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A sequence of electrophile induced cyclisation and concomitant *N*-deprotection of alkenylsulfinimines and alkenylsulfinamides as a direct route to cyclic or spirocyclic imines, pyrrolidines and piperidines

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Abstract—Alkenylsulfinimines and alkenylsulfinamides underwent electrophile induced cyclisation reactions with phenylselenyl bromide, iodine and bromine to cyclic and spirocyclic imines, pyrrolidines and piperidines with spontaneous cleavage of the protective group at nitrogen in good to excellent yield.

Electrophile induced cyclisations of nitrogen derivatives carrying an alkenyl group such as amines,[1] imines,[2] hydrazines,[3] hydrazones,[4] hydroxamic acids,[5] oximes[6] and oxime ethers[7] have been extensively studied.[1–7] Various electrophiles such as halogenating agents (I_2, Br_2, NBS, NIS), chalcogen (PhSeBr), metal ions (Pd, Hg, Ag) have been reported to promote cyclisation.[8–13]

To date, *tert*-butanesulfinimines and *tert*-butanesulfinamides have not been used as nitrogen nucleophiles in electrophile induced cyclisation processes. As part of our ongoing research program developing novel electrophile induced cyclisation reactions, we now report the use of sulfinimines and sulfinamides, which can undergo electrophile induced cyclisation and, most importantly, spontaneous *N*-fragmentation in the presence of phenylselenyl bromide, iodine or bromine under mild conditions to generate cyclic and spirocyclic imines, pyrrolidines and piperidines in good to excellent yield. These substances can also undergo further modification particularly depending on the introduced heteroatom by the electrophile. Spontaneous removal of the *tert*-butanesulfinyl moiety along the reaction is a great advantage of this cascade reaction.

The *tert*-butanesulfinimines (**3a**,**b**) were prepared from the corresponding aldehydes (**1**)[14] and *tert*-butanesulfinamide (**2**)[15] in the presence of $Ti(OEt)_4$ (THF, N_2, rt) in excellent yield by modification of a literature procedure (96–98%).[15] Reduction of these imines with $NaBH_4$ (THF, −40 °C, 8 h) gave the corresponding sulfinamides (**10**) in excellent yield (94–98%). The *tert*-butanesulfinimines (**3a**,**b**) react readily with electrophiles such as phenylselenyl bromide, iodine or bromine in dichloromethane or acetonitrile at 0 °C to room temperature via attack of the *N*-atom on the intermediate onium ion to give the intermediate iminium salts (**4**). Stirring the reaction mixture at room temperature for 22 h resulted in fragmentation in the *N*-deprotected iminium salts (**5**) in quantitative yield (Scheme 1). Treatment with 2 N aqueous NaOH (E = PhSe) or aqueous $Na_2S_2O_3$ (E = I) afforded cyclic and spirocyclic imines (**6**) in 74–89% overall yield from the corresponding *N*-sulfinylimines (**3**). Reduction of the cyclic imines (**6**) or iminium compounds (**5**) with $NaBH_4$ ($MeOH/CH_2Cl_2$, rt, 8 h) or $LiAlH_4$ (ether, reflux, 12 h) afforded pyrrolidines (**7**) in 84–89% overall yield from (**3**). Addition of dry HCl to pyrrolidines (**7**) in 4:1 ether/CH_2Cl_2 gave pyrrolidinium salt (**8**) in quantitative yield.[17]

Treatment of iminium salts (**5**) with KCN in THF/H_2O (1:1, v/v) at room temperature for 16 h gave rise to

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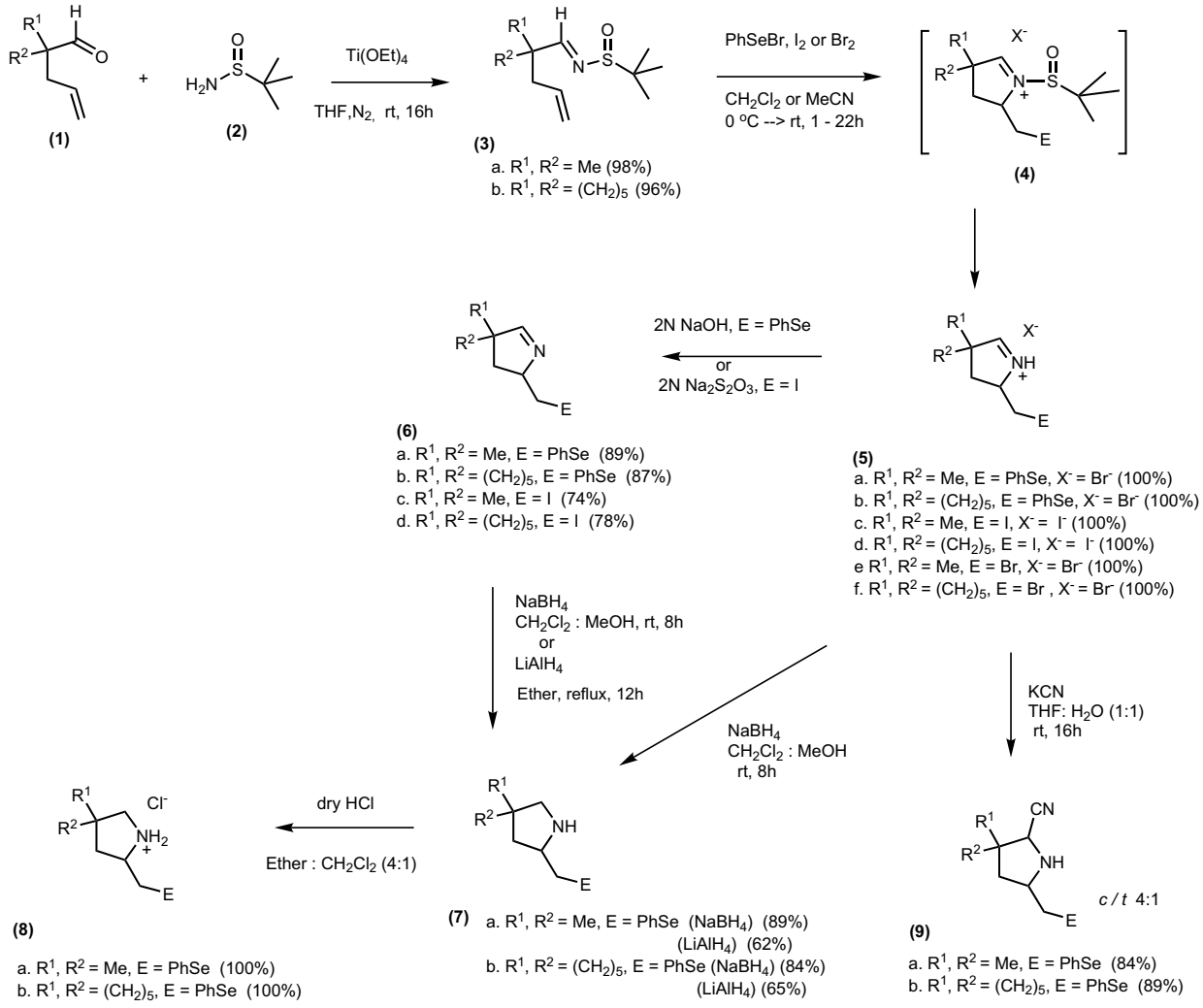


Scheme 1.

2-cyanopyrrolidines (**9**) in 82–84% yield as a 4:1 mixture of cis- and trans-isomers.

An alternative route to cyclic and spirocyclic pyrrolidines and piperidines was investigated as outlined in Scheme 2. The reaction of *tert*-butanesulfinamides (**10**) with PhSeBr or I_2 in dichloromethane resulted in the cyclisation to pyrrolidinium salts, which suffered *N*-deprotection into pyrrolidinium salts (**12**). Treatment of these salts with 2 N NaOH (E = PhSe) or $Na_2S_2O_3$ (E = I) afforded pyrrolidines (**7**) in 77–94% overall yield from the corresponding sulfinamide (**10**).[18]

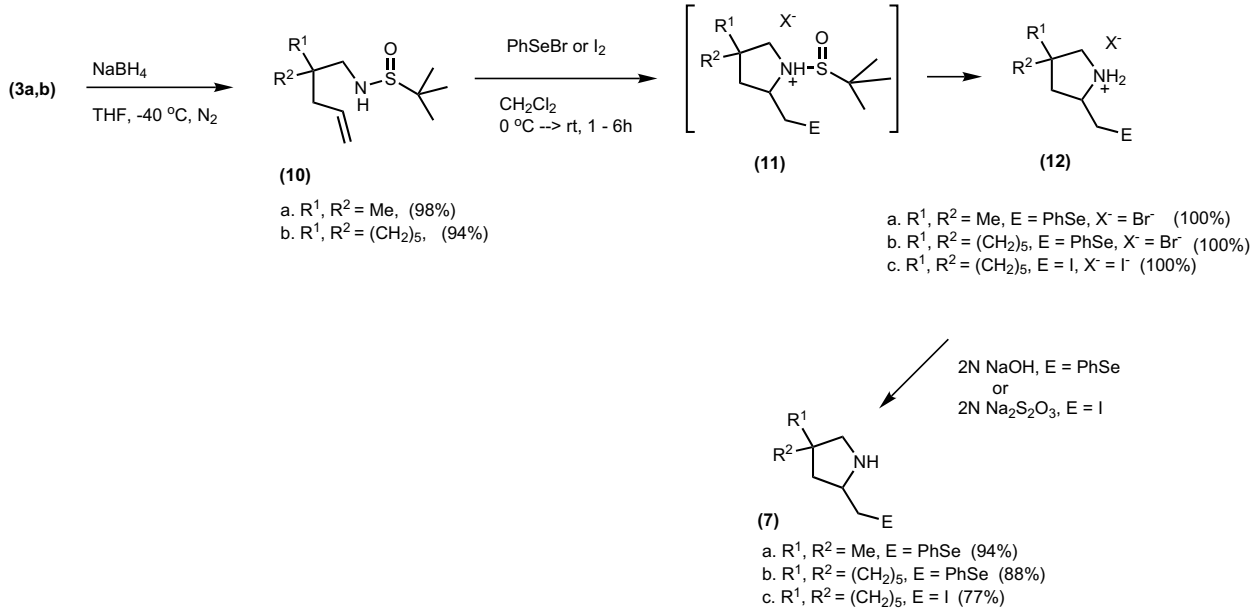
In the case of the reaction of *tert*-butanesulfinamides (**10a**,**b**) with bromine as electrophile (CH_2Cl_2, rt, 16 h), the piperidinium salts **15a**,**b** and pyrrolidinium salts **14a**,**b** were obtained in a 1:1 ratio quantitative yield (Scheme 3).

The *tert*-butanesulfinamide moiety is fragmented in the conversion **4**→**5** or **13**→**14** presumably owing to its instability to acid.[15,16] The acid is formed during the course of the reaction. Thus, the expulsion of volatile by-products[15,16] of the fragmentation step provided the iminium salts and ammonium salts in high yield and purity.

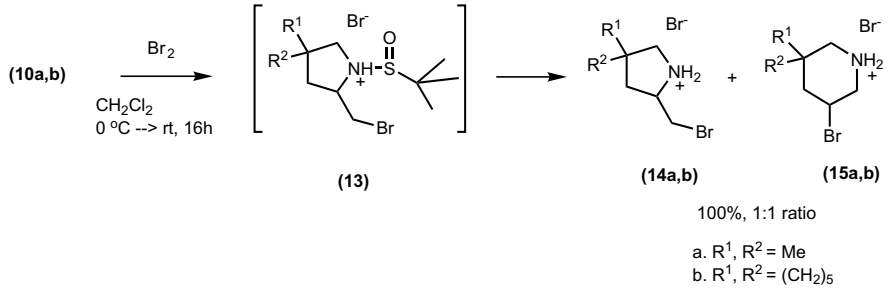
Attempts to try out the chiral version of cyclisation did not meet with great success as very low ee's were obtained. For example, reaction of imine (*R*)-(**3b**) prepared from enantiomerically pure (*R*)-*tert*-butanesulfinamide (**2**), in the presence of phenylselenyl bromide in dichloromethane at 0 °C for 6 h and reduction with $NaBH_4$ ($MeOH/CH_2Cl_2$, rt, 8 h), afforded spiropyrrolidine (**7b**) in 20% ee, measured by chiral HPLC. Because of this result, no further experiments were directed towards the use of chiral substrates in this cyclisation protocol.

A highly practical and efficient synthesis of cyclic and spirocyclic imines, pyrrolidines and piperidines in good yield is described by two routes.

The efficiency of this strategy for the synthesis of azaheterocycles stems from the electrophile induced cyclisation and fragmentation in a one pot cascade procedure.



Scheme 2.



Scheme 3.

Varieties of functionalised cyclic and spirocyclic pyrrolidines and piperidines can be prepared from these simple and high yielding processes.

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17. General procedure for the cascade PhSeBr-induced cyclisation of sulfinylimines: Phenylselenyl bromide (1.0 mmol) in 5 ml of dry solvent (CH_2Cl_2 or MeCN) was added dropwise to a stirred solution of *tert*-butanesulfinylimine (**3**) (1 mmol) in the same solvent (10 ml) at 0 °C under nitrogen atmosphere, and stirring was continued at room temperature for 18–22 h. The solvent was then evaporated under vacuum to give the iminium salt (**5**). The iminium salt (**5**) was treated with 2 N aq NaOH and extracted with CH_2Cl_2 (two times), dried ($MgSO_4$) and the solvent was evaporated (at room temperature) under reduced pressure to give the cyclic imines (**6**), which were further purified by short flash chromatography eluting with ether to give a pale yellow thick oil. These imines (**6**) can be reduced by $LiAlH_4$ (ether, reflux, 12 h) or $NaBH_4$ (CH_2Cl_2/MeOH, 1:1 rt, 8 h) to afford the desired pyrrolidines (**7**). The iminium salts (**5**) can also be reduced with sodium borohydride (2 equiv) in 1:1 (v/v) methanol/CH_2Cl_2 at room temperature for 8 h. Removal of the solvent under reduced pressure afforded the crude pyrrolidines (**7**), which were purified by flash chromatography on silica gel. Diphenyldiselenide was first eluted by ether. The pyrrolidines (**7**) were next eluted with EtOAc/CH_2Cl_2 (4:1) to give the desired cyclic and spirocyclic pyrrolidines (**7**) as a colourless thick oil. These pyrrolidines when treated with dry HCl in 4:1 ether/CH_2Cl_2 afforded the pyrrolidinium salts (**8**) in quantitative yield. Compound (**5b**): The product (100%) was obtained as a pale brown thick oil. ^{1}H NMR δ_H (300 MHz, $CDCl_3$): 9.92 (br s, 1H, CH=N^+), 7.59–7.58 (m, 2H, ArH), 7.30–7.29 (m, 3H, ArH), 6.91 (br, 1H, NH), 4.71 (m, 1H, N*CH*), 3.68 (dd, 1H, *J* 13.5 and 3.65 Hz, H*CH*Se), 3.10 (dd, 1H, *J* 13.4 and 6.6 Hz, H*CH*Se), 2.37 (dd, 1H, *J* 13.3 and 8.6 Hz, H*CH*CHN), 1.84 (dd, 1H, *J* 13.3 and 5.1 Hz, H*CH*CHN), 1.80–1.30 (m, 10H, $(CH_2)_5$). ^{13}C NMR δ_C: 185.01, 133.63, 131.5, 129.7, 128.2, 66.9, 53.67, 37.9, 34.1, 32.5, 30.3, 24.6, 21.96, 21.7. MS *m*/*z* (%) (ES): 308 (MH-Br, 100). IR (NaCl, cm^{-1}): 2960, 2930, 1650. Compound (**6b**): the product (87%) was obtained as a pale yellow thick oil. ^{1}H NMR δ_H (300 MHz, $CDCl_3$): 7.65–7.61 (m, 2H, ArH), 7.30–7.29 (m, 3H, ArH), 7.27 (s, 1H, CH=N), 4.27 (m, 1H, N*CH*), 3.33 (dd, 1H, *J* 12.4 and 3.5 Hz, H*CH*Se), 3.01 (dd, 1H, *J* 12.4 and 6.0 Hz, H*CH*Se), 2.04 (dd, 1H, *J* 13.0 and 8.0 Hz, H*CH*CHN), 1.78–1.32 (m, 11H, H*CH*CHN and $(CH_2)_5$). ^{13}C NMR δ_C (75 MHz, $CDCl_3$): 174.7, 132.6, 131.60 (2CH–Ar), 129.2, 129.1, 71.8, 55.3, 40.1, 35.4, 34.7, 33.2, 25.6, 23.1, 23.0. MS *m*/*z* (%) (ES): 308(M+1, 100). IR (NaCl, cm^{-1}): 2965, 2929, 1625. Compound (**7b**): the product (84%) was obtained as a colourless thick oil. ^{1}H NMR δ_H (300 MHz, $CDCl_3$): 7.49–7.48 (m, 2H, ArH), 7.23–7.21 (m, 3H, ArH), 3.36 (m, 1H, N*CH*), 3.04–3.03 (m, 2H, HCH_2Se), 2.81 and 2.82 (2 × d, 2H, *J* 10.4 Hz, CH_2N), 2.33 (br, NH), 1.82 (dd, 1H, *J* 12.0 and 5.9 Hz, H*CH*CH), 1.41–1.31 (m, 10H, $(CH_2)_5$), 1.21 (dd, 1H, *J* 12.0 and 3.1 Hz, H*CH*CH). ^{13}C NMR δ_C (75 MHz, $CDCl_3$): 132.5, 130.6, 129.1, 128.8, 58.5, 57.9, 45.1, 43.9, 38.3, 37.0, 35.0, 31.5, 26.8, 23.9. MS *m*/*z* (%) (ES): 310 (M+1, 100). IR (NaCl, cm^{-1}): 3333, 2950, 1470. Compound (**10b**): the product was obtained as a white amorphous solid in quantitative yield. ^{1}H NMR δ_H (300 MHz, $CDCl_3$): 8.04 (br, 2H, $^+NH_2$), 7.92–7.90 (m, 2H, ArH), 7.28–7.26 (m, 3H, ArH), 3.83 (m, 1H, N*CH*), 3.51 (dd, 1H, *J* 13.7 and 3.7 Hz, H*CH*Se), 3.38–3.17 (m, 3H, H*CH*Se and CH_2NH), 2.09 (dd, 1H, *J* 12.7 and 6.1 Hz, H*CH*CH), 1.63–1.03 (m, 11H, H*CH*CH and $(CH_2)_5$). ^{13}C NMR δ_C (75 MHz, $CDCl_3$): 134.0 129.5, 128.3, 128.0, 59.24, 54.9, 43.0, 42.8, 36.9, 35.5, 31.0, 25.5, 23.6, 22.9. MS *m*/*z* (%) (ES): 310 (MH−Cl, 100). IR (NaCl, cm^{-1}): 3432, 2925, 1454.
18. General procedure for the cascade PhSeBr-induced cyclisation of sulfinylamides: Phenylselenyl bromide (1.05 mmol) in 5 ml of dry (CH_2Cl_2) was added dropwise to a stirred solution of *tert*-butanesulfinamide (1 mmol) in CH_2Cl_2 (10 ml) at 0 °C under nitrogen atmosphere and stirring was continued at room temperature for 16–20 h. The solvent was then evaporated under vacuo to give ammonium salts (**12**). The salts were then treated with 2 N aq NaOH and extracted with CH_2Cl_2 (two times), the combined extracts were dried ($MgSO_4$) and the solvent was evaporated under reduced pressure to give the pyrrolidines (**7**), which were further purified by flash chromatography on silica gel. Diphenyldiselenide was first eluted by diethyl ether. The pyrrolidines (**7**) were next eluted with EtOAc/CH_2Cl_2 (4:1) to give the desired cyclic and spirocyclic pyrrolidines (**7**) as colourless thick oil. Compound (**12b**): the product was obtained as a yellow thick oil in quantitative yield. ^{1}H NMR δ_H (300 MHz, $CDCl_3$): 9.17 and 9.61 (2 × br, 2H, $^+NH_2$), 7.70–7.54 (m, 2H, ArH), 7.29–7.27 (m, 3H, ArH), 3.80 (m, 1H, N*CH*), 3.54 (dd, 1H, *J* 13.7 and 3.7 Hz, H*CH*Se), 3.21–3.12 (m, 3H, H*CH*Se and CH_2NH), 2.11 (dd, 1H, *J* 12.7 and 6.1 Hz, H*CH*CH), 1.59–1.13 (m, 11H, H*CH*CH and $(CH_2)_5$). ^{13}C NMR δ_C (75 MHz, $CDCl_3$): 134.0, 131.60, 129.5, 128.04, 59.34, 54.8, 43.0, 42.7, 36.9, 35.5, 30.6, 25.4, 23.6, 22.9. MS *m*/*z* (%) (ES): 310 (MH−Br, 100); IR (NaCl, cm^{-1}): 3430, 2925, 1476.