Reactions of Ketenimines with Arene-sulfanyl and -selanyl Chlorides: a General Route to Secondary Amide Derivatives and a New Synthesis of *C*-Sulfanyl- and *C*-Selanyl-ketenimines[1]

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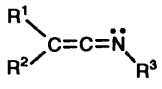
Ketenimines **1**, react with arene-sulfanyl and -selanyl chlorides to give the imidoyl chlorides **3** that either yield the substituted amides **4** upon solvolysis in aqueous acetone, or the *C*-sulfanyl- and *C*-selanyl-ketenimines **5** by dehydrochlorination with triethylamine.

Ketenimines **1**, have attracted considerable interest as substrates for the synthesis of heterocycles, largely through processes involving cycloaddition reactions.[2] Other aspects of ketenimine chemistry have received little attention, particularly towards the development of new synthetic methods. Recent studies[3] on the rearrangements of transient *N*-allylic ketenimines to the isomeric nitriles, have identified potential new applications of ketenimine chemistry in synthesis. Although ketenimines are known[4,5] to be reactive towards electrophilic species at the β-carbon of the heterocumulene linkage (see resonance structure **2**), this feature of their reactivity has not been extensively studied.



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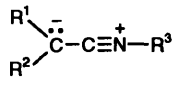
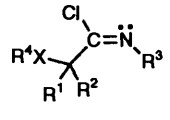


2

a $R^1 = R^3 = Ph$, $R^2 = H$
b $R^1 = Ph$, $R^2 = Et$, $R^3 = Bu^s$
c $R^1 = Ph$, $R^2 = H$, $R^3 = Pr^i$
d $R^1 = Ph$, $R^2 = H$, $R^3 = Bu^s$
e $R^1 = Ph$, $R^2 = CH_2{=}CHCH_2{-}$, $R^3 = Pr^i$
f $R^1 = Me$, $R^2 = CH_2{=}CH{-}$, $R^3 = Ph$
g $R^1 = Bu^t$, $R^2 = H$, $R^3 = p$-Tolyl
h $R^1 = Pr^i$, $R^2 = H$, $R^3 = p$-Tolyl

Following earlier reports[6] on the additions of arenesulfanyl chlorides to triarylketenimines, we have examined the reactions of other more reactive ketenimines with these reagents and also with areneselanyl chlorides for the first time. The reactions provide a general route to a range of α-substituted secondary amides and, in addition, a new synthesis of *C*-sulfanyl- and *C*-selanyl-ketenimines has been developed.

The ketenimines **1** were readily obtained by the dehydration of secondary amides using established procedures.[7] Additions of these heterocumulenes with the sulfanyl and selanyl chlorides occurred rapidly † at ambient or lower temperatures to give, *via* addition across the α,β-bond of compound **1**, the substituted imidoyl chlorides **3** in quantitative yields. These compounds were not generally isolated and characterised in detail, but instead converted immediately into the substituted amides **4** and the ketenimines **5** through solvolysis[8] and eliminations, respectively.



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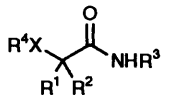
† Disappearance of the heterocumulene and development of the imidoyl chloride imine IR absorptions at *ca.* 2020 and 1680 cm^{-1} respectively, were almost complete upon mixing of the reagents.

The former reactions were accomplished by dissolution of the chlorides in acetone–water mixtures and these gave the amides **4** as crystalline solids, in high yields (Table 1), either by evaporation of the organic solvent, or by further dilution of the solvolysis medium with water. Several of the arenesulfanyl substituted compounds **4**, could be isolated in an analytically pure state using these procedures. The other compounds were purified by recrystallisation from aqueous alcohol, or by chromatography on silica gel. Thus, synthetically useful arenesulfanyl and areneselanyl substituted amides are readily available from ketenimines under essentially neutral reaction conditions.



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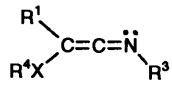

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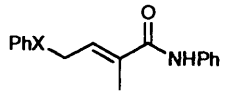
Reaction of benzenesulfanyl chloride with the ketenimine **1e** was conducted at −78 °C in order to achieve maximum chemoselectivity in the addition process, and this gave the α-substituted amide **4e** following hydrolysis of the intermediate imidoyl chloride. Poor yields of the related areneselanyl derivative **4i** were obtained, however, under a variety of conditions. Addition of the sulfanyl and selanyl reagents to the conjugated ketenimine **1f** occurred at the delta-carbon of the vinylketenimine[9] group, to give the amides **6** (X = S, Se) in high yields, after hydrolysis of the respective imidoyl chlorides.



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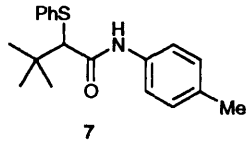

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Dehydrochlorination of the imidoyl chlorides **3**, derived from the *C*,*N*-disubstituted ketenimines **1** (R^2 = H), with an excess of triethylamine, gave the *C*-sulfanylketenimines **5** (X = S)—a previously unreported route to these compounds (Table 2). Interestingly, dehydrochlorination of the chlorides **3**, derived from the *C*-arylketenimine precursors, occurred readily at room temperature, whereas the corresponding reactions with the *C*-alkyl compounds **3** (R^1 = alkyl) could only be conducted successfully above 60 °C, *e.g.* in refluxing benzene. The addition–dehydrochlorination process could be readily extended to yield several *C*-selanylketenimines. To the best of our knowledge, *C*-selanylketenimines are unknown in the literature. *C*-Sulfanylketenimines have been prepared[10] by dehydration of amide precursors and the related *C*-silylatedketenimines are readily available *via* lithiation of imido thioesters.[11] The synthesis and reactions of several *C*-phosphonatoketenimine derivatives has also been described.[12]

Incorporation of arenesulfanyl and selanyl groups at the β-

Table 1 Preparation of α-substituted amides **4**

Compound **4**	R^1	R^2	R^3	X	R^4	Yield (%)
a	Ph	H	Ph	S	Ph	93
b	Ph	Et	Bu^s	S	Ph	89[a]
c	Ph	H	Pr^i	S	o-$NO_2C_6H_4$	85
d	Ph	H	Bu^s	S	Ph	90[a]
e	Ph	CH_2=$CHCH_2$	Pr^i	S	Ph	70
f	Ph	H	Bu^s	Se	Ph	90[a]
g	Ph	H	Pr^i	Se	Ph	90
h	Ph	H	Bu^s	Se	o-$NO_2C_6H_4$	83[a]
i	Ph	CH_2=$CHCH_2$	Pr^i	Se	o-$NO_2C_6H_4$	35

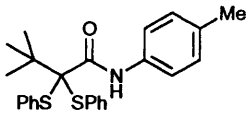
[a] Mixture of diastereoisomers. (All compounds are racemic.)

Table 2 Preparation of *C*-sulfanyl- and *C*-selanyl-ketenimines **5**

Compound **5**	R^1	R^3	R^4	X	Yield (%)	B.p. (°C/mmHg)[a]
a	Ph	Bu^s	Ph	S	69	160–162/0.17
b	Bu^t	*p*-Tolyl	Ph	S	89	146–148/0.10
c	Pr^i	*p*-Tolyl	Ph	S	68	125–127/0.20
d[b]	Bu^t	*p*-Tolyl	Bu	S	70	121–124/0.25
e	Ph	Bu^s	Ph	Se	74	145–148/0.15
f	Bu^t	*p*-Tolyl	Ph	Se	79	142–144/0.15
g	Pr^i	*p*-Tolyl	Ph	Se	60	145–147/0.18

[a] Kugelrohr distillation, b.p. = oven temperature. [b] δ_C 13.6, 21.05, 21.7, 29.6, 31.6, 34.6, 36.8, 75.0, 123.45, 130.3, 137.0, 139.2 and 187.8.

carbon of the ketenimines **5** induced small shielding effects in the ^{13}C NMR chemical shifts of the heterocumulene α-carbons ($\Delta\delta_C$, 4–8 ppm). Small, variable effects ($\Delta\delta_C$, −2 to +7 ppm) were observed for the β-carbons in the same molecules.



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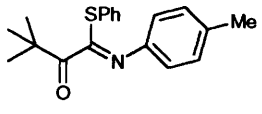

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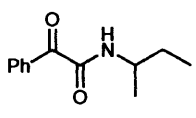
Hydration of compounds **5** to give the corresponding amides occurred readily. For example, ketenimine **5b** was converted into the amide **7** in acetone–water mixtures in the absence of an acid catalyst.[5] Reaction of compound **5b** with benzenesulfanyl chloride and solvolysis of the resulting imidoyl chloride gave a mixture of the α-amidodisulfanylketal derivative **8** (21%) and the α-ketosulfanylimidate **9** (56%). Under similar conditions, ketenimines **5a** and **5g** gave compounds **10** (70%) and **11** (54%) following reaction with the corresponding sulfur and selenium electrophiles. Further investigations of the chemistry of the ketenimines **5** are in progress.



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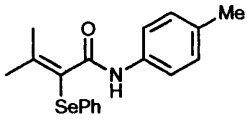

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Experimental

All reactions that involved ketenimines were carried out in dry solvents and under a nitrogen atmosphere. NMR spectra were measured in $CDCl_3$ and *J* values are reported in Hz.

N-Isopropyl-2-phenyl-2-(phenylsulfanyl)pent-4-enoamide **4e**.—Benzenesulfanyl chloride (0.293 g, 2.03 mmol) in dichloromethane (5 cm^3) was added dropwise (10 min) to a cold (−78 °C) solution of compound **1e** (0.405 g, 2.03 mmol) in the same solvent (20 cm^3). The mixture was allowed to warm to room temperature over 2 h and was then evaporated. Dissolution of the residue in acetone–water (20:1, 20 cm^3; 0 °C), evaporation of the solvent after 2 h and chromatography of the product (PLC-silica gel, diethyl ether–hexane, 1:1) gave the title compound **4e** (0.455 g); m.p. 87–88.5 °C (from 95% ethanol) (Found: C, 73.85; H, 7.3; N, 4.35; S, 10.1. $C_{20}H_{23}NOS$ requires C, 73.85; H, 7.1; N, 4.3; S, 9.85%); ν(KBr)/cm^{-1} 3315 and 1642; δ_H 1.03 (3 H, d, *J* 6), 1.06 (3 H, d, *J* 6), 2.76 (1 H, ddt, *J* 15.3, 7.7 and 1.5), 2.91 (1 H, ddt, *J* 15.3, 7.7 and 1.5), 4.02 (1 H, m), 4.93 (2 H, m), 5.75 (1 H, m), 6.3 (1 H, brd) and 7.05–7.35 (10 H, m); δ_C 22.4, 41.6, 42.0, 64.45, 118.3, 127.5, 128.1, 128.65, 128.9, 130.55, 133.5, 135.55, 140.2 and 170.9.

N-Isopropyl-2-phenyl-2-(phenylselanyl)acetamide **4g**.—A solution of benzeneselanyl chloride (0.383 g, 2 mmol) was added to a cold (0 °C) solution of compound **1c** (0.318 g, 2 mmol), after which the mixture was allowed to warm to ambient temperature over 2 h; hydrolysis of the resulting imidoyl chloride in acetone–water gave *the title amide* (0.6 g, 90%) as a yellow solid after recrystallisation from 95% alcohol, m.p. 133–134 °C (Found: C, 61.35; H, 5.8; N, 3.9. $C_{17}H_{19}NOSe$ requires C, 61.5; H, 5.8; N, 4.2%); ν(KBr)/cm^{-1} 3300 and 1640; δ_H 1.06 (3 H, d, *J* 7), 1.09 (3 H, d, *J* 7), 4.02 (1 H, septet) 4.95 (1 H, s), 6.26 (1 H, brd), 7.25–7.43 (8 H, m) and 7.50–7.55 (2 H, m); δ_C 22.3, 22.5, 42.0, 52.0, 127.8, 128.1, 128.3, 128.7, 129.2, 129.5, 134.1, 137.1 and 168.3.

N-(sec-Butyl)-C-phenyl-C-(phenylsulfanyl)ketenimine **5a**.—Benzenesulfanyl chloride (1.5 g, 10.4 mmol) dissolved in benzene or dichloromethane (5 cm^3), was added dropwise, over 10 min, to a cold, stirred solution of compound **1d** (1.97 g, 10.4 mmol) in the same solvent (45 cm^3). The resulting solution was allowed to warm to room temperature, then dry triethylamine (2 cm^3) in benzene or dichloromethane (5 cm^3) was added in one portion and the mixture was stirred at ambient temperature for 5 h. Filtration of the reaction mixture, washing of the solid with dry diethyl ether (15 cm^3), followed by evaporation of the combined filtrate and washings and finally bulb to bulb distillation of the residue gave the title compound **5a** (2.02 g, 69%) as a pale yellow oil; ν(film)/cm^{-1} 3060, 3025, 2970, 2880, 2020, 1660, 1580, 1480 and 1320; δ_H 0.93 (3 H, t, *J* 7), 1.26 (3 H, d, *J* 7), 1.47 (2 H, quin), 3.62 (1 H, m) and 7.22 (10 H, m); δ_C

10.6, 21.3, 30.5, 60.6, 61.7 (*C*=C=N), 124.2, 125.5, 127.1, 128.65, 128.8 and 179.4 (C=*C*=N).

C-*Isopropyl*-C-(*phenylsulfanyl*)-N-p-*tolylketenimine* **5g**.— 60% ν(film)/cm^{-1} 3075–2870, 2000, 1580 and 1505; δ_H 1.18 (6 H, d, *J* 7), 2.28 (3 H, s), 2.30 (1 H, m), 7.12–7.50 (9 H, m); δ_C 21.05, 22.55, 31.1, 64.4 (*C*=C=N), 120.0, 123.5, 126.6, 129.05, 130.0, 130.3, 137.2, 138.8 and 184.65 (C–*C*=N).

3,3-*Dimethyl*-2-(*phenylsulfanyl*)-N-p-*tolylbutyramide* **7**.— The ketenimine **5b** (0.54 g, 1.8 mmol) was dissolved in acetone–water (10:1, 10 cm^3) and the resulting solution was stirred at room temperature for 30 min. Dilution of this solution with water, cooling of the resulting mixture in an ice-bath and isolation of the resultant solid by filtration, gave the *amide* (0.50 g, 87%) as a pale yellow solid, m.p. 120–122 °C after recrystallisation from dichloromethane–hexane (Found: C, 72.3; H, 7.2; N, 5.0; S, 10.4. $C_{19}H_{23}NOS$ requires C, 72.8; H, 7.35; N, 4.5; S, 10.2%); ν(KBr)/cm^{-1} 3290, 1662 and 1608; δ_H 1.26 (9 H, s), 2.28 (3 H, s), 3.63 (1 H, s), 7.10–7.45 (9 H, m) and 8.25 (1 H, br s).

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