A SIMPLE SYNTHESIS OF HIGHLY FUNCTIONALIZED KETENIMINES DERIVED FROM *N*-ARYL-2,2,2-TRICHLOROACETAMIDES, ALKYL ISOCYANIDES AND DIALKYL ACETYLENEDICARBOXYLATES

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The 1:1 reactive intermediates produced in the reaction between alkyl isocyanides and dialkyl acetylenedicarboxylates were trapped with *N*-aryl-2,2,2-trichloroacetamides. When the aryl group was 1-naphthyl, two products were obtained in nearly 2:1 ratio.
Keywords: Ketenimines; Alkyl isocyanides; Dialkyl acetylenedicarboxylates; NH-acids.

In recent years, synthetic applications of multifunctional heteroallenes have been widely investigated[1,2]. In spite of extensive developments in the chemistry of modified ketenes and isocyanates[3], little attention has been paid to the uses of ketenimines[4]. These compounds have attracted interest as dehydrating agents in peptide synthesis, as complexing agents for transition metal ions, and as co-reagents for DMSO oxidations[5]. In general, unsubstituted ketenimines and those with small unbranched alkyl substituents are elusive substances. Preparation of ketenimines by treatment of dialkyl acetylenedicarboxylates with isocyanides in the presence of C-acid[6,7] or O-acid[8] has been reported. Ketenimines play a role as discrete but transient intermediates in many interconversions, especially in elimination-addition processes and in the formation of heterocyclic systems[9–12]. Spectroscopic properties of ketenimines have been intensively investigated[13,14]. We wish to report a simple one-pot preparation of stable ketenimines using alkyl isocyanides **1**, dialkyl acetylenedicarboxylates **2**, and strong NH-acids, such as *N*-aryl-2,2,2-trichloroacetamides **3**, i.e. 2,2,2-trichloro-*N*-phenylacetamide (**3a**), *N*-(4-bromophenyl)-2,2,2-trichloroacetamide (**3b**), or 2,2,2-trichloro-*N*-(1-naphthyl)acetamide (**3c**). This condensation reaction produces highly functionalized ketenimines **4** in fairly good yields (Schemes 1 and 3).

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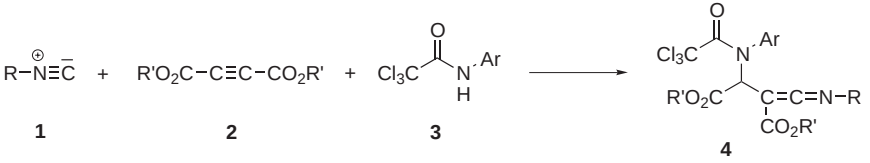
RESULTS AND DISCUSSION

The reaction of ester **2** with amide **3** in the presence of isocyanide **1** proceeded at room temperature in dichloromethane, and was complete within a few hours. ^{1}H and ^{13}C NMR spectra of the crude product clearly indicated the formation of **4** (Scheme 1).



1	R
a	*t*-Bu
b	cyclohexyl

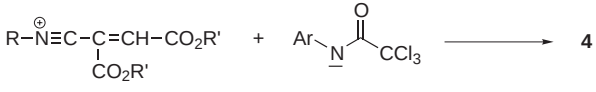
2	R
a	Me
b	*t*-Bu

3	Ar
a	Ph
b	4-BrPh

4	R	R'	Ar
a	*t*-Bu	Me	Ph
b	*t*-Bu	*t*-Bu	Ph
c	cyclohexyl	Me	Ph
d	*t*-Bu	Me	4-BrPh

SCHEME 1

On the basis of the well established chemistry of isocyanides[15,16], it is reasonable to assume that compound **4** results from initial addition of an alkyl isocyanide to the acetylenic ester and subsequent protonation of the 1:1 adduct by the NH-acid. Then, the positively charged ion **5** is attacked by the nitrogen atom of the bidentate anion of the NH-acid to form ketenimine **4** (Scheme 2).



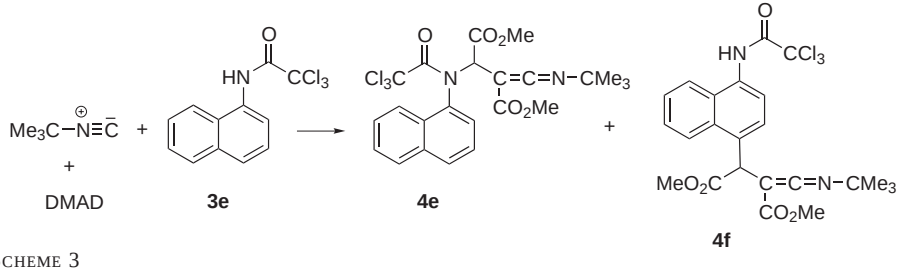
SCHEME 2

The benzene region of the ^{13}C NMR spectra of **4a**–**4d** in $CDCl_3$ at ambient temperature (30 °C) exhibits four fairly broad singlets for the *ortho* and *meta* aromatic CH groups. Decreasing the temperature to 10 °C leads to sharper signals. Increasing the temperature to about 42 °C results in coalescence of CH resonances. At 55 °C, the *ortho* and *meta* carbon atoms appear as two relatively sharp single resonances. This dynamic NMR effect is attributed to slow rotation around the phenyl–N bond in **4a**–**4d**. Hindered rotation around the N–CO bond in **4a**–**4d** is ruled out, because only one signal is observed for the *para* (or *ipso*) carbon atom of the phenyl ring at various temperatures.

Although an extensive line-shape analysis in relation to the dynamic ^{13}C NMR effect observed for **4a**–**4d** was not undertaken, the variable tempera-

ture spectra of **4b** allowed to calculate the Gibbs energy barrier (if not the enthalpy and entropy of activation) for the dynamic NMR process. From coalescence of the *ortho* carbons resonances and using the expression $k = \pi\Delta\nu/\sqrt{2}$, we calculate that the first-order rate constant (k) for dynamic NMR effect in **4b** is 77 s^{-1} at 42 °C. Application of the absolute rate theory with a transmission coefficient of 1 gives a Gibbs energy of activation ($\Delta G^{\#}$) of 66.7 ± 2 kJ mol^{-1}, where all known sources of errors are estimated and included[17]. The experimental data available are not suitable for obtaining meaningful values of $\Delta H^{\#}$ and $\Delta S^{\#}$, even though the errors in $\Delta G^{\#}$ are not large[18].

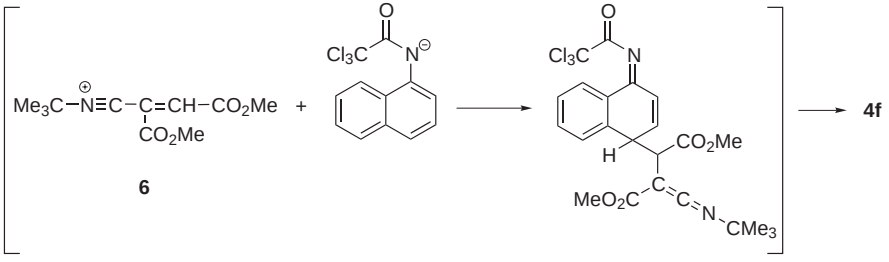
The reaction of *tert*-butyl isocyanide with dimethyl acetylenedicarboxylate (DMAD) in the presence of 2,2,2-trichloro-*N*-(1-naphthyl)acetamide afforded the isomeric dimethyl 2-[(*tert*-butylimino)methylidene]-3-[2,2,2-trichloro-*N*-(1-naphthyl)acetamido]succinate (**4e**) and dimethyl 2-[(*tert*-butylimino)methylidene]-3-[4-(2,2,2-trichloroacetamido)-1-naphthyl]succinate (**4f**) in nearly 4:1 ratio and good yields (Scheme 3). The structures of **4e** and **4f** were deduced from their ^{1}H and ^{13}C NMR spectra. The ^{1}H NMR spectrum of **4e** displayed six sharp signals for the *tert*-butyl (δ 1.38 and 1.44) and methoxy (δ 3.51, 3.53, 3.90 and 3.91) protons, in agreement with the presence of two rotamers (major and minor) in nearly 60:40 ratio. The protons of the naphthyl residue appear as a fairly complex multiplet in aromatic region. Due to the restricted rotation around the amide N–CO bond[19] in **4e**, two rotational isomers are expected. In fact, the ^{13}C NMR spectrum of **4e** exhibits the major (M) and minor (m) rotamers of **4e**, which display two sharp lines for the two *tert*-butyl groups (δ 30.03 and 30.01) together with four signals for the methoxy groups (δ 51.67, 52.95, 52.67 and 52.97).



SCHEME 3

The ^{1}H NMR spectrum of **4f** displays four sharp signals for the *tert*-butyl (δ 1.03), methoxy (δ 3.73 and 3.74), and methine (δ 5.40) protons. In the aromatic region of the spectrum, there are two doublets (δ 7.86 and 8.13, $^3J_{HH}$ = 8.5 Hz) in agreement with the two adjacent methine groups in the

naphthyl residue. The NH group exhibits a broad line at (δ 8.77). The ^{13}C NMR spectrum of **4f** displays a sharp signal for the *tert*-butyl group (δ 29.90). Partial assignment of the ^{13}C signals of **4e** and **4f** is given in Experimental. Compound **4e** is formed by a mechanism similar to that shown in Scheme 2. A mechanism for formation of **4f** is proposed in Scheme 4.



SCHEME 4

The structure assignments of compounds **4a**–**4f** made on the basis of their NMR spectra were supported by their IR spectra. Of special interest are the strong ketenimine absorption bands at about 2050 cm^{-1} in all compounds.

In conclusion, the reaction of alkyl isocyanides with electron-deficient acetylenic esters in the presence of strong NH-acids provides a simple one-pot entry into the synthesis of polyfunctionalized ketenimines of potential synthetic interest. The present procedure brings the advantage that not only is the reaction performed under neutral conditions, but also the substances can be reacted without any activation or modification.

EXPERIMENTAL

Melting points were measured on an Electrothermal 9100 apparatus. Elemental analyses for C, H and N were performed using a Heraeus CHN-O-Rapid analyzer. These results agreed well with the calculated values. IR spectra (ν, cm^{-1}) were measured on a Shimadzu IR-460 spectrometer. ^1H and ^{13}C NMR spectra (δ, ppm; *J*, Hz) were measured with a Bruker DRX-500 AVANCE instrument with $CDCl_3$ as solvent at 500.1 and 125.7 MHz, respectively. Mass spectra were recorded on a Finnigan–Matt 8430 mass spectrometer operating at an ionization potential of 70 eV. Dialkyl acetylenedicarboxylates and alkyl isocyanides were obtained from Fluka (Buchs, Switzerland) and were used without further purification. *N*-Aryl-2,2,2-trichloroacetamides were prepared by a known method[20].

General Procedure for Preparation of **4**

A magnetically stirred solution of 2,2,2-trichloro-*N*-phenylacetamide (0.48 g, 2 mmol) and DMAD (0.28 g, 2 mmol) in CH_2Cl_2 (6 ml) at –10 °C was treated dropwise over 10 min with

tert-butyl isocyanide (0.45 g) in CH_2Cl_2 (2 ml, 2 mmol). The reaction mixture was then allowed to warm to room temperature and to stand for 48 h. Evaporation of the solvent under reduced pressure gave the desired product, which was purified by silica gel column chromatography (Merck 230–400 mesh) using hexane–EtOAc as eluent. Compounds **4e** and **4f** were separated using the same column with hexane–EtOAc as eluent.

Dimethyl2-[(tert-butylimino)methylidene]-3-(2,2,2-trichloro-N-phenylacetamido)succinate (**4a**). Brown oil, yield 0.91 g (98%). IR (KBr): 2050 (C=C=N); 1738 and 1678 (C=O). ^{1}H NMR ($CDCl_3$, Me_4Si): 1.28 (9 H, s, CMe_3); 3.62 and 3.72 (6 H, 2 s, 2 OCH_3); 5.33 (1 H, s, CH); 7.26–7.51 (5 H, m, C_6H_5). ^{13}C NMR ($CDCl_3$, Me_4Si): 29.96 (C**Me**$_3$); 51.66 and 52.75 (2 OCH_3); 59.54 (CH); 62.09 (**C**=C=N); 64.82 (N-**C**Me$_3$); 92.66 (CCl_3); 128.35 and 128.55 (2 C_{ortho}); 129.08 (C_{para}); 130.73 and 130.88 (2 C_{meta}); 139.97 (C_{ipso}); 160.42 and 161.43 (C=**C**=N and C=O amide); 168.64 and 169.70 (2 C=O ester). MS, *m/z* (%): 463 (M^+, 4), 237 (18), 171 (46), 120 (100), 54 (64). For $C_{19}H_{21}Cl_3N_2O_5$ (463.5) calculated: 49.23% C, 4.53% H, 6.04% N; found: 49.2% C, 4.5% H, 6.0% N.

Di-tert-butyl 2-[(tert-butylimino)methylidene]-3-(2,2,2-trichloro-N-phenylacetamido)succinate (**4b**): Yellow crystals, m.p. 86–87 °C, yield 0.52 g (95%). IR (KBr): 2040 (C=C=N); 1728 and 1676 (C=O). ^{1}H NMR ($CDCl_3$, Me_4Si): 1.30, 1.42 and 1.56 (27 H, 3 s, 3 CMe_3); 5.31 (1 H, s, CH); 7.33–7.34 (5 H, m, C_6H_5). ^{13}C NMR ($CDCl_3$, Me_4Si): 28.01, 28.30, and 30.00 (3 C**Me**$_3$); 61.56 (CH); 65.21 (**C**=C=N); 61.94 (N-**C**Me$_3$); 80.09 and 82.45 (2 O-**C**Me$_3$); 92.93 (CCl_3); 128.16 and 128.43 (2 C_{ortho}); 129.31 (C_{para}); 131.12 and 131.39 (2 C_{meta}); 140.05 (C_{ipso}); 160.09 and 165.00 (C=**C**=N and C=O amide); 167.11 and 168.70 (2 C=O ester). MS, *m/z* (%): 547 (M^+, 2), 419 (30), 254 (38), 198 (66), 142 (52), 54 (100). For $C_{25}H_{33}Cl_3N_2O_5$ (547.5) calculated: 54.83% C, 6.03% H, 5.11% N; found: 54.8% C, 6.0% H, 5.1% N.

Dimethyl 2-[(cyclohexylimino)methylidene]-3-(2,2,2-trichloro-N-phenylacetamido)succinate (**4c**): Brown oil, yield 0.48 g (94%). IR (KBr): 2050 (C=C=N); 1737 and 1675 (C=O). ^{1}H NMR ($CDCl_3$, Me_4Si): 1.27–1.91 (10 H, m, 5 CH_2); 3.68 and 3.82 (6 H, 2 s, 2 OCH_3); 3.80 (1 H, m, CHN); 5.30 (1 H, s, CH); 7.14–7.60 (5 H, m, C_6H_5). ^{13}C NMR ($CDCl_3$, Me_4Si): 23.90, 25.10, 25.14, 32.95, and 33.01 (5 CH_2); 51.72 and 52.90 (2 OCH_3); 58.34 (CH); 60.47 (**C**=C=N); 65.07 (CHN); 92.72 (CCl_3); 128.36 and 128.55 (2 C_{ortho}); 129.10 (C_{para}); 130.91 and 130.99 (2 C_{meta}); 140.16 (C_{ipso}); 160.60 and 161.40 (C=**C**=N and C=O amide); 168.78 and 169.80 (C=O ester). MS, *m/z* (%): 489 (M^+, 5), 239 (46), 237 (70), 171 (22), 120 (100), 98 (16), 92 (60), 76 (72), 63 (20). For $C_{21}H_{23}Cl_3N_2O_5$ (489.5) calculated: 51.52% C, 4.72% H, 5.72% N; found: 51.5% C, 4.7% H, 5.7% N.

Dimethyl 2-[N-(4-bromophenyl)-2,2,2-trichloroacetamido]-3-[(tert-butylimino)methylidene]-succinate (**4d**): White powder, m.p. 97–98 °C, yield 0.51 g (98%). IR (KBr): 2050 (C=C=N); 1737 and 1681 (C=O). ^{1}H NMR ($CDCl_3$, Me_4Si): 1.38 (9 H, s, CMe_3); 3.69 and 3.79 (6 H, 2 s, 2 OCH_3); 5.39 (1 H, s, CH); 7.37 (2 H, br, 2 CH_{ortho}); 7.49 (2 H, d, $^3J_{HH}$ = 7.8, 2 CH_{meta}). ^{13}C NMR ($CDCl_3$, Me_4Si): 30.01 (C**Me**$_3$); 51.79 and 52.89 (2 OCH_3); 59.21 (CH); 62.25 (**C**=C=N); 64.79 (**C**Me$_3$); 92.49 (CCl_3); 123.29 (C-Br); 131.55 and 131.86 (2 C_{ortho}); 132.77 and 132.98 (2 C_{meta}); 139.04 (C-N); 160.37 and 160.56 (C=**C**=N and C=O amide); 168.67 and 169.80 (C=O ester). MS, *m/z* (%): 543 (M^+, 2), 227 (52), 198 (18), 170 (44), 54 (100). For $C_{19}H_{20}N_2O_5Cl_3Br$ (543.5) calculated: 41.9% C, 3.67% H, 5.15% N; found: 42.0% C, 3.7% H, 5.1% N.

Dimethyl 2-[(tert-butylimino)methylidene]-3-[(2,2,2-trichloro-N-(1-naphthyl)acetamido]succinate (**4e**): Brown powder, m.p. 111–112 °C, yield 0.31 g (60%). MS, *m/z* (%): 513 (M^+, 2), 169 (34), 143 (12), 54 (100). Major rotamer: IR (KBr): 2050 (C=C=N); 1731 and 1676 (C=O). ^{1}H NMR ($CDCl_3$, Me_4Si): 1.38 (9 H, 3 s, CMe_3); 3.51 and 3.90 (6 H, 2 s, 2 OCH_3); 5.36 (1 H, s, CH);

7.38–8.52 (7 H, m, $C_{10}H_7$). ^{13}C NMR ($CDCl_3$, Me_4Si): 30.03 (C**Me**$_3$); 51.67 and 52.95 (2 OCH_3); 59.53 (CH); 60.71 (**C**=C=N); 66.14 (**C**Me$_3$); 92.15 (CCl_3); 124.03, 124.52, 126.48, 127.19, 128.30, 129.30 and 130.25 (7 CH); 131.28, 134.22 and 135.44 (3 C); 162.04 and 168.68 (C=**C**=N and C=O amide); 168.81 and 169.71 (2 C=O ester) Minor rotamer: IR (KBr): 2050 (C=C=N); 1738 and 1678 (C=O). ^1H NMR ($CDCl_3$, Me_4Si): 1.44 (9 H, s, CMe_3); 3.53 and 3.91 (6 H, 2 s, 2 OCH_3); 5.18 (1 H, s, CH); 7.38–8.46 (7 H, m, $C_{10}H_7$). ^{13}C NMR ($CDCl_3$, Me_4Si): 30.01 (C**Me**$_3$); 52.67 and 52.97 (2 OCH_3); 62.30 (CH); 62.45 (**C**=C=N); 66.66 (**C**Me$_3$); 92.60 (CCl_3); 124.61, 124.80, 126.41, 126.66, 128.11, 128.73 and 129.95 (7 CH); 131.44, 134.13 and 135.83 (3 C); 161.60 and 164.08 (C=**C**=N and C=O amide); 169.82 and 170.07 (2 C=O ester). MS, *m/z* (%): 513 (M^+, 2), 169 (34), 143 (12), 54 (100). For $C_{23}H_{23}Cl_3N_2O_5$ (513.5) calculated: 53.79% C, 4.47% H, 5.45% N; found: 53.8% C, 4.5% H, 5.4% N.

Dimethyl 2-[(tert-butylimino)methylidene]-3-[4-(2,2,2-trichloroacetamido)-1-naphthyl]succinate (**4f**): Brown powder, m.p. 88–90 °C, yield 0.17 g (35%). IR (KBr): 2035 (C=C=N); 1716 and 1684 (C=O). ^1H NMR ($CDCl_3$, Me_4Si): 1.03 (9 H, s, CMe_3); 3.73 and 3.74 (6 H, 2 s, 2 OCH_3); 5.40 (1 H, s, CH); 7.41 (1 H, d, $^3J_{HH}$ = 7.8, CH); 7.60 (2 H, dd, $^3J_{HH}$ = 7.5 and 3.8, 2 CH); 7.79 (1 H, d, $^3J_{HH}$ = 7.8, CH); 7.86 (1 H, d, $^3J_{HH}$ = 7.5, CH); 8.13 (1 H, d, $^3J_{HH}$ = 8.4, CH); 8.77 (1 H, s, NH). ^{13}C NMR ($CDCl_3$, Me_4Si): 29.90 (C**Me**$_3$); 51.78 and 52.63 (2 OCH_3); 44.12 (CH); 61.81 (**C**=C=N); 66.33 (**C**Me$_3$); 93.07 (CCl_3); 120.78, 120.96, 124.62, 124.70, 127.14 and 127.31 (6 CH); 128.01, 130.57, 131.91 and 133.33 (4 C); 160.24 and 168.58 (C=**C**=N and C=O amide); 170.05 and 173.02 (2 C=O ester). MS, *m/z* (%): 512.5 (2), 166 (34), 56 (72), 54 (100). For $C_{23}H_{23}Cl_3N_2O_5$ (513.5) calculated: 53.79% C, 4.47% H, 5.45% N; found: 53.9% C, 4.3% H, 5.5% N.

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