# Alkyl Isocyanides Promoted Synthesis of Functionalized Azadienes from Dialkyl Acetylene Dicarboxylates and N-Hydroxysuccinimide

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*The reaction between N-Hydroxy succinimide with dialkyl acetylene dicarboxylates in the presence of isocyanides, leads to functionalized azadienes in good yields. The product were analized and the structures of reaction compounds were deduced from their IR, $^{1}$HNMR and $^{13}$CNMR spectra.*

*Keywords: azadienes, alkyl isocyanides, dialkyl acetylene dicarboxylates, N-hydroxysuccinimide*

Succinimide and its N-substituted derivatives are the key structural units in many important compounds including plant growth stimulators, additives for lubricative oils, corrosion inhibitors, and anti-convulsants drugs for memory enhancement, anti-tumor agents and for other purposes [1–7].

On the other hand MCRs that involve isocyanides are by far the most flexible reactions in terms of scaffolds and versatile compounds [8, 9].The trapping of the 1:1 intermediate formed between dialkyl acetylenedicarboxylates and isocyanides with OH, NH, and CH acids has been widely studied [10–12].

Moreover azadienes have been employed in a range of different reactions to access a wide variety of N-heterocycles, including e.g. di- and tetrahydropyridines, pyrimidines, quinolines, thiazines, pyrroles, triazinane diones, and aziridines [13–16]. The reactivity that a 1-azadiene displays in a given reaction depends both on the reaction partner and on the nature of the substituents [17].

In combination with MCR-based strategies, 1-azadienes represent a challenging array of functionalities that can be employed to explore chemical space efficiently and identify small molecular probes for biology [18–22].

Recently, we have described a convenient method for the preparation of l-azabutadienes, by three component reactions of some NH and OH acids with dialkyl acetylenedicarboxylates and alkyl isocyanides [23-26]. In continuation of our interest in the application of isocyanides in MCRs [27, 28], we extend this methodology using N-hydroxysuccinimide. Thus, the reaction of alkyl isocyanides **1** and dialkyl acetylenedicarboxylates **2** in the presence of strong OH-acid, such as N-Hydroxysuccinimide **3** leads 1-Azadienes **4** in good yields (scheme 1).

## Experimental part

*General*

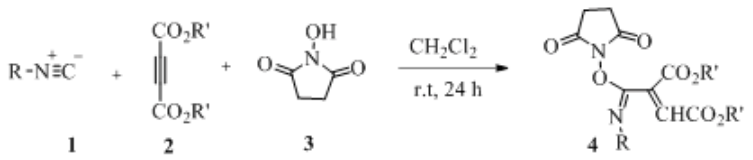
Elemental analyses for C, H, and N were performed using a Heraeus CHN-O-Rapid analyzer. IR spectra were measured on a Perkin Elmer Precisely-100 FTIR spectrometer. $^{1}$H and $^{13}$C NMR spectra were measured with a Bruker DRX-300 AVANCE instrument with $CDCl_3$ as solvent at 300.1 and 75.5 MHz, respectively. Mass spectra were recorded on a Finnigan-Matt 8430 mass spectrometer operating at an ionization potential of 70 eV. Alkyl isocyanides, alkyl acetylene dicarboxylates and N-Hydroxysuccinimide were obtained from Merck and were used without further purification.

*Typical procedure for preparation of compounds **4***

To a magnetically stirred solution of N-Hydroxy-succinimide (2 mmol) and dimethyl acethylene dicarboxylate (2 mmol) in $CH_2Cl_2$ (6 mL), was added drop wise a mixture of cyclohexyl isocyanide (2 mmol) in $CH_2Cl_2$ (3 mL) at room temperature over 10 min. After completion of the reaction [24 h; TLC (hexane/AcOEt 2:1)], the solvent was evaporated and the residue was purified by column chromatography [silica gel (230–240 mesh; Merck), hexane/AcOEt 2:1)].

*Dimethyl-2- [(2, 5-dioxo-1-pyrilydinyl oxy) (cyclohexyl imino) methyl]-2- buthene dionate* **(4a)**

Colorless oil yield 0.60 g (82%); IR (KBr): 1659 (C=N), 1737 (C=O) cm$^{-1}$. $^{1}$H NMR (300 MHz, $CDCl_3$): δ 1.24-1.65




Scheme 1. Synthesis of compounds **4**

| 1 | R |
|---|---|
| a | *c*-Hexyl |
| b | *t*-Butyl |
| c | *1,1,3,3-tetra methyl* Butyl |

| 2 | R' |
|---|---|
| a | Me |
| b | Et |
| c | *t*-Butyl |

| 4 | R | R' | yield of **4** % |
|---|---|---|---|
| a | *c*-Hexyl | Me | 82 |
| b | *c*-Hexyl | Et | 87 |
| c | *c*-Hexyl | *t*-Bu | 74 |
| d | *t*-Butyl | Me | 86 |
| e | *t*-Butyl | Et | 81 |
| f | *1,1,3,3-tetra methyl* Butyl | Me | 83 |
| g | *1,1,3,3-tetra methyl* Butyl | Et | 82 |

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(10H, m, $5CH_2$), 2.79 (4H, s, $2CH_2$), 3.08 (1H, m, CH), 3.87 (3H, s, $OCH_3$), 3.91 (3H, s, $OCH_3$), 7.20 (H, s, CH). $^{13}C$ NMR (75 MHz, $CDCl_3$): δ 23.6 (CH), 24.6 ($CH_2$), 25.6 ($CH_2$), 33.1 ($2CH_2$), 52.8 ($OCH_3$), 53.4 ($OCH_3$), 57.6 (CH-N), 132.0 (C=), 135.2 (CH=), 146.2 (CON), 162.9 ($CO_2$), 163.4 ($CO_2$), 169.7 (CO=N). EI-MS *m/z* (rel.int): 366 [$M^+$] (14), 283 (86). Anal. Calcd. for $C_{17}H_{22}N_2O_7$: C, 55.73; H, 6.05; N, 7.65; found: C, 55.67; H, 6.14; N, 7.58.

*Diethyl-2- [(2, 5-dioxo-1-pyrilydinyl oxy) (cyclohexyl imino) methyl]-2- buthene dionate* **(4b)**

Colorless oil yield 0.68 g (87%); IR (KBr): 1626 (C=N), 1731 (C=O) $cm^{-1}$. $^1H$ NMR (300 MHz, $CDCl_3$): δ 1.08-1.33 (10H, m, $5CH_2$), 1.50 (3H, t, *J*=7.1, $CH_3$), 1.61 (3H, t, *J*=7.1, $CH_3$), 2.77 (4H, s, $2CH_2$), 3.08 (1H, m, CHN), 4.32 (2H, m, $OCH_2$), 4.33 (2H, m, $OCH_2$), 7.16 (1H, s, CH). $^{13}C$ NMR (75 MHz, $CDCl_3$): δ 13.8 ($CH_3$), 13.9 ($CH_3$), 23.6 ($CH_2$), 25.6 ($CH_2$), 33.1 ($2CH_2$), 57.5 (CH-N), 62.2 ($OCH_2$), 62.8 ($OCH_2$), 132.1 (C=), 135.5 (CH=), 146.4 (CO-N), 162.5 ($CO_2$), 163.1 ($CO_2$), 169.6 (CO=N). EI-MS *m/z* (rel.int): 394 [$M^+$] (23), 365 (52), 341 (93). Anal. Calcd. for $C_{19}H_{26}N_2O_7$: C, 57.86; H, 6.64; N, 7.10; found: C, 57.77; H, 6.59; N, 7.02.

*Ditert-Buthyl-2- [(2, 5-dioxo-1-pyrilydinyl oxy) (cyclohexyl imino) methyl]-2- buthene dionate* **(4c)**

Colorless oil yield 0.67 g (74%); IR (KBr): 1634 (C=N), 1730 (C=O) $cm^{-1}$. $^1H$ NMR (300 MHz, $CDCl_3$): δ 1.25-1.64 (10H, m, $5CH_2$), 1.52 (9H, m, $3CH_3$), 1.54 (9H, m, $3CH_3$), 2.78 (4H, s, $2CH_2$), 3.09 (1H, m, CHN), 7.06 (1H, s, CH). $^{13}C$ NMR (75 MHz, $CDCl_3$): δ 23.7 (CH), 25.6 ($CH_2$), 27.8 ($3CH_3$), 27.9 ($3CH_3$), 29.68 ($CH_2$), 33.2 ($2CH_2$), 57.6 (CH-N), 83.2 (C-O), 83.9 (C-O), 132.2 (C=), 136.4 (CH=), 146.9 (CO-N), 161.7 ($CO_2$), 162.3 ($CO_2$), 169.5 (CO=N); EI-MS *m/z* (rel.int): 450 [$M^+$] (16), 393 (100), 367 (71). Anal. Calcd. for $C_{23}H_{34}N_2O_7$: C, 61.32; H, 7.61; N, 6.22; found: C, 61.24; H, 7.50; N, 6.17.

*Dimethyl-2- [(2, 5-dioxo-1-pyrilydinyl oxy) (t-butylimino) methyl]-2- buthene dionate* **(4d)**

Colorless oil yield 0.58 g (86%); IR (KBr): 1629 (C=N), 1739 (C=O) $cm^{-1}$. $^1H$ NMR (300 MHz, $CDCl_3$): δ 1.27 (9H, s, $CH_3$), 2.79 (4H, s, $2CH_2$), 3.75 (3H, s, $OCH_3$), 3.87 (3H, s, $OCH_3$), 5.54 (1H, s, CH). $^{13}C$ NMR (75 MHz, $CDCl_3$): δ 25.6 ($3Ch_3$), 29.5 ($2CH_2$), 49.0 (C-N), 52.4 (OMe), 53.6 (OMe), 131.0 (C=), 132.6 (CH=), 147.2 (CON), 163.1 ($CO_2$), 169.1 (CO=N). EI-MS *m/z* (rel.int): 340 [$M^+$] (27), 283 (71), 57 (100). Anal. Calcd. for $C_{15}H_{20}N_2O_7$: C, 52.94; H, 5.92; N, 8.23; found: C, 52.83; H, 5.83; N, 8.15.

*Diethyl-2- [(2, 5-dioxo-1-pyrilydinyl oxy) (t-bu imino) methyl]-2- buthene dionate* **(4e)**

Colorless oil yield 0.60 g (81%); IR (KBr): 1646(C=N), 1738 (C=O) $cm^{-1}$. $^1H$ NMR (300 MHz, $CDCl_3$): δ 1.13 (9H, s, $3CH_3$), 1.30-1.38 (6H, m, $2CH_3$), 2.67 (4H, s, $2CH_2$), 4.26-4.33 (4H, m, $2OCH_2$), 7.09 (1H, s, CH). $^{13}C$ NMR (75 MHz, $CDCl_3$): δ14.04, ($2CH_3$), 25.4 ($3CH_3$), 30.5 ($2CH_2$), 54.5 (C-N), 61.5 ($OCH_2$), 62.1 ($OCH_2$), 133.4 (C=), 134.6 (CH=), 141.0 (CO-N), 162.9 ($CO_2$), 163.2 ($CO_2$), 170.1 (CO=N); EI-MS *m/z* (rel.int): 368 [$M^+$] (37), 339 (45), 57 (100). Anal. Calcd. for $C_{17}H_{24}N_2O_7$: C, 55.43; H, 6.57; N, 7.60; found: C, 55.35; H, 6.62; N, 7.52.

*Dimethyl-2- [(2, 5-dioxo-1-pyrilydinyl oxy) (1, 1, 3, 3-tetra methyl butyl imino) methyl]-2- buthene dionate* **(4f)**

Colorless oil yield 0.66 g (83%); IR (KBr): 1668 (C=N), 1732 (C=O) $cm^{-1}$. $^1H$ NMR (300 MHz, $CDCl_3$): δ 0.99 (9H, s, $3CH_3$), 1.25 (6H, s, $2CH_3$), 1.56 (2H, s, $CH_2$), 2.72 (4H, s, $2CH_2$), 3.79 (3H, s, $OCH_3$), 3.83 (3H, s, $OCH_3$), 7.00 (1H, s, CH). $^{13}C$ NMR (75 MHz, $CDCl_3$): δ 28.5 ($CH_3$), 28.7 ($CH_3$), 31.3 ($3CH_3$), 31.5 ($2CH_2$), 31.6 (C), 31.7 ($CH_2$), 51.6 (C-N), 52.4 ($OCH_3$), 53.0 ($OCH_3$), 131.8 (C=), 134.2 (CH=), 138.2 (CO-N), 159.0 ($CO_2$), 165.4 ($CO_2$), 167.1 (CO=N); EI-MS *m/z* (rel.int): 396 [$M^+$] (18), 57 (100). Anal. Calcd. for $C_{19}H_{28}N_2O_7$: C, 57.56; H, 7.12; N, 7.07; found: C, 57.49; H, 7.19; N, 7.10.

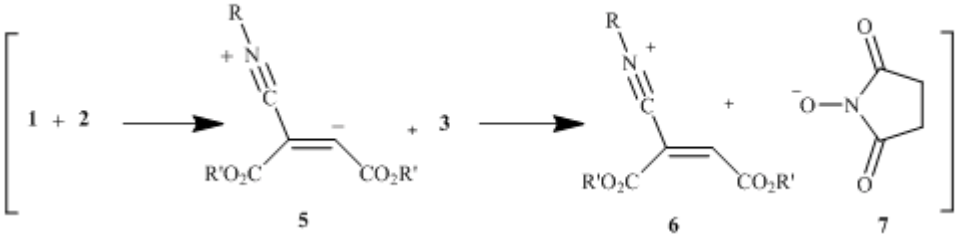
*Diethyl-2- [(2, 5-dioxo-1-pyrilydinyl oxy) (1, 1, 3, 3-tetra methyl butyl imino) methyl]-2- buthene dionate* **(4g)**

Colorless oil yield 0.69 g (82%); IR (KBr): 1668 (C=N), 1732 (C=O) $cm^{-1}$. $^1H$ NMR (300 MHz, $CDCl_3$): δ 1.01 (9H, s, $3CH_3$), 1.31 (3H, t, *J*=7.1, $CH_3$), 1.34 (3H, t, *J*=7.1, $CH_3$), 1.47 (6H, s, $2CH_3$), 1.74 (2H, s, $CH_2$), 2.70 (4H, s, $2CH_2$), 4.28 (4H, q, *J*=6, $2OCH_2$), 6.98 (1H, s, CH). $^{13}C$ NMR (75 MHz, $CDCl_3$): δ 13.9 ($2CH_3$), 28.6 ($2CH_3$), 28.8 ($3CH_3$), 31.3 ($2CH_2$), 31.4 (C), 31.6 ($CH_2$), 51.5 (C-N), 55.7 ($OCH_2$), 61.5 ($OCH_2$), 132.5 (C=), 134.7 (CH=), 137.4 (CO-N), 159.3 ($CO_2$), 160.7 ($CO_2$), 166.6 (CO=N); EI-MS *m/z* (rel.int): 424 [$M^+$] (23), 395 (68), 57 (100). Anal. Calcd. for $C_{21}H_{32}N_2O_7$: C, 59.42; H, 7.60; N, 6.60; found: C, 59.31; H, 7.48; N, 6.69.

## Results and discussions

Reaction of **3**, acetylenic esters **2**, and isocyanides **1** proceeded spontaneously in $CH_2Cl_2$, and was completed within a few hours. The $^1H$ and $^{13}C$ NMR spectra of the crude products clearly indicated the formation of **4**. The structures of compounds **4a**–**4g** were deduced from their IR, $^1H$ NMR and $^{13}C$ NMR spectra. The mass spectra of these compounds displayed molecular ion peaks at appropriate m/z values. The $^1H$ NMR spectrum of **4a** in $CDCl_3$ showed multiplet for the cyclohexyl (δ 1.24-1.65 and δ 3.08 ppm) protons and four singlets for 2 methylenes of succinimide (δ 2.79 ppm), methoxy groups (δ 3.87 and 3.91 ppm) and methine (δ 7.20 ppm) porotons. The $^{13}C$ NMR spectrum of **4a** exhibited thirteen resonances in agreement with the proposed structure. $^1H$ and $^{13}C$ NMR spectra of **4b**–**4g** were similar to those of **4a** except for the side chains, which exhibited characteristic resonances in the appropriate regions of the spectra. Partial assignments of these resonances are given in the experimental section. The structural assignments of compounds **4** made on the basis of their NMR spectra are supported by their IR spectra. Of special interest are the imine and ester absorption bands at about 1640 and 1730 $cm^{-1}$ in all compounds.

It is conceivable that the reaction involves the initial formation of the zwitterionic intermediate **5** between the isocyanide and dialkyl acetylene dicarboxylates (scheme 3). The protonation of **5** by the OH compound **3** leads to **6**. Subsequent attack of the resulting nucleophile **7** on the positively charged ion **6** affords azadiene **4** (scheme 2). The absence of the strong ketenimine absorption bands at




Scheme 2. A plausible mechanism for the formation of compounds **4**

about 2060 $cm^{-1}$ in all compounds excludes the conjugate addition of the anion **7** to the intermediate **6**.

## Conclusions

In conclusion, the three-component reaction of N-Hydroxy succinimide with acetylenic esters in the presence of isocyanides provides a simple one-pot synthesis of stable functionalized azadienes. This procedure has the advantages of high yields and mild reaction conditions.

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