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Synthesis and Ag^+-catalyzed cyclization of 2,3-dienamides

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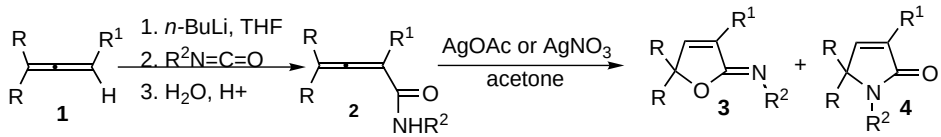
Abstract—Reaction of 1-lithiated methoxyallene and lithiated 3-methyl-1,2-butadiene with isocyanates, RN=C=O (R = alkyl) followed by hydrolysis affords the dienamides $H_2C{=}C{=}C(OCH_3)C(=O)NHR$ and $(CH_3)_2C{=}C{=}CHC(=O)NHR$, respectively, in good to excellent yields. Cyclization to 2-(5*H*)-furanylidenamines or mixtures of these compounds with 1,5-dihydro-2*H*-pyrrol-2-ones can be achieved with silver acetate or silver nitrate in acetone.

The reaction of metallated unsaturated compounds with isothiocyanates and further conversions of the adducts has been applied in syntheses of a wide variety of heterocyclic systems.[1–3] Treatment of the adducts $H_2C{=}C{=}C(X)C(=NR)SLi$ formed from 1-lithiated methoxyallene (X = OCH_3), 1-lithiated methylthioallene (X = SCH_3) or lithiated 2-butyne (X = CH_3) and isothiocyanates, RN=C=S, with dilute hydrochloric acid[4,5] or potassium *t*-butoxide in DMSO[5,6] led to the formation of 2-aminothiophenes or if X = OCH_3, of mixtures of the latter and the 2-imino tautomers. We wondered whether it would be possible to achieve similar cyclization reactions with the adducts from reactions of metallated allenic compounds with *isocyanates*, RN=C=O. In a previous communication we showed that the addition of lithiated 4,4-dimethyl-1,2-pentadiene, *t*-BuCH=C=CHLi, and lithiated 3-methyl-1,2-butadiene, $(CH_3)_2C{=}C{=}CHLi$, to isocyanates proceeds in a way analogous to reactions of lithiated allenic compounds with isothiocyanates.[7]

The present article deals with the first results from attempts to apply the adducts from lithiated allenes and isocyanates in syntheses of heterocyclic compounds. Methoxyallene and 3-methyl-1,2-butadiene **1** were lithiated using well-established procedures,[8] after which an alkyl isocyanate was added at very low temperatures. Both propyl and *i*-propyl isocyanate reacted very smoothly. Final treatment of the reaction mixture with an aqueous solution of ammonium chloride afforded the *N*-monosubstituted carboxamides **2** in excellent yields.

Cyclization of *N*-monosubstituted allenic carboxamides has not been reported so far. The reaction can be imagined to afford derivatives of dihydrofuran or dihydropyrrole by attack of oxygen or nitrogen, respectively, on the allenic system. Dihydrofuran and dihydropyrrole rings, including some unsaturated five-membered lactones and lactams, are not only important structural units or pivotal skeletons in many natural compounds with an unusual range of biological activity, but can also serve as building blocks of bioactive molecules and very useful synthons.[9–16]

Several attempts to achieve cyclization of **2** using dilute hydrochloric acid, catalytic amounts of potassium *t*-



a, **b**: R = H, R^1 = OMe, R^2 = *n*-C_3H_7 or *i*-C_3H_7

c, **d**: R = Me, R^1 = H, R^2 = *n*-C_3H_7 or *n*-C_4H_9

R = H, R^1= OMe, R^2 = alkyl : only **3**

R = Me, R^1= H, R^2 = alkyl : **3** + **4**

Keywords: isocyanates; allenes; lithiation; 2-(5*H*)-furanylideneamines; 2,5-dihydro-2*H*-pyrrol-2-ones.

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butoxide in DMSO,[5,6] copper(II) bromide[16] or palladium compounds either led to recovery of **2** or to the formation of intractable material. With silver acetate in acetone,[12–15] however, the carboxamides **2a**,**b** obtained from methoxyallene and alkyl isocyanates underwent a smooth cyclization under mild conditions to the so far unknown *N*-[3-methoxy-2(5*H*)-furanyliden]amines **3**.[17] The AgOAc-catalyzed cyclization of the carboxamides **2c**,**d** proceeded sluggishly and required at least 50 h at ~50°C. The major products were the dihydrofuran derivatives **3**, in addition ~10% of the dihydropyrroles **4** were detected by NMR spectroscopy. Using silver nitrate as a catalyst (room temperature, 23 h) mixtures of **3** and **4** (ratio ~4:1) were also obtained. The conversions were not complete however, ~30% of the dienamides **2c**,**d** still being present. Longer reaction times and higher temperatures did not give better results. Silver cyanide, silver bromide and copper(I) halides appeared to be ineffective.

Confirmation of the structures **3** and **4** is based on IR, ^{1}H, ^{13}C and ^{15}N NMR spectroscopy.[17,18] The IR spectra of **3a**,**b** suggested the presence of the C=C–C=N functionality. The ^{1}H and ^{13}C NMR spectra of these compounds indicated the presence of the dihydrofuran ring and the absence of amide **4**. The proton doublets (2H) at δ 4.78 or δ 4.66 correlated to the methylene carbon resonating at δ 70.50 or 70.37 (for **3a** and **3b**, respectively) were assigned to 5-CH_2O. The ^{15}N spectra provided additional support for the proposed dihydrofuran structures. The nitrogen resonating at −164.96 or −148.60 ppm corresponds to the imino-group.[9,19] according to the literature data for 2-pyrrolinone[9] or 2-pyrrolidinone,[19] structures closely similar to **4**, the nitrogen resonates at −258 or −260 ppm, respectively. For 4-butyl-1-methyl-5-(methylthio)-1,5-dihydro-2*H*-pyrrol-2-one we found the ^{15}N signal at –263 ppm.[20] So, the values of chemical shifts for ^{15}N for the products **3a**,**b** correspond better to iminodihydrofurans than to pyrrolinones. Moreover, the ^{1}H and ^{13}C NMR spectra of the pyrrolinone fragment[9] in palinurine A show signals at 4.08 ppm (broad singlet) and at δ 53.7 ppm, corresponding to 5-CH_2N.

The ^{1}H, ^{13}C and ^{15}N NMR spectra of the compounds **3c**,**d**, obtained from **2c**,**d**, showed close resemblance with the spectra of the products obtained from **2a**,**b**.

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17. To a solution of 0.05 mol of *n*-BuLi in 32 ml of hexane and 35 ml of THF cooled to –90°C was added in one portion 0.06 mol of methoxyallene, the cooling bath was removed and the temperature of the solution allowed to rise to –40°C. The solution was cooled again to –90°C, after which a mixture of PrN=C=O or *i*-PrN=C=O and 10 ml of THF was added dropwise over ~5 min while keeping the temperature in the region of –90°C. After an additional 10 min a solution of 20 g of ammonium chloride in 100 ml of water was added with vigorous stirring (in view of the expected sensitivity of the allenic ether system no acidic work-up was applied (compare Ref. 7). The product was isolated by extraction with Et_2O, drying over $MgSO_4$, removal of the solvents and distillation in a high vacuum. Dienamide **2a** (R^2 = *n*-Pr): yield 100%, purity ~100% (GC); the ^{1}H NMR spectrum showed inter alia signals at 6.44 (s, 1H, NH), 5.85 (s, 2H, CH_2=), 3.50 (s, 3H, OMe) and 3.29 (m, 2H, NCH_2) ppm. Compound **2b** (R^2 = *i*-Pr): yield 93%, purity 99% (GC); yield 43% after distillation (bp ~80°C/0.5 mmHg). The IR spectra of compounds **2a**,**b** showed inter alia absorption's at 1960 (C=C=C), 1540 and 1650–1700 cm^{-1} (CONH). Dienamides **2c**,**d** were prepared in >90% yield as described in Ref. 7.
A mixture of dienamide **2a** (0.05 mol) and AgOAc (1.5 g, ~3 mol%) in dry acetone (20 ml) was stirred under nitrogen at room temperature for 1 h, (conversion ~16%) and additionally at 40–45°C (for ~10–15 min) and monitored by GC. After the reaction was complete, the

reaction mixture was concentrated under reduced pressure and the residue was treated with an aqueous solution of LiBr after which diethyl ether was added. The ethereal solution was purified by column chromatography on Al_2O_3. The yield of dihydrofuran **3a** was 82.6%, isolated yield 45.2% (after distillation in vacuum); n_D^{20} 1.4900, bp ~85°C/0.5 mmHg; purity 98.3% (GC); IR (film): 1645 (C=C) and 1700(C=N) cm^{-1}; ^1H NMR: $\delta = 5.61$ (t, 1H, $J = 2.0$ Hz, 4-CH=), 4.78 (d, 2H, $J = 2.0$ Hz, 5-OCH_2), 3.77 (s, 3H, OMe), 3.31 (t, 2H, $J = 7.1$ Hz, NCH_2), 1.64 (m, 2H, CH_2), 0.93 (t, 3H, $J = 7.4$ Hz, Me) ppm; ^{13}C NMR: $\delta = 156.49$ (2-C=N), 149.66 (3-C=), 104.44 (4-CH=), 70.50 (5-OCH_2), 57.68 (OMe), 48.86 (NCH_2), 24.12 (CH_2), 12.11 (Me) ppm; ^{13}C NMR: $\delta = 169.59$ (2-C=N), 154.63 (3-C=), 123.07 (4-C=), 93.54 (5-O$\underline{C}Me_2$), 48.75 (NCH_2), 34.22 (CH_2), 25.78 (C$\underline{Me_2}$), 20.30 (CH_2), 13.90 (Me) ppm; ^{15}N NMR: $\delta = -164.96$ ppm.

1,5-dihydro-2*H*-pyrrol-2-one **4c**: ^1H NMR: $\delta = 6.98$ (d, 1H, $J = 5.8$ Hz, CH=), 6.25 (d, 1H, $J = 5.8$ Hz, CH=), 3.00 (t, 2H, $J = 7.2$ Hz, NCH_2), 1.93 (s, 6H, CMe_2), 1.35 (m, 2H, CH_2), 0.78 (t, 3H, $J = 7.4$ Hz, Me) ppm; ^{13}C NMR: $\delta = 177.41$ (2-C=O), 155.89 (3-C=), 113.97 (4-C=), 52.60 (N$\underline{C}Me_2$), 41.79 (NCH_2), 25.54 (C$\underline{Me_2}$), 22.67. Dihydrofuran **3b** was obtained similarly from 0.05 mol of **2b** in the presence of AgOAc (1.3 g) in 20 mL of dry acetone at rt for ~1.5 h: yield ~75% (after purification by column chromatography on Al_2O_3), purity ~100% (GC); isolated yield 58.4% (after distillation in vacuum), n_D^{20} 1.4870; bp 80–82°C/0.5 mmHg; purity 97.3% (GC); IR (film): 1650 (C=C) and 1700(C=N) cm^{-1}; ^1H NMR: $\delta = 5.49$ (t, 1H, $J = 2.0$ Hz, 4-CH=), 4.66 (d, 2H, $J = 2.0$ Hz, 5-OCH_2), 3.80 (m, 1H, NCH), 3.65 (s, 3H, OMe), 1.03 (d, 6H, $J = 6.4$ Hz, CMe_2) ppm; ^{13}C NMR: $\delta = 155.22$ (2-C=N), 149.59 (3-C=), 104.22 (4-CH=), 70.37 (5-OCH_2), 57.51 (OMe), 46.77 (NCH), 23.78 (C$\underline{Me_2}$) ppm; ^{15}N NMR: $\delta = -148.60$ ppm.

Dihydrofuran **3c**: IR (film): 1560, 1660 and 3070 cm^{-1}; ^1H NMR: $\delta = 6.75$ (d, 1H, $J = 5.7$ Hz, CH=), 6.16 (d, 1H, $J = 5.7$ Hz, CH=), 3.21 (t, 2H, $J = 7.2$ Hz, NCH_2), 1.53 (m, 2H, CH_2), 1.34 (s, 6H, CMe_2), 0.83 (t, 3H, $J = 7.6$ Hz, Me) ppm; ^{13}C NMR: $\delta = 166.37$ (2-C=N), 152.30 (3-C=), 123.10 (4-C=), 91.19 (O$\underline{C}Me_2$), 49.93 (NCH_2), 25.89 (C$\underline{Me_2}$), 24.56 (CH_2), 11.67 (Me); ^{15}N NMR: $\delta = -181.86$ ppm.

Dihydrofuran **3d**: ^1H NMR: $\delta = 7.10$ (d, 1H, $J = 5.6$ Hz, CH=), 6.28 (d, 1H, $J = 5.6$ Hz, CH=), 3.41 (t, 2H, $J = 7.3$ Hz, NCH_2), 1.65 (m, 2H, CH_2), 1.48 (s, 6H, CMe_2), 1.38 (m, 2H, CH_2), 0.91 (t, 3H, $J = 7.4$ Hz, Me) ppm; ^{13}C NMR: $\delta = (CH_2)$, 11.38 (Me) ppm.

18. The ^1H, ^{13}C and ^{15}N NMR spectra were recorded on a Bruker DPX 400 (^1H: 400.13; ^{13}C: 100.61; ^{15}N: 40.56 MHz) spectrometer. The solvent was $CDCl_3$ and the internal references were HMDS and $MeNO_2$ (for ^{15}N).
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