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Synthesis of Highly Functionalized 1-Azadienes and Ketenimines

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Summary. The 1:1 reactive intermediate generated by the addition of alkyl isocyanides to dialkyl acetylenedicarboxylates was trapped by fairly strong NH-acids such as carbazole, indole, or pyrrole to yield highly functionalized 1-azadienes and ketenimines.

Keywords. 1-Azadienes; Ketenimines; Alkyl isocyanides; Acetylenic esters; NH-Acids; *Ugi* reaction.

Introduction

Multicomponent reactions (MCRs), by virtue of their convergence, productivity, facile execution, and generally high yields of products, have attracted much attention from the point of combinatorial chemistry. Of pivotal importance in this area are the isocyanide based MCRs such as the versatile *Ugi* and *Passerini* reactions [1–4]. The addition of nucleophilic carbenes such as isocyanides to dialkyl acetylenedicarboxylates has been investigated in detail by a number of research groups [5–9]. The initially formed 1:1 zwitterionic species undergo further reactions with alkyl isocyanides and dialkyl acetylenedicarboxylates, ultimately leading to a variety of complex heterocyclic systems [10, 11]. The reaction of 1-azadienes with various chiral dienophiles, which leads to substituted pyridines, has been reported [12, 13]. We wish to report here an efficient synthetic route to 1-azadienes and stable ketenimines using alkyl isocyanides **1**, dialkyl acetylenedicarboxylates **2**, and a fairly strong NH-acid, such as carbazole (**3a**), indole (**3b**), or pyrrole (**3c**) (Scheme 1).

Results and Discussion

The reaction of alkyl isocyanides **1** with acetylenic esters **2** in the presence of an NH-acid such as carbazole or indole afforded the isomeric 1-azadienes **4** and

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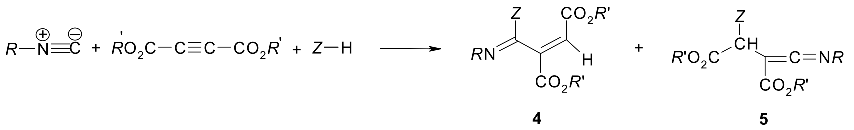


R	R'	Z
1a *t-Bu*	**2a** *Me*	**3a** 1-Carbazolyl
1b *c*-Hexyl	**2b** *t-Bu*	**3b** 1-Indolyl
		3c 1-Pyrrolyl

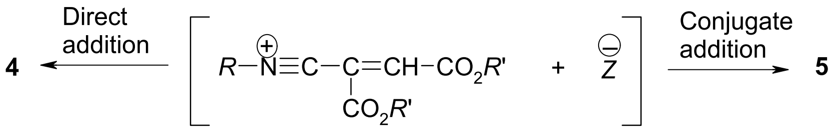
	Z	R	R'	Yield of **4**/%	Yield of **5**/%
4a,5a	1-Carbazolyl	*t-Bu*	*Me*	58	37
4b,5b	1-Carbazolyl	*t-Bu*	*t-Bu*	90	5
4c,5c	1-Carbazolyl	*c*-Hexyl	*Me*	58	37
4d,5d	1-Carbazolyl	*c*-Hexyl	*t-Bu*	58	37
4e,5e	1-Indolyl	*t-Bu*	*Me*	58	37
4f	1-Pyrrolyl	*t-Bu*	*Me*	90	–
4g	1-Pyrrolyl	*t-Bu*	*t-Bu*	90	–
4h	1-Pyrrolyl	*c*-Hexyl	*Me*	85	–

Scheme 1

highly functionalized ketenimines **5** in fairly good yields. However, using pyrrole as the NH-acid, only the 1-azadiene derivative **4** was obtained (Scheme 1).

The structures of **4** and **5** were deduced from their elemental analyses, mass spectrometric data, and their ^{1}H and ^{13}C NMR and IR spectra. The ^{1}H NMR spectrum of **4a** exhibited four sharp lines for *tert*-butyl ($\delta = 1.17$ ppm), metoxy ($\delta = 3.68$ and 3.70 ppm), and vinyl ($\delta = 6.44$ ppm) protons. The carbazole moiety appeared as a multiplet at $\delta = 7.2$–8.1 ppm. The ^{13}C NMR spectrum of **4a** showed signals for *tert*-butyl ($\delta = 29.68$ ppm), methoxy ($\delta = 52.10$ and 52.56 ppm), and olefinic ($\delta = 123.11$ ppm) carbons in agreement with the proposed structure. Partial assignments of these resonances are given in the Experimental. The ^{1}H NMR spectra of **4b**–**4h** are similar to that of **4a**, except for the signals of the cyclohexyl, ester, and heterocyclic moieties. The ^{1}H NMR spectrum of **5a** displayed sharp signals for the *tert*-butyl ($\delta = 1.10$ ppm), methoxy ($\delta = 3.57$ and 3.98 ppm), and methine ($\delta = 5.07$ ppm) protons. The ^{13}C NMR spectrum of **5a** exhibited fifteen sharp lines in agreement with the proposed structure. Partial assignment of these resonances is given in the Experimental. The structural assignments of **5a**–**5e** made on the basis of their NMR spectra were supported by their IR spectra. Of special interest is the strong ketenimine absorption band at about $\bar{\nu} = 2050\,\mathrm{cm}^{-1}$.

On the basis of the well established chemistry of isocyanides [14–16] it is reasonable to assume that **4** and **5** result from initial addition of the alkyl isocyanide to the acetylenic ester and subsequent protonation of the 1:1 adduct by the NH-acid. Then, the positively charged ion can be attacked at two positions by the nitrogen atom of the anion of the NH-acid. Direct addition leads to 1-azadienes **4** and conjugate addition produces ketenimines **5** (Scheme 2).



$$\mathbf{4} \xleftarrow{\text{Direct addition}} \left[R-\overset{\oplus}{N}\equiv C-\underset{\displaystyle CO_2R'}{C}=CH-CO_2R' \;+\; \overset{\ominus}{Z} \right] \xrightarrow{\text{Conjugate addition}} \mathbf{5}$$

Scheme 2

In conclusion, we have found a simple and efficient method for the preparation of highly functionalized ketenimines and 1-azadienes. The present method carries the advantage that not only the reaction is performed under neutral conditions, but also the starting materials and reagents can be mixed without any activation or modification.

Experimental

Melting points were measured on an Electrothermal 9100 apparatus. Elemental analyses (C, H, N) were performed using a Heraeus CHN-O-Rapid analyzer. Their results agreed favorably with the calculated values. IR spectra were measured on a Shimadzu IR-460 spectrometer. ^{1}H and ^{13}C NMR spectra were measured with a Bruker DRX-500 AVANCE instrument with $CDCl_3$ as solvent at 500.1 and 125.7 MHz. Mass spectra were recorded on a Finnigan-Matt 8430 mass spectrometer operating at an ionization potential of 70 eV. Dialkyl acetylenedicarboxylates, alkyl isocyanides, carbazole, pyrrole, and indole were obtained from Fluka (Buchs, Switzerland) and were used without further purification.

General Procedure (*examplified by **4a** and **5a***)

To a magnetically stirred solution of 0.33 g of carbazole (2 mmol) and 0.28 g of dimethyl acetylenedicarboxylate (2 mmol) in 10 cm^3 of CH_2Cl_2 0.45 g of *tert*-butyl isocyanide (2 mmol) were added dropwise at -10°C over 10 min. The reaction mixture was then allowed to warm up to room temperature and stand for 24 h. The solvent was removed under reduced pressure and the mixture of products was obtained as a yellow oil. The two isomeric products were separated by silica gel column chromatography (Merck 230–400 mesh) using *n*-hexane:ethyl acetate as eluent. The first compound was eluted using a 9:1 mixture and identified as **4a**, subsequent elution with a 7:1 mixture gave **5a**.

Dimethyl 2-(tert-butylimino(carbazol-9-yl)methyl)but-2-enedioate (**4a**, $C_{23}H_{24}N_2O_4$)

White crystals (from diethyl ether), yield 0.45 g (58%), mp 97–98°C; IR (KBr): $\bar{\nu} = 1715$ and 1739 (C=O) cm^{-1}; ^{1}H NMR: $\delta = 1.17$ (s, CMe_3), 3.68 and 3.70 (2s, $2OCH_3$), 6.44 (s, CH), 7.27–8.12 (m, 8CH) ppm; ^{13}C NMR: $\delta = 29.68$ (CMe_3), 52.10 and 52.56 ($2OCH_3$), 59.07 (CMe_3), 110.47, 120.23, 120.68, and 126.69 (8CH), 122.39 and 140.11 (4C), 123.11 (CH vinyl), 142.73 (*C*=CH), 147.50 (C=N), 164.73 and 166.16 (2C=O, ester) ppm; MS: m/z (%) = 392 (M$^+$, 4), 267 (4), 246 (4), 216 (20), 170 (76), 167 (100), 166 (80).

Dimethyl 2-(tert-butyliminomethylene)-3-(carbazol-9-yl)succinate (**5a**, $C_{23}H_{24}N_2O_4$)

Yellow oil, yield 0.29 g (37%), IR (KBr): $\bar{\nu} = 2035$ (C=C=N), 1741 and 1680 (C=O) cm^{-1}; ^{1}H NMR: $\delta = 1.10$ (s, CMe_3), 3.57 and 3.98 (2s, $2OCH_3$), 5.07 (s, CH), 7.27–8.12 (m, 8CH) ppm; ^{13}C NMR: $\delta = 29.71$ (CMe_3), 51.82 and 53.02 ($2OCH_3$), 58.60 (CH), 62.11 (*C*=C=N), 62.18 (CMe_3), 109.96, 119.71, 120.29, and 125.90 (8CH), 123.35 and 139.75 (4C), 165.01 (C=*C*=N), 169.30, and 170.01 (2C=O, ester) ppm; MS: m/z (%) = 392 (M$^+$, 4), 267 (4), 246 (4), 216 (20), 170 (76), 167 (100), 166 (80).

Di-tert-butyl 2-(tert-butylimino(carbazol-9-yl)methyl)but-2-enedioate (**4b**, $C_{29}H_{36}N_2O_4$)

White crystals (from diethyl ether), yield 0.85 g (90%), mp 240–241°C; IR (KBr): $\bar{\nu} = 1709$ and 1676 (C=O) cm^{-1}; ^{1}H NMR: $\delta = 1.09$, 1.30 and 1.41 (3s, $3CMe_3$), 6.22 (s, CH), 7.21–8.08 (m, 8CH) ppm; ^{13}C NMR: $\delta = 27.76$, 28.37 and 29.64 ($3CMe_3$), 55.01 ($NCMe_3$), 80.30 and 82.58 ($2OCMe_3$), 110.58, 119.41, 120.31, and 125.81 (8CH), 123.35 and 139.51 (4C), 125.53 (CH vinyl), 140.02 (*C*=CH), 151.01 (C=N), 167.67 and 168.81 (2C=O, ester) ppm; MS: m/z (%) = 475 ($M^+ - 1$, 2), 168 (20), 167 (100), 140 (30), 139 (42), 61 (56), 54 (52).

Di-tert-butyl 2-(tert-butyliminomethylene)-3-(carbazol-9-yl)succinate (**5b**, $C_{29}H_{36}N_2O_4$)

Yellow oil, yield 0.04 g (5%), IR (KBr): $\bar{\nu} = 2040$ (C=C=N), 1720 and 1678 (C=O) cm^{-1}; ^{1}H NMR: $\delta = 1.01$, 1.25, and 1.34 (3s, 3CMe$_3$), 5.21 (s, CH), 7.21–8.08 (m, 8CH) ppm; ^{13}C NMR: $\delta = 27.61$, 28.21, and 29.52 (3C*Me*$_3$); 54.88 (CH), 61.44 (*C*=C=N), 64.45 (N*C*Me$_3$), 74.02 and 85.02 (2O*C*Me$_3$), 110.38, 119.34, 119.97, and 125.53 (8CH), 123.03 and 139.21 (4C), 165.27 (C=*C*=N), 168.01, and 168.66 (2C=O, ester) ppm; MS: m/z (%) = 475 ($M^+ - 1$, 2), 168 (20), 167 (100), 140 (30), 139 (42), 61 (56), 54 (52).

Dimethyl 2-(carbazol-9-yl(cyclohexylimino)methyl)but-2-enedioate (**4c**, $C_{25}H_{26}N_2O_4$)

White crystals (from diethyl ether), yield 0.48 g (58%), mp 142–144°C; IR (KBr): $\bar{\nu} = 1727$ and 1714 (C=O) cm^{-1}; ^{1}H NMR: $\delta = 1.23$–1.87 (m, 5CH$_2$), 3.65 (m, CHN), 3.66 and 3.68 (2s, 2OCH$_3$), 6.44 (s, CH), 7.23–8.12 (m, 8CH) ppm; ^{13}C NMR: $\delta = 23.43$, 25.72, 32.76, and 32.88 (5CH$_2$), 52.13 and 52.36 (2O*CH*$_3$), 60.87 (CHN), 109.96, 120.69, 120.90, and 126.75 (8CH), 123.11 and 139.79 (4C), 123.64 (CH vinyl), 145.27 (*C*=CH), 145.81 (C=N), 164.64 and 165.93 (2C=O, ester) ppm; MS: m/z (%) = 417 ($M^+ - 1$, 2), 238 (42), 220 (100), 167 (100), 166 (36), 113 (20), 52 (14).

Dimethyl 2-(cyclohexyliminomethylene)-3-(carbazol-9-yl)succinate (**5c**, $C_{25}H_{26}N_2O_4$)

Yellow oil, yield 0.31 g (37%), IR (KBr): $\bar{\nu} = 2045$ (C=C=N), 1731 and 1683 (C=O) cm^{-1}; ^{1}H NMR: $\delta = 1.22$–1.67 (m, 5CH$_2$), 3.34 (m, CHN), 3.57 and 3.97 (2s, 2OCH$_3$), 5.32 (s, CH), 7.20–8.10 (m, 8CH) ppm; ^{13}C NMR: $\delta = 23.88$, 25.44, 31.93, and 33.22 (5CH$_2$), 51.74 and 52.63 (2OCH$_3$), 54.21 (CH), 60.64 (*C*=C=N), 60.73 (CHN), 109.96, 119.67, 120.11, and 125.84 (8CH), 123.11 and 139.59 (4C), 165.35 (C=*C*=N), 169.34 and 169.96 (2C=O, ester) ppm; MS: m/z (%) = 417 ($M^+ - 1$, 2), 238 (42), 220 (100), 167 (100), 166 (36), 113 (20), 52 (14).

Di-tert-butyl 2-(carbazol-9-yl(cyclohexylimino)methyl)but-2-enedioate (**4d**, $C_{31}H_{38}N_2O_4$)

White crystals (from diethyl ether), yield 0.29 g (58%), mp 130–132°C; IR (KBr): $\bar{\nu} = 1708$ and 1687 (C=O) cm^{-1}; ^{1}H NMR: $\delta = 1.12$–1.66 (m, 5CH$_2$), 1.30 (s, 2CMe$_3$), 3.60 (m, CHN), 6.25 (s, CH), 7.14–8.06 (m, 8CH); ^{13}C NMR: $\delta = 23.76$, 25.23, 27.94, 30.87, and 32.78 (5CH$_2$), 27.79 and 28.38 (2C*Me*$_3$), 60.74 (CHN), 80.84 and 82.63 (2O*C*Me$_3$), 110.41, 119.36, 120.63, and 125.51 (8CH), 123.49 and 139.75 (4C), 124.99 (CH vinyl), 139.43 (*C*=CH), 146.43 (C=N), 167.77 and 168.71 (2C=O, ester); MS: m/z (%) = 502 (M^+, 2), 341 (8), 280 (12), 217 (18), 216 (36), 167 (38), 166 (100), 142 (30), 82 (58), 54 (46).

Di-tert-butyl 2-(cyclohexyliminomethylene)-3-(carbazol-9-yl)succinate (**5d**, $C_{31}H_{38}N_2O_4$)

Yellow oil, yield 0.18 g (37%), IR (KBr): $\bar{\nu} = 2040$ (C=C=N), 1719 and 1642 (C=O) cm^{-1}; ^{1}H NMR: $\delta = 1.22$–1.66 (m, 5CH$_2$), 1.40 (s, 2CMe$_3$), 3.41 (m, CHN), 5.44 (s, CH), 7.14–8.06 (m, 8CH) pp; ^{13}C NMR: $\delta = 23.82$, 25.31, 28.10, 31.61, and 32.92 (5CH$_2$), 27.56 and 28.09 (2C*Me*$_3$), 55.30 (CH), 60.06 (*C*=C=N), 62.79 (CHN), 75.94 and 83.32 (2O*C*Me$_3$), 110.12, 119.34, 120.49, and 126.15 (8CH), 123.01 and 139.42 (4C), 164.34 (C=*C*=N), 168.45 and 168.75 (2C=O, ester) ppm; MS: m/z (%) = 502 (M^+, 2), 341 (8), 280 (12), 217 (18), 216 (36), 167 (38), 166 (100), 142 (30), 82 (58), 54 (46).

Dimethyl 2-(tert-butylimino(indol-1-yl)methyl)but-2-enedioate (**4e**, $C_{19}H_{22}N_2O_4$)

White crystals (from diethyl ether), yield 0.39 g (58%), mp 91–92°C; IR (KBr): $\bar{\nu} = 1717$ and 1657 (C=O) cm^{-1}; ^{1}H NMR: $\delta = 1.36$ (s, CMe$_3$), 3.60 and 3.79 (2s, 2OCH$_3$), 6.51–8.63 (m, 6CH$_{\mathrm{arom}}$), 7.21 (s, CH vinyl) ppm; ^{13}C NMR: $\delta = 30.95$ (C*Me*$_3$), 52.53 and 53.39 (2OCH$_3$), 55.41 (*C*Me$_3$), 105.07, 116.34, 120.44, 121.83, 123.42, and 125.34 (6CH), 130.41 and 135.86 (2C), 132.25 (CH vinyl), 140.22 (*C*=CH), 142.14 (C=N), 163.86 and 164.48 (2C=O, ester) ppm; MS: m/z (%) = 343 (M$^+$ + 1, 2), 302 (8), 226 (28), 213 (26), 170 (90), 169 (8), 138 (26), 118 (32), 117 (100), 54 (100).

Dimethyl 2-(tert-butyliminomethylene)-3-(indol-1-yl)succinate (**5e**, $C_{19}H_{22}N_2O_4$)

Yellow oil, yield 0.25 g (37%), IR (KBr): $\bar{\nu} = 2040$ (C=C=N), 1729 and 1687 (C=O) cm^{-1}; ^{1}H NMR: $\delta = 1.32$ (s, CMe$_3$), 3.69 and 3.73 (2s, 2OCH$_3$), 6.05 (s, CH), 6.52–7.59 (m, 6CH) ppm; ^{13}C NMR: $\delta = 30.06$ (C*Me*$_3$), 51.89 and 52.86 (2OCH$_3$), 55.33 (CH), 62.51 (*C*=C=N), 63.19 (*C*Me$_3$), 102.73, 109.62, 119.97, 120.99, 121.98, and 126.10 (6CH), 128.79 and 136.05 (2C), 164.85 (C=*C*=N), 169.45 and 169.45 (2C=O, ester) ppm; MS: m/z (%) = 343 (M$^+$ + 1, 2), 302 (8), 226 (28), 213 (26), 170 (90), 169 (8), 138 (26), 118 (32), 117 (100), 54 (100).

Dimethyl 2-(tert-butylimino(pyrrol-1-yl)methyl)but-2-enedioate (**4f**, $C_{15}H_{20}N_2O_4$)

White crystals (from diethyl ether), yield 0.26 g (90%), mp 95–97°C; IR (KBr): $\bar{\nu} = 1661$ and 1617 (C=O) cm^{-1}; ^{1}H NMR: $\delta = 1.18$ (s, CMe$_3$), 3.61 and 3.75 (2s, 2OCH$_3$), 7.11 (s, CH), 6.11–7.07 (m, 4CH) ppm; ^{13}C NMR: $\delta = 30.59$ (C*Me*$_3$), 52.36 and 53.28 (2OCH$_3$), 58.34 (*C*Me$_3$), 110.26 and 118.27 (4CH), 132.44 (CH vinyl), 140.03 (*C*=CH), 140.36 (C=N), 163.63 and 164.20 (2C=O, ester) ppm; MS: m/z (%) = 292 (M$^+$, 2), 216 (6), 80 (4), 54 (40), 39 (38), 35 (100).

Di-tert-butyl 2-(tert-butylimino(pyrrol-1-yl)methyl)but-2-enedioate (**4g**, $C_{21}H_{32}N_2O_4$)

White crystals (from diethyl ether), yield 0.67 g (90%), mp 138–140°C; IR (KBr): $\bar{\nu} = 1661$ and 1617 (C=O) cm^{-1}; ^{1}H NMR: $\delta = 1.26$, 1.27, and 1.40 (3s, 3CMe$_3$), 6.93 (s, CH), 6.13–7.12 (m, 4CH) ppm; ^{13}C NMR: $\delta = 27.57$, 27.71, and 30.87 (3C*Me*$_3$), 54.76 (N*C*Me$_3$), 82.94 and 83.31 (2O*C*Me$_3$), 109.94 and 118.32 (4CH), 133.60 (CH vinyl), 139.95 (*C*=CH), 140.05 (C=N), 162.84 and 162.92 (2C=O, ester) ppm; MS: m/z (%) = 367 (M$^+$, 2), 311 (6), 198 (22), 143 (40), 142 (100), 54 (100).

Dimethyl 2-(cyclohexylimino(pyrrol-1-yl)methyl)but-2-enedioate (**4h**, $C_{17}H_{22}N_2O_4$)

White crystals (from diethyl ether), yield 0.27 g (85%), mp 86–88°C; IR (KBr): $\bar{\nu} = 1720$ and 1657 (C=O) cm^{-1}; ^{1}H NMR: $\delta = 1.25$–1.85 (m, 5CH$_2$), 3.20 (m, CHN), 3.67 and 3.81 (2s, 2OCH$_3$), 7.25 (s, CH), 6.22–7.21 (m, 4CH) ppm; ^{13}C NMR: $\delta = 23.98$, 25.45, 33.10, and 33.34 (5CH$_2$), 52.12 and 53.05 (2OCH$_3$), 59.70 (CHN), 110.43 and 118.21 (4CH), 132.46 (CH vinyl), 136.86 (*C*=CH), 143.66 (C=N), 163.25 and 163.41 (2C=O, ester) ppm; MS: m/z (%) = 319 (M$^+$ + 1, 2), 253 (8), 170 (100), 169 (8), 138 (32), 82 (36), 52 (46).

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