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CONVENIENT SYNTHESIS OF 2-ALKYNYLSULFINAMIDES AND 2,5-DIHYDROISOTHIAZOLE *S*-OXIDES USING ALLENYLCOPPER(I) COMPOUNDS

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Summary

Allenylcopper(I) species, RR'C=C=CR''Cu, add to *N*-sulfinylaniline to give *N*-phenyl 2-alkynylsulfinamides, R''C≡CCRR'S(O)NHPh. The latter cyclise to *N*-phenyl 2,5-dihydroisothiazole *S*-oxides upon treatment with either sodium ethoxide in ethanol or butyllithium and subsequent addition of $AgBr \cdot (LiBr)_3$.

Introduction

Allenylcopper(I) compounds are converted regiospecifically into allenes by electrophiles such as 2-alkynoic esters [1], alkyl halides [1,2], and 1-alkynyl halides [3]. The corresponding allenylsilver(I) species demonstrate similar regiochemical behaviour upon treatment with various electrophiles [4], but there is one interesting exception, viz. the reaction with carbon disulfide. With this electrophile allenylsilver(I) reagents produce 3-alkynedithioates, which cyclise to β,γ-unsaturated γ-dithiolactones [5].

The present paper concerns the reaction of allenylcopper(I) compounds with *N*-sulfinylaniline, PhN=S=O. It is shown that the initial adducts are precursors of isothiazole derivatives.

Results and discussion

(a) Allenylcopper(I) compounds

Allenylcopper(I) species, RR'C=C=C=CR''Cu (I) smoothly add, even at −60°C, to *N*-sulfinylaniline, to give 2-alkynylsulfinic acid amides, R''C≡CCRR'S(O)NHPh (II) after protolysis. An excellent solvent for this addition reaction is tetrahydrofuran (THF). The reaction is highly regioselective. The regiochemistry of the reaction is quite unexpected in view of the reaction pattern which is generally observed for reactions of I with electrophiles [1–3].

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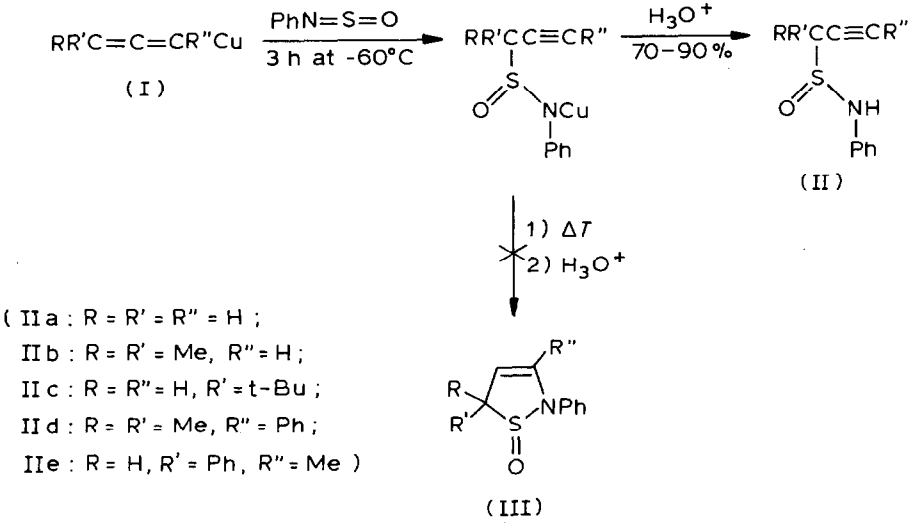
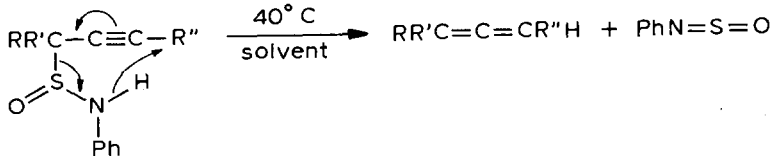
Attempts to cyclise the intermediate adducts into compounds III by heating (see Scheme 1) were unsuccessful.

SCHEME 1



The sulfinamides II are crystalline at room temperature, and as solids are very stable. In solution, however, they undergo a retro-ene cleavage to give allenes and *N*-sulfinylaniline. Such a retro-ene reaction is known for many other propargylic compounds, e.g. for propargylic ethers and amines, propynoic esters etc. [6]. In our case, however, the retro-ene cleavage takes place under much milder conditions (quantitative conversion within 30 min at 40°C) than are normally required for such 1,5-hydrogen shifts (scheme 2) [6].

SCHEME 2



(Solvent: $CHCl_3$, CCl_4, C_2Cl_4, benzene, or toluene)

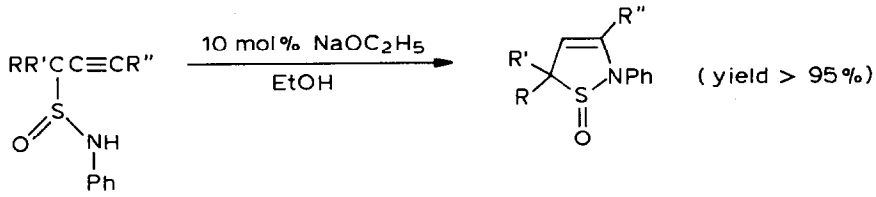
In principle this route to allenes can be used to prepare selectively deuterated allenes RR′=C=CR″D starting from R″C≡CCRR′S(O)NDPh.

(b) Formation of 2,5-dihydroisothiazole S-oxides (III)

We noted in section (a) that the intermediate adducts arising from the reaction of I with *N*-sulfinylaniline could not be cyclised by heat. The target heterocycles III seem never to have been reported. We therefore attempted to obtain III by means of a mild base-catalysed cyclisation of the amides II, and found that the compounds II do, indeed, undergo ring closure to III on treatment with base, albeit not in all cases

(Scheme 3).

SCHEME 3



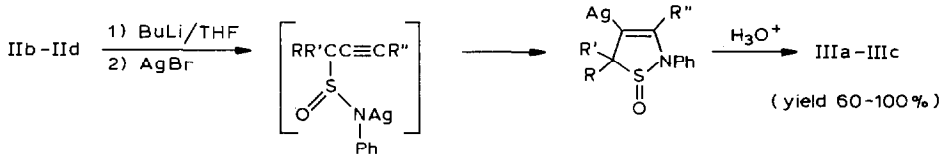
(IIb, IIc, IId)

(IIIa : R = R' = Me, R" = H ;
IIIb : R = R" = H, R' = t-Bu ;
IIIc : R = R' = Me, R" = Ph)

Compounds IIa (R = R′ = R″ = H) and IIe (R = H, R′ = Ph, R″ = Me) gave polymeric material under these conditions. We attribute this to the occurrence of a prototropic isomerization in the two compounds with formation of allenic sulfinamides, R″CH=C=CR′S(O)NHPh followed by further decomposition of these allenes. Isomerization of IIa into the allenic compound was induced by treating IIa with K_2CO_3 in a mixture of H_2O/EtOH (50/50 v/v). The product mixture contained much polymer, but also a substantial amount of H_2C=C=CHS(O)NHPh. Apparently, the presence of hydrogen atoms at the propargylic centre in II is not favourable for the conversion of II into III. That compound IIc can nevertheless be converted in excellent yield into IIIc must be due to strong hindrance to the isomerization by the bulky t-butyl group.

Another route from II to III is the subsequent treatment of II with butyllithium followed by the complex $AgBr(LiBr)_3$. We assume that this reaction proceeds as indicated in Scheme 4. Unfortunately, also this route can only be used to convert amides IIb, IIc, and IId into III, similar treatment of compounds IIa and IIe again producing polymeric material.

SCHEME 4



Except for the conversion of IId into IIIc the yields are lower than when the sodium ethoxide catalyzed cyclisation is used. This is probably due to an incompletely selective deprotonation in II when R″ is hydrogen, since we found a considerable amount of DC≡CCH(t-Bu)S(O)N(H or D)Ph upon treatment of IIc with an equimolar amount of butyllithium followed by deuterolysis. This indicates that abstraction of the acetylenic proton cannot be ignored.

It is noteworthy that the intermediate silver(I) salts of the 2-alkynylsulfinamides II spontaneously cyclised into the silver(I) salts of III. They therefore resemble the silver(I) salts of 3-alkynedithioates, which also spontaneously cyclise [5].

An alternative route to the silver(I) salts of II would be the addition of allen-

ylsilver(I) species to *N*-sulfinylaniline. We explored this route for Me_2-C=C=CHAg(LiBr)$_3$. Treatment of this compound with *N*-sulfinylaniline did produce IIIa, but only in 30% yield. We have not yet tried to optimize this route.

(c) Conclusion

Allenylcopper(I) species I are excellent reagents for the preparation of *N*-phenyl 2-alkynylsulfinamides, and hence *N*-phenyl 2,5-dihydroisothiazole-*S*-oxides.

The regiochemistry of the reaction of I with *N*-sulfinylaniline differs from that generally observed for reaction of I with electrophiles. It also differs from that of the reaction of η^5-$C_5H_5Fe(CO)_2CH_2C{\equiv}CR$ with *N*-sulfinylaniline, which proceeds through Fe^{II} salts of allenic sulfinamides to give 2,3-dihydroisothiazole-*S*-oxides in moderate yields (18–30%; see ref. 7).

Experimental section

All reactions were performed under dry nitrogen. The allenylcopper(I) reagents I were prepared by lithiation of RR'C=C=CHR'' using butyllithium and addition of $LiCuBr_2$ [3]. Tetrahydrofuran was distilled from $LiAlH_4$; butyllithium was purchased as a 1.5 *M* solution in hexane from Metallgesellschaft A.G., Frankfurt am Main. Lithium bromide was dried at 220°C in high vacuum and was used as a 3.0 *M* solution in THF for the preparation of the cuprate $LiCuBr_2$ by mixing it with an equimolar amount of cuprous bromide. The products were analyzed by means of NMR (Varian EM-390 and CFT-20 spectrometer) and IR, spectroscopy. For a number of the products mass spectra were determined (AEI-MS-902 mass spectrometer).

(a) Reaction of allenylcopper(I) compounds I with PhN=S=O

N-Sulfinylaniline (0.010 mol) was added to a stirred solution of I (0.010 mol) in THF (30 ml) * at −60°C. The mixture was stirred for 3 h at −60°C and then poured into an aqueous solution of ammonium chloride containing NaCN (1 g). The sulfinamides II were isolated by extraction with methylene chloride (3 × 100 ml). After washing and drying ($MgSO_4$) of the combined extracts the solvent was evaporated in vacuo and the residue crystallized from ether/pentane (50/50 v/v).

Compounds R''C≡CCRR'S(O)NHPh (II)

IIa: R = R' = R'' = H. Yield 95%, m.p. 80.0°C. IR (KBr) 3301, 3285, 1055 cm^{-1}. ^1H NMR ($CDCl_3$, TMS): δ 2.47 (HC≡), 3.69 + 3.87 (H^α and H^β in $\equiv CCH^\alpha H^\beta S(O)$), 6.90–7.50 ($C_6H_5$). ^{13}C NMR ($CDCl_3$, TMS): δ 140.2, 129.3, 123.5, and 119.1 (aromatic carbons), 76.2 (*HC*≡), 72.6 (≡*C*C), 45.8 (*C*H_2).

IIb: R = R' = Me, R'' = H. Yield 85%, m.p. 90.0–92.0°C. IR (KBr) 3250, 3210, 2110, 1050 cm^{-1}. ^1H NMR ($CDCl_3$, TMS): δ 1.49 (CH_3), 1.62 (CH_3), 2.65 (HC≡), 6.90–7.50 (C_6H_5). ^{13}C NMR ($CDCl_3$, TMS): δ 140.9, 129.3, 123, and 118.7 (aromatic carbons), 81.6 (≡*C*C), 75.5 (*HC*≡), 57.0 (*C*Me_2), 23.5 (2 × *C*H_3). Mass spectrum, *m/e* 207 (M^+).

IIc: R = R'' = H, R' = t-Bu. Yield 81% **, m.p. 66.0–68.0°C. IR (KBr) 3280,

* Some hexane (coming from the butyllithium solution) was also present.

** The compound is formed as a mixture of diastereoisomers (relative ratio ≈ 50/50).

3140, 1075 cm^{-1}. ^1H NMR ($CDCl_3$, TMS): δ 1.12 (t-C_4H_9), 1.23 (t-C_4H_9), 2.72 (HC≡), 2.84 (HC≡), 3.38 (≡CCH), 3.63 (≡CCH), 6.90–750 (C_6H_5). ^{13}C NMR ($CDCl_3$, TMS): δ 140.3, 140.1, 129.4, 123.5, 119.1 and 118.7 (aromatic carbons), 79.3 (*H*C≡), 78.3 (H*C*≡), 74.8 (≡*C*C), 72.2 (≡C*C*), 68.3 (≡CC<), 34.7 ($(CH_3)_3C$), 34.3 ($(CH_3)_3C$), 27.9 ($(CH_3)_3C$), 27.6 ($(CH_3)_3C$). Mass spectrum, *m/e* 235 (M^+).

IId: R = R′ = Me, R″ = Ph. Yield 72%. m.p. 127.0–128.0°C. IR (KBr) 3170, 1070 cm^{-1}. ^1H NMR ($CDCl_3$, TMS): δ 1.58 (CH_3), 1.70 (CH_3), 6.90–7.60 (2 × C_6H_5). ^{13}C NMR ($CDCl_3$, TMS): δ 141.2, 131.9, 129.3, 128.7, 128.2, 123.1, 121.8 and 118.6 (aromatic carbons), 87.7 + 86.5 (2 × *C*≡), 57.9 (≡*C*C<), 24.0 (*C*H_3), 23.4 (*C*H_3).

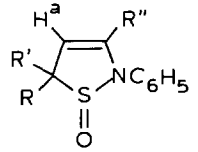
IIe: R = H, R′ = Ph, R″ = Me. Yield 75% *, m.p. 110.0–111.0°C. IR (KBr) 3150, 2220, 1060 cm^{-1}. ^1H NMR ($CDCl_3$, TMS): δ 1.98 (CH_3, isomer B), 2.05 (CH_3, isomer A), 4.90 (≡CCH <, isomer B), 4.97 (≡CCH <, isomer A), 6.70–7.70 (2 × C_6H_5, isomer A + B). ^{13}C NMR ($CDCl_3$, TMS) for isomer A: δ 140.2, 130.6, 129.3, 128.8, 123.4, 119.0 (aromatic carbons), 87.5 + 69.5 (2 × *C*≡), 64.4 (≡*C*CH <), 4.4 (*C*H_3). Mass spectrum, *m/e* 269 (M^+).

(b) Preparation of N-phenyl 2,5-dihydroisothiazole-S-oxides (III)

(A) $NaOC_2H_5$ method. A solution of II (0.010 mol) and $NaOC_2H_5$ (0.001 mol) in ethanol (150 ml) was kept for 2 h at 25°C then added to aqueous NH_4Cl. Extraction of III with ether (3 × 50 ml) followed by evaporation of solvent in vacuo gave a residue which was crystallized from ether/pentane (30/70 v/v). Yield of III > 95%.

(B) BuLi/AgBr method. Butyllithium (0.002 mol) in hexane was added to a stirred solution of II (0.002 mol) in THF (20 ml) at −60°C. After 5 min a homogeneous solution of AgBr $(LiBr)_3$ (0.002 mol) in THF (5 ml) was added, and the temperature was then allowed to rise to 25°C and stirring was continued at 25°C for 1 h. The cyclized compounds III were isolated as described under method A, (yield 60–100%) using an aqueous NH_4Cl solution containing NaCN (0.5 g).

Compounds



(III)

IIIa: R = R′ = Me, R″ = H. Method A, yield > 95%, Method B, yield 85%; m.p. 60–61°C; ^1H NMR ($CDCl_3$, TMS): δ 1.40 (CH_3), 1.51 (CH_3), 5.12 (H^a), 6.50 (R″), 7.0–7.5 (C_6H_5). ^{13}C NMR ($CDCl_3$, TMS): δ 140.9, 129.4, 124.0 and 118.8 (aromatic carbons); 128.9 + 114.0 (2 × *C*=), 70.7 (>*C*S(O)), 23.0 (*C*H_3), 17.8 (*C*H_3).

IIIb: R = H, R′ = t-Bu, R″ = H. Method A, yield > 95%; Method B, yield 61%; m.p. 104–106°C; ^1H NMR ($CDCl_3$, TMS): δ 1.05 (t-C_4H_9), 3.55 (>CHS(O)). 5.32 (*H*C=C–N), 6.68 (=*CH*N), 7.0–7.5 (C_6H_5). ^{13}C NMR ($CDCl_3$, TMS): δ 140.7, 129.6, 124.3 and 118.7 (aromatic carbons); 131.2 + 103.8 (2 × *C*=), 90.2 (*C*S(O)), 33.6 ($(CH_3)_3C$), 27.1 ($(CH_3)_3C$).

* Relative ratio of diastereoisomers 87/13 with isomer A as the most abundant diastereoisomer.

IIIc: R = R′ = Me, R″ = Ph. Method A, yield > 95%; Method B, yield 99%; m.p. 141–142°C; ^{1}H NMR ($CDCl_3$, TMS): δ 1.43 (CH_3), 1.50 (CH_3), 5.42 (*CH*=CN), 6.9–7.5 ($2 \times C_6H_5$) ^{13}C NMR ($CDCl_3$, TMS): δ 142.7, 141.2, 129.0, 128.5 128.1, 127.4, 124.8 and 122.8 (aromatic carbons), 131.3 + 116.0 ($2 \times$ C=), 68.5 (⩾*C*S(O)), 23.9 (*C*H_3), 18.0 (*C*H_3).

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