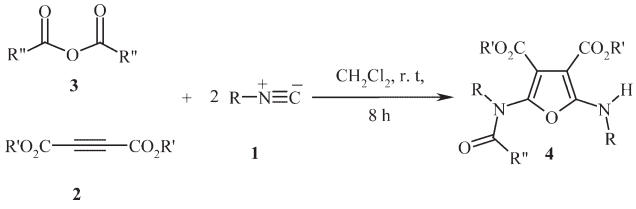
The reaction of alkyl isocyanides (2 equiv.) with dialkyl acetylenedicarboxylates (1 equiv.) in the presence of acid anhydrides (1 equiv.) in dichloromethane for 8 h at room temperature, affords 2,5-diaminofuran derivatives **4a–o** in high yields (Scheme 2 and Table 1). Derivatives **4** have been reported to have formed over 24h at room temperature in the presence of aliphatic carboxylic acids,[17] while when acid anhydrides are used, the reaction is faster and produces comparable yields.

Compounds **4a–j** are known and their structures were deduced by comparison of spectroscopic data with authentic samples.[17] Compounds **4k–o** were new and their structures were deduced by elemental and spectroscopic analysis. The ^{1}H NMR spectrum of compound **4k** was simple and exhibited two sharp singlets, which were due to two methoxy groups protons (δ 3.71 and 3.84 ppm) and one NH group (δ 6.62 ppm, disappeared with addition of D_2O) and one sharp line (δ 1.32 ppm) for the protons of the three methyl groups of *tert*-butyl. Cyclohexyl fragments protons resonated as multiplets at δ 0.91–2.11 and a multiplet at δ 4.13–4.35 ppm.

The ^{13}C NMR spectrum of compound **4k** showed 19 distinct resonances in agreement with the proposed structure. The signals at 85.9, 115.2, 137.8, 160.2, 163.7, 165.1 and 172.0 ppm are related to furan ring carbons and three carbonyl groups. The IR spectrum showed an absorption bond at 3332 cm^{-1} for the NH group. The carbonyl stretching vibrations were observed as strong absorption bonds at 1730, 1683 and 1671 cm^{-1}. The molecular ion peak at 462 in the mass spectrum of compound **4k** supported the 2:1:1 adduct of cyclohexyl isocyanide, acid anhydride and dimethyl acetylenedicarboxylate.

A reasonable mechanism for the formation of compound **4** is presented in Scheme 3.

On the basis of the well established chemistry of isocyanides[1–3,16] it is reasonable to assume that compound **4** is produced by initial formation of a highly reactive 1:1 zwitterionic intermediate **5** by the Michael-type addition reaction of the alkyl isocyanide **1** with the dialkyl acetylenedicarboxylate **2**, which adds to the carbonyl group of the acid anhydride **3** leading to species **6** and **7**. The addition of carboxylate anion **7** on nitrilium cation **6** affords intermediate **8** which then rearranges to unsaturated imide **9**. Cycloaddition of another molecule of isocyanide to imide **9** leads to dihydrofuran intermediate **10**. Attack by adventitious water at the ketone carbonyl followed by loss of the carboxylic acid which forms the furan derivative **4**.



Scheme 2

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Table 1 Reaction of alkyl isocyanides with dialkyl acetylenedicarboxylates and acid anhydrides

Entry	R	R'	R''	Product	Yield/%[a]	
					Found	From ref.17
1	*tert*-Bu	Me	Me	**4a**	93	95
2	*tert*-Bu	Et	Me	**4b**	92	95
3	*tert*-Bu	*t*-Bu	Me	**4c**	92	90
4	Cy	Me	Me	**4d**	95	94
5	*tert*-Bu	Me	Et	**4e**	89	90
6	*tert*-Bu	Et	Et	**4f**	92	93
7	*tert*-Bu	*t*-Bu	Et	**4g**	94	95
8	Cy	Me	Et	**4h**	90	90
9	*tert*-Bu	Me	CF_3	**4i**	88	85
10	Cy	Me	CF_3	**4j**	90	88
11	Cy	Me	*t*-Bu	**4k**	85	–
12	Cy	Et	*t*-Bu	**4l**	87	–
13	*tert*-Bu	Et	CF_3	**4m**	90	–
14	Cy	*t*-Bu	CF_3	**4n**	88	–
15	Cy	Et	CF_3	**4o**	91	–

Cy, cyclohexyl.
[a] Isolated yield.

In summary, we report here the reaction between two equivalents of an isocyanide, a dialkyl acetylenedicarboxylate and an acid anhydride for the synthesis of functionalised 2,5-diaminofuran derivatives. The procedure has advantages including the use of simple starting materials, short reaction times, easy work-up and good yields. Also not only is the reaction performed under neutral conditions but also the substances can be mixed without any activation or modification.

Experimental

Elemental analyses were performed using a Heraeus CHN-O-Rapid analyser. Mass spectra were recorded on a finnigan-MAT 8430 mass spectrometer operating at an ionisation potential of 70 eV. IR spectra were recorded on a Shimadzu IR-470 spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on Bruker DRX-500 Avance spectrometer on solution in $CDCl_3$ using TMS as internal standard. The chemicals used in this work were purchased from Fluka (Buchs, Switzerland) and were used without further purification.

General procedure

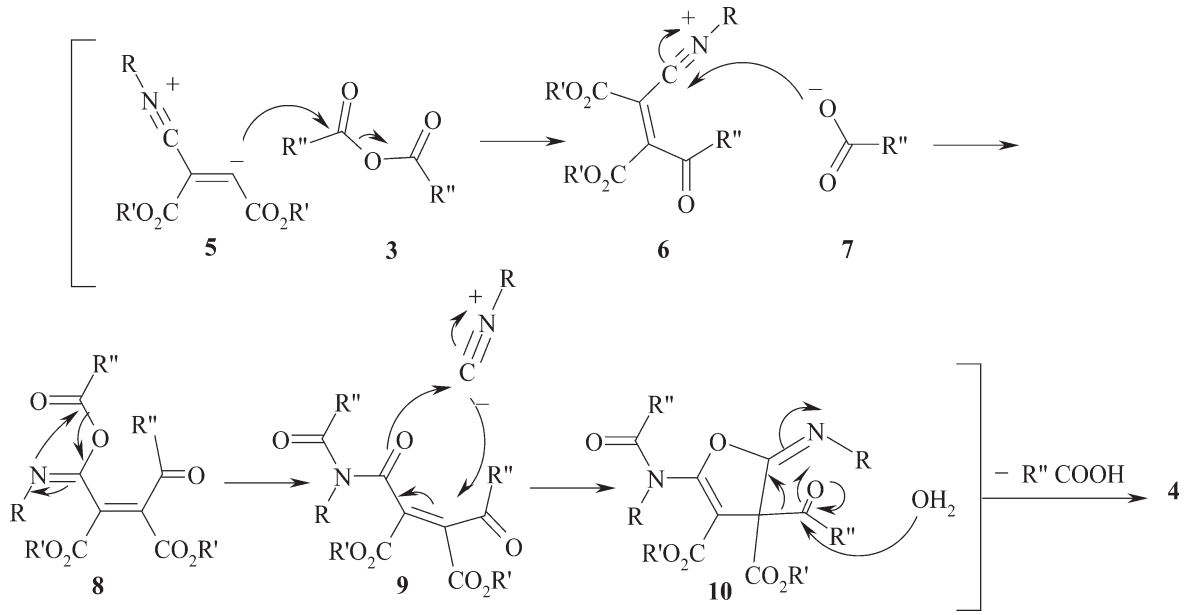
To a magnetically stirred solution of an isocyanide (2.0 mmol) and an acid anhydride (1 mmol) in dichloromethane (15 mL) was added a mixture of dialkyl acetylenedicarboxylate (1.0 mmol) in dichloromethane (2 mL) at room temperature. The reaction mixture was then stirred for 8 h. The solvent was removed and the residue was purified by silica gel column chromatography using hexane–ethyl acetate (3:1) as eluent. The solvent was removed under reduced pressure to afford the product.

Dimethyl 2-[cyclohexyl(2,2-dimethyl propionyl)amino]-5-(cyclohexylamino)furan-3,4-dicarboxylate (**4k**): Yellow oil, (85%); IR (KBr) (ν_{max}, cm^{-1}): 3332 (NH), 1730, 1683 and 1671 (carbonyl groups). Anal. Calcd for $C_{25}H_{38}N_2O_6$: C, 64.91; H, 8.28; N, 6.06. Found: C, 64.82; H, 8.45; N, 5.92%. MS (*m/z*, %): 462 (M$^+$, 5). ^{1}H NMR (500.1 MHz, $CDCl_3$): δ 0.91–2.11 (20H, 10 CH_2 of cyclohexyl), 1.32 (9H, s, 3 CH_3), 3.71 (3H, S, OCH_3) and 3.84 (3H, s, OCH_3), 4.13–4.35 (2H, m, 2CH of cyclohexyl), 6.62 (1H, s, NH). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 28.1 ($3CH_3$), 24.5, 25.5, 25.7, 26.4, 33.1, 33.9 (10 CH_2 of cyclohexyl groups), 51.4 and 51.8 (2 NCH), 52.8 and 55.7 (2 OCH_3), 81.3 (C), 85.9, 115.2, 137.9, 160.2 (4C of furan ring), 163.7, 165.1 and 172.0 (3 C=O).

Diethyl 2-[cyclohexyl(2,2-dimethyl propionyl)amino]-5-(cyclohexylamino)furan-3,4-dicarboxylate **(4l):** Yellow oil, (87%); IR (KBr) (ν_{max}, cm^{-1}): 3335 (NH), 1728, 1680 and 1673 (carbonyl groups). Anal. Calcd for $C_{27}H_{42}N_2O_6$: C, 66.10; H, 8.63; N, 5.71. Found: C, 65.87; H, 8.49; N, 5.90%. MS (*m/z*, %): 490 (M$^+$, 7). ^{1}H NMR (500.1 MHz, $CDCl_3$): δ 1.27 (3H, t, J = 7Hz, CH_3) and 1.34 (3H, t, J = 7 Hz, CH_3), 0.88–2.04 (20H, 10 CH_2 of cyclohexyl), 1.30 (9H, s, 3 CH_3), 4.07–4.42 (2H, m, 2CH of cyclohexyl), 4.25 (4H, m, 2 OCH_2), 6.74 (1H, s, NH). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 14.3 and 14.9 (2 CH_3), 28.1 ($3CH_3$), 24.3, 25.7, 25.7, 26.4, 33.4, 33.8 (10 CH_2 of cyclohexyl groups), 51.5 and 51.8 (2 NCH), 60.1 and 61.9 (2 OCH_2), 81.3 (C), 85.8, 115.3, 138.0, 160.4 (4C of Furan ring), 163.6, 165.4 and 172.2 (3 C=O).

Diethyl 2-[tert-butyl(trifluoroacetyl)amino]-5-(tert-butylamino)furan-3,4-dicarboxylate (**4m**): Yellow oil, (90%); IR (KBr) (ν_{max}, cm^{-1}): 3333 (NH), 1737, 1689, (carbonyl groups). Anal. Calcd for $C_{20}H_{29}F_3N_2O_6$: C, 53.33; H, 6.49; N, 6.22. Found: C, 53.50; H, 6.32; N, 6.12%. MS (*m/z*, %): 450 (M$^+$, 5). ^{1}H NMR (500.1 MHz, $CDCl_3$): δ 1.29 (3H, t, J = 7Hz, CH_3) and 1.31 (3H, 2 t, J = 7 Hz, CH_3), 1.51 (9H, s, *tert*-butyl) and 1.58 (9H, s, *tert*-butyl), 4.15 (4H, m, 2 OCH_2), 6.93 (1H, s, NH). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 14.2 and 14.7 (2 CH_3), 28.0, 30.7 (methyl groups of 2 *tert*-butyl), 53.4 and 64.0 (2 NC), 60.0 and 61.7 (2 OCH_2), 86.4, 114.9, 135.1, 157.7 (4C of Furan ring), 162.5 and 165.4 (two ester carbonyl carbons), 117.1 (d, J = 281 Hz, CF_3), 157.7 (q, J = 36 Hz, $COCF_3$).

Ditert-butyl 2-[cyclohexyl(trifluoroacetyl)amino]-5-(cyclohexylamino) furan-3,4-dicarboxylate (**4n**): Yellow oil, (88%); IR (KBr) (ν_{max}, cm^{-1}): 3336 (NH), 1732, 1680, (carbonyl groups). Anal. Calcd for $C_{28}H_{41}F_3N_2O_6$: C, 60.20; H, 7.40; N, 5.01. Found: C, 60.35; H, 7.50; N, 5.15%. MS (*m/z*, %): 558 (M$^+$, 3). ^{1}H NMR (500.1 MHz, $CDCl_3$):



Scheme 3 Suggested mechanism for formation of compound **4**.

δ 0.89–2.05 (20H, 10 CH_2 of cyclohexyl), 1.41 (9H, s, *tert*-butyl) and 1.48 (9H, s, *tert*-butyl), 4.10–4.38 (2H, m, 2CH of cyclohexyl), 7.16 (1H, s, NH). ^{13}C NMR (125.7 MHz, $CDCl_3$): 28.57 and 29.11 (methyl groups of 2 *tert*-butyl), δ 24.9, 25.3, 25.5, 26.8, 32.7, 33.8 (10 CH_2 of cyclohexyl groups), 51.6 and 51.9 (2 NCH), 80.6 and 82.4 (2 OC), 85.9, 115.1, 135.8, 158.1, (4C of Furan ring), 163.0 and 165.2 (two ester carbonyl carbons), 117.6 (d, J = 280 Hz, CF_3), 157.2 (q, J = 36 Hz, $COCF_3$).

Diethyl 2-[cyclohexyl(trifluoroacetyl)amino]-5-(cyclohexylamino) furan-3,4-dicarboxylate (**4o**): Yellow oil, (91%); IR (KBr) (ν_{max}, cm^{-1}): 3337 (NH), 1736, 1689, (carbonyl groups). Anal. Calcd for $C_{24}H_{33}F_3N_2O_6$: C, 57.36; H, 6.62; N, 5.57. Found: C, 57.25; H, 6.52; N, 5.39%. MS (*m/z*, %): 502 (M^+, 5). ^{1}H NMR (500.1 MHz, $CDCl_3$): δ 0.91–1.92 (20H, 10 CH_2 of cyclohexyl), 1.23 (3H, t, J = 7 Hz, CH_3) and 1.37 (3H, t, J = 7 Hz, CH_3), 4.12 (4H, m, 2 OCH_2), 4.24–4.51 (2H, m, 2CH of cyclohexyl), 7.04 (1H, s, NH). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 14.3 and 14.7 (2 CH_3), 24.9, 25.5, 25.5, 26.8, 32.6, 33.9 (10 CH_2 of cyclohexyl groups), 51.7 and 52.0 (2 NCH), 60.1 and 61.7 (2 OCH_2), 86.2, 113.9, 135.7, 158.0 (4C of Furan ring), 162.9 and 165.4 (two ester carbonyl carbons), 117.5 (d, J = 280 Hz, CF_3), 157.1 (q, J = 36 Hz, $COCF_3$).

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