SYNTHESIS AND FLASH VACUUM PYROLYSIS OF ISOXAZOLO- AND ISOTHIAZOLO[5,4-*d*]PYRIMIDINES†

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Abstract - The multi-step synthesis of isothiazolo[5,4-*d*]pyrimidines (**1c,d**) and isoxazolo[5,4-d]pyrimidine (**1b**) is described. Flash vacuum pyrolysis of **1b** leads to phenyliminopropadienone, Ph-N=C=C=C=O, which was identified by Ar matrix infrared spectroscopy.

In recent publications we have demonstrated that isoxazolo[5,4-*d*]pyrimidin-4(5*H*)-ones are suitable precursors for the generation of a new class of heterocumulenes, the iminopropadienones, RN=C=C=C=O.[1] These cumulenes have been identified by ir[1a,c] and mass spectrometry,[1a,b] in addition to chemical trapping reactions.[1a] A particulary good precursor is the 3-phenyl derivative (**1a**), which under flash vacuum pyrolysis (FVP) conditions gives Ph-N=C=C=C=O (**3a**) in high yield.[1a] The mechanism involves initial breaking of the relatively weak N-O bond in **1a** and subsequent rearrangement to a transient pyrimidine (**2a**), which in turn fragments into Ph-NC_3O, HNCO, and HCN. Based on this mechanistic pathway it was anticipated that the corresponding sulfur derivative, Ph-N=C=C=C=S (**3b**), could be obtained by FVP of either isoxazolopyrimidine (**1b**), or isothiazolopyrimidines (**1c**) or (**1d**) (Scheme 1). In the present paper we detail the synthesis of the heterobicycles(**1b-d**),and report results of FVP reactions on these compounds.

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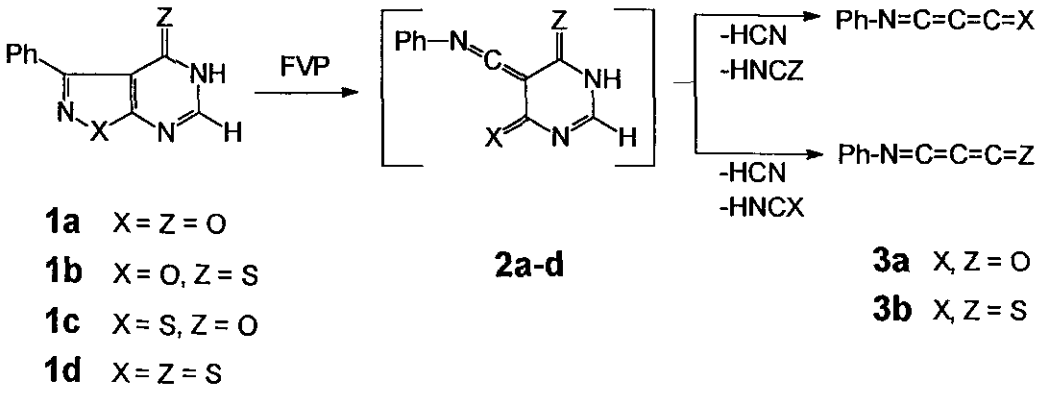
†This paper is dedicated to Professor Alan R. Katritzky on the occasion of his 65th birthday.



1a X = Z = O
1b X = O, Z = S
1c X = S, Z = O
1d X = Z = S

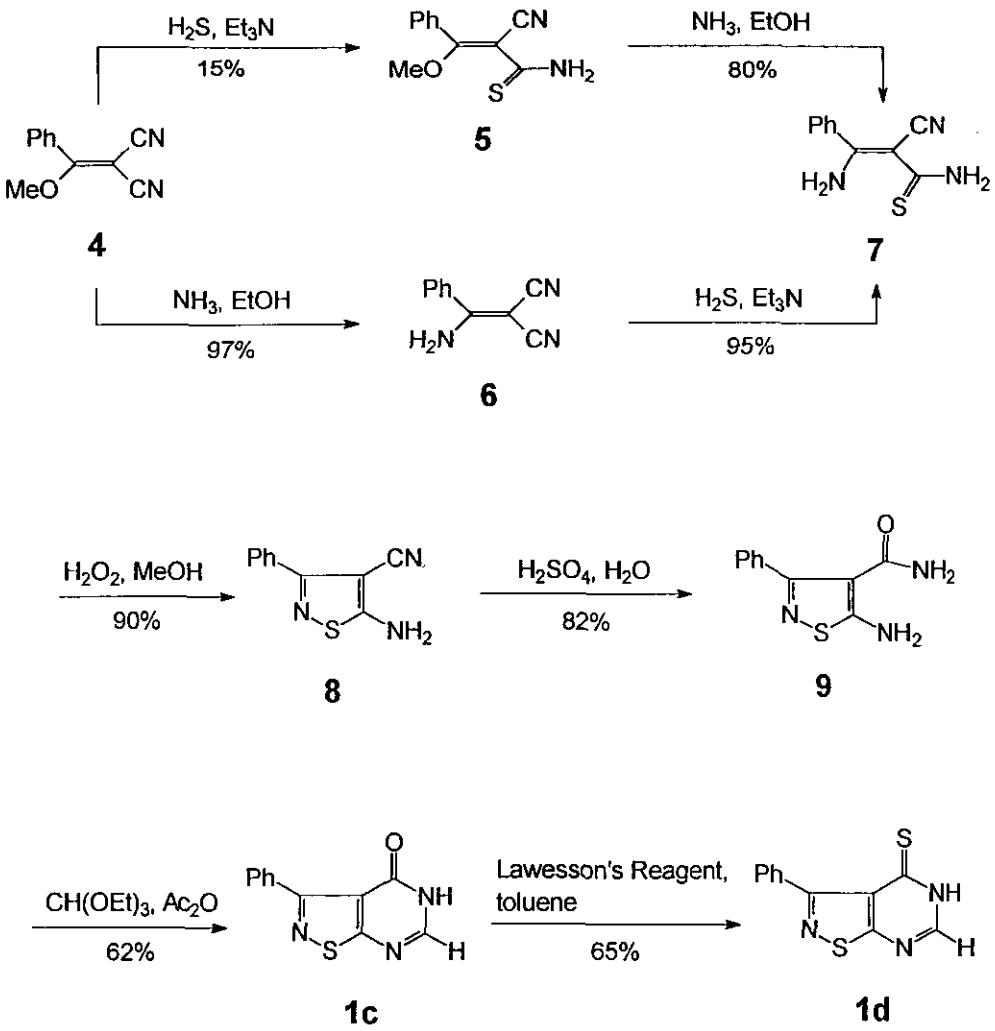
2a-d

3a X, Z = O
3b X, Z = S

Scheme 1

The synthesis of 3-phenylisothiazolo[5,4-*d*]pyrimidine-4(5H)-thione (**1d**) is outlined in Scheme 2. α–Methoxybenzylidenemalononitrile (**4**) was prepared by condensation of commercially avaiable trimethyl orthobenzoate and malononitrile in 65% yield.[2] An attempt to prepare the key intermediate (**7**) by thiolysis (**4** → **5**) and subsequent aminolysis (**5** → **7**) of nitrile(**5**)gave the desired thioacrylamide (**7**) in only 12% total yield, the major product in the reaction **4** → **5** being 2-cyanothioacetamide (60%). A detailed previous study on the analogous thiolysis of α-ethoxy*ethylidene*malononitrile showed that under identical reaction conditions the corresponding thiocrotonamide could be obtained in 72% yield, 2-cyanoacetamide being only a minor by-product.[3] We were not able to improve the yield of **5** in this reaction. However, we found that it is highly advantageous to reverse the order thiolysis/aminolysis in the preparation of **7**, thus reacting **4** first with ethanolic ammonia,[4] and then treating the resulting α-aminobenzylidenemalononitrile (**6**) with hydrogen sulfide/triethylamine. In this sequence (**4** → **6** → **7**) 3-amino-2-cyano-3-phenylthioacrylamide (**7**) was obtained from **4** in a total yield of 92%.

Oxidative cyclization of **7** employing hydrogen peroxide in methanol[5] provided 5-amino-3-phenylisothiazole-4-carbonitrile (**8**) in good yield. However, the hydrolysis of the nitrile group in **8** could not be achieved by reaction with hydrogen peroxide in concentrated aqueous ammonia, following a procedure used successfully to hydrolyse the 3-methylisothiazole analogue.[5] By substituting potassium hydroxide for ammonia[6] the corresponding amide (**9**) was formed in ca 20% yield. Eventually, we found that standard acid hydrolysis[7] with 96% sulfuric acid at 65-70 °C gave the desired amide (**9**) in 82% yield.



Scheme 2

Cyclization of **9** with a mixture of triethyl orthoformate and acetic anhydride provided isothiazolopyrimidinone (**1c**), which finally was converted to the thioketone (**1d**) by treatment with Lawesson's reagent in refluxing toluene. It is worthwhile to note that a direct thiolysis of the nitrile function in **8**, which would have led to a thioamide susceptible to direct conversion into **1d**,[8] was not possible. Instead, reductive ring-opening of the isothiazole ring by hydrogen sulfide occurred, and thioacrylamide (**7**) was isolated in 80% yield. Isoxazolopyrimidinethione (**1b**) was prepared in a manner analogous to **1d** by treatment of **1a** with Lawesson's reagent.

The FVP of isoxazolopyrimidine (**1b**) was carried out under the same conditions that were used to pyrolyze **1a**[1a,c] with isolation of the products in an Ar matrix at 18 K. The ir spectrum (Figure 1) clearly demonstrates the formation of Ph-N=C=C=C=O (2247vs cm^{-1})[1a,c] and HNCS (1981 cm^{-1}),[9] together with small amounts of unidentified by-products. Apparently, the fragmentation of the transient pyrimidine (**2b**) (X = O, Z = S) leads almost exclusively to $PhNC_3O$, HNCS and HCN, whereas $PhNC_3S$, HNCO and HCN are either not formed at all or at best only to a very minor extent (Scheme 1). The thiazolopyrimidines (**1c,d**) proved to be stable under the FVP conditions employed. Even at nominal FVP temperatures above 1000 °C no significant decomposition was observed. It appears that the N-S bond in **1c,d** is not as easily cleaved as the N-O bond in **1a,b**, thus preventing the formation of the key intermediates (**2**), required for the generation of Ph-N=C=C=C=S.

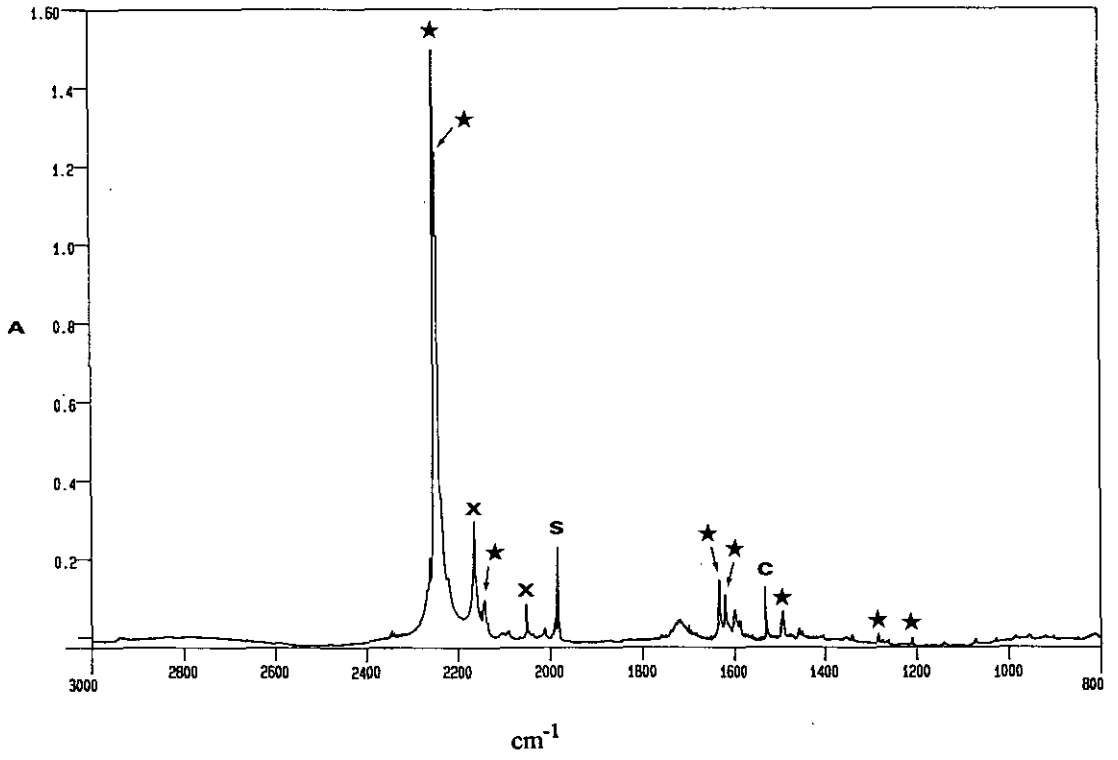


Figure 1: FTir spectrum (Ar matrix, 18 K) of the FVP of **1b** (900 °C, 5 x 10^{-5} mbar). Ph-NC_3O (★) appears at 2247vs, 2243vs, 2141w, 1661m, 1620m, 1490w, 1284w, and 1210w cm^{-1}. Other bands are due to HNCS (S, 1981 cm^{-1}), CS_2 (C, 1528 cm^{-1}), and unidentified by-products (X, 2163, 2049 cm^{-1}).

EXPERIMENTAL

Melting points are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 1720-X FTIR spectrophotometer. ^{1}H-Nmr (200 MHz) and ^{13}C-nmr (50 MHz) spectra were recorded on a Bruker ACF-200 nmr spectrometer. Mass spectra were obtained on a Kratos MS25RFA instrument. The progress of most reactions was monitored by thin layer chromatography (tlc) using silica gel 60 F_{254} plates. Flash vacuum pyrolysis reactions with Ar matrix isolation were performed as previously described.[10]

α-Methoxybenzylidenemalononitrile (4). Improved procedure:[2] A mixture of freshly distilled malononitrile (10.80 g, 0.165 mol), trimethyl orthobenzoate (29.55 g, 0.165 mol) and distilled acetic anhydride (60 ml, 0.6 mol) was stirred under dry nitrogen at 65 °C for 5 days. After unreacted starting materials and volatile products were distilled off at 0.1 mm Hg (bath temperature ca 100 °C), the oily residue was treated with hexane whereupon crystallization occurred. Recrystallization from ethanol gave 19.70 g (65%) of pure **4** as colorless crystals, mp 94-96 °C (lit.,[2] 94 °C).

2-Cyano-3-methoxy-3-phenylthioacrylamide (5). Through a stirred solution of **4** (5.52 g, 0.03 mol) in dry benzene (40 ml) containing 3 drops of triethylamine as catalyst was passed a slow stream of anhydrous hydrogen sulfide. After 3 h the precipitated solid was collected by filtration and the filtrate was treated again with hydrogen sulfide. This procedure was repeated several times, until no more starting material could be detected by tlc. The total amount of solid amounted to 3.0 g. Recrystallization of this material from ethanol provided 0.96 g (15%) of pure **5** as yellow needles, mp 230 °C; ir (KBr) 3375, 3265, 3162, 2224, 1622, 1553; ^{1}H-nmr (DMSO-d_6) 3.61 (s, 3 H, OMe), 7.55 (s, 5 H, Ph); ^{13}C-nmr (DMSO-d_6) 60.1, 98.8, 117.8, 128.6, 128.9, 130.4, 131.3, 170.9, 190.2; ms (m/z) 218 (M^+, 11), 184 (37), 165 (18), 127 (20), 105 (100), 77 (58). Anal. Calcd for $C_{11}H_{10}N_2OS$: C, 60.53; H, 4.62; N, 12.83. Found: C, 60.91; H, 4.89; N, 12.53. Evaporation of the ethanolic filtrate left crude 2-cyanothioacetamide which could be recrystallized from ethanol to give 1.80 g (60%) of pure 2-cyanothioacetamide, mp 119 °C (lit.,[3] 116-117 °C). The original bright yellow benzene mother liquor contained essentially pure (gc-ms) thiobenzoic acid, *O*-methyl ester.

α-Aminobenzylidenemalononitrile (6).[4] To a well stirred solution of **4** (12.0 g, 0.065 mol) in ethanol (1000 ml), saturated ethanolic ammonia (60 ml) was added. After stirring for 15 min at room temperature the solvent was evaporated to leave 10.70 g (97%) of pure **6**, mp 178 °C (lit.,[4] 180 °C).

3-Amino-2-cyano-3-phenylthioacrylamide (7). a) From **5**: To a stirred suspension of **5** (660 mg, 3 mmol) in ethanol (150 ml) saturated ethanolic ammonia (10 ml) was added. After stirring for 3 h at room temperature, ethanol was removed under vacuum and the remaining solid was digested with ether to give 500 mg (80%) of **7**. An analytical sample was prepared by recrystallization from ethanol, mp 200-204 °C.
b) From **6**: A slow stream of hydrogen sulfide was passed through a solution of **6** (5.07 g, 0.03 mol) and triethylamine (3.03 g, 0.03 mol) in ethanol (500 ml) at 60 °C. After no starting material could be detected by tlc (*ca.* 3 h) the solution was evaporated and the resulting solid digested with ether to leave 5.80 g (95%) of **7**, mp 200-204 °C.
c) From **8**: A slow stream of hydrogen sulfide was passed through s solution of **8** (250 mg, 1.24 mmol) and triethylamine (125 mg, 1.24 mmol) in dry benzene (100 ml). After no starting material could be detected by tlc (*ca.* 3-4 h) the solution was evaporated and the crude product purified by column chromatography (silica gel 60, $CHCl_3$) to give 200 mg (ca 80%) of pure **7**, mp 200-204 °C; identical in all respects with samples prepared under a) and b). Ir (KBr) 3372, 3288, 3200, 3062, 2192, 1617; ^{1}H-nmr (DMSO-d_6) 7.55 (s, 5 H, Ar), 9.13, 8.84, 7.93, 6.95 (4 s, 4 H, 2 NH_2); ^{13}C-nmr (DMSO-d_6) 78.5, 119.3, 127.9, 128.5, 130.8, 135.9, 169.3, 190.7; ms (m/z) 203 (M^+, 13), 169 (100), 142 (11). Anal. Calcd for $C_{10}H_9N_3S$: C, 59.09; H, 4.46; N, 20.67. Found: C, 59.09; H, 4.63; N, 20.34.

5-Amino-3-phenylisothiazole-4-carbonitrile (8). To a solution of **7** (6.10 g, 0.03 mol) in methanol (250 ml) hydrogen peroxide (30% solution, 6.0 ml, 0.06 mol) was slowly added with stirring. After stirring overnight the mixture was filtered, and evaporated to dryness. Water was removed in high vacuum to leave 5.40 g (90%) of pure isothiazol (**8**). An analytical sample was prepared by recrystallization from toluene or ethanol, mp 186-190 °C; ir (KBr) 3356, 3313, 3207, 2218, 1643, 1540; ^{1}H-nmr (DMSO-d_6) 7.47-7.51 (m, 3 H, Ar-H), 7.80-7.85 (m, 2 H, Ar-H), 8.15 (s, 2 H, NH_2); ^{13}C-nmr (DMSO-d_6) 84.3, 115.2, 127.1, 128.7, 129.9, 133.7, 164.5, 181.0; ms (m/z) 201 (M^+, 100), 174 (21), 103 (93), 77 (26), 76 (34), 66 (26). Anal. Calcd for $C_{10}H_7N_3S$: C, 59.68; H, 3.51; N, 20.88. Found: C, 60.00; H, 3.52; N, 20.99.

5-Amino-3-phenylisothiazole-4-carboxamide (9). Nitrile (**8**) (4.02 g, 0.02 mol) was dissolved in 96% sulfuric acid (25 ml) and was stirred for 2 h at 65-70 °C. After cooling, the reaction mixture was poured onto 300 ml of ice-water and filtered. The clear solution was made slightly alkaline by careful addition of concentrated aqueous ammonia (with ice-cooling). The precipitate so formed was filtered, washed with water, dried, and recrystallized from benzene to leave 3.60 g (82%) of pure amide (**9**), mp 180-182 °C; ir (KBr) 3462, 3395, 3260, 3160, 1648, 1576; ^{1}H-nmr (DMSO-d_6) 5.95 (s, 2 H, NH_2), 7.21 (s, 2 H, NH_2), 7.42-7.54 (m, 5 H, Ph); ^{13}C-nmr (DMSO-d_6) 108.6, 128.3, 128.4, 128.9, 136.4, 165.1, 166.3, 176.3; ms (m/z) 219 (M^+, 69), 202 (74), 186 (18), 144 (17), 135 (51), 104 (42), 103 (100), 77 (32), 76 (35), 66 (18), 51 (24), 50 (19). Anal. Calcd for $C_{10}H_9N_3OS$: C, 54.78; H, 4.14; N, 19.16. Found: C, 55.15; H, 4.18; N, 19.12.

3-Phenylisothiazolo[5,4-*d*]pyrimidin-4(5*H*)-one (1c). A mixture of amide (**9**) (2.19 g, 0.01 mol), trimethyl orthoformate (7 ml, 0.064 mol) and acetic anhydride (7 ml, 0.07 mol) was heated in an open flask at 130 °C (bath temperature) for 1 h, allowing volatile reaction products to distill off. After cooling the reaction mixture to 0 °C for 2 h the precipitated solid was filtered, washed with ethanol, and then recrystallized from ethanol to give 1.42 g (62%) of **1c**, mp 210 °C; ir (KBr) 3057, 1674, 1583; ^{1}H-nmr (DMSO-d_6) 7.50 (s, 3 H, Ar-H), 7.94 (s, 2 H, Ar-H), 8.36 (s, 1 H, H-6); ^{13}C-nmr (DMSO-d_6) 118.5, 127.7, 129.4, 129.5, 134.7, 148.9, 157.2, 165.5, 181.2; ms (m/z) 229 (M^+, 100), 228 (40), 135 (14), 126 (31), 77 (13). Anal. Calcd for $C_{11}H_7N_3OS$: C, 57.63; H, 3.08; N, 18.33. Found: C, 57.61; H, 3.11; N, 18.38.

3-Phenylisothiazolo[5,4-*d*]pyrimidine-4(5*H*)-thione (1d). A solution of **1c** (458 mg, 2 mmol) and Lawesson's reagent (485 mg, 1.2 mmol) in dry toluene (60 ml) was refluxed under nitrogen for 4 h. After cooling to 0 °C for 2 h the crude reaction product was filtered and purified by column chromatography (silica gel 60, CH_2Cl_2/MeOH : 30/1) to give 320 mg (65%) of pure **1d** as yellow needles, mp 208-210 °C; ir (KBr) 3133, 2965, 1576, 1537; ^{1}H-nmr (DMSO-d_6) 7.38-7.56 (m, 5 H, Ph), 8.32 (s, 1 H, H-6); ^{13}C-nmr (DMSO-d_6) 127.2, 127.3, 129.0, 129.8, 135.9, 146.9, 167.7, 176.5, 180.0; ms (m/z) 245 (M^+, 60), 244 (100), 77 (8). Anal. Calcd for $C_{11}H_7N_3S_2$: C, 53.85; H, 2.88; N, 17.13. Found: C, 53.99; H, 3.25; N, 16.83.

3-Phenylisoxazolo[5,4-*d*]pyrimidine-4(5*H*)-thione (1b). A solution of **1a**[7] (426 mg, 2 mmol) and Lawesson's reagent (485 mg, 1.2 mmol) in dry toluene (60 ml) was refluxed under nitrogen for 5 h. After evaporation of the solvent, the crude reaction mixture was purified by column chromatography (silica gel 60, CH_2Cl_2/MeOH : 30/1) to give 233 mg (51%) of **1b** as pale yellow crystals, mp 166-170 °C; ir (KBr) 3117, 2997, 2922, 2861, 1597, 1567; ^{1}H-nmr (DMSO-d_6) 7.48-7.55 (m, 3 H, Ar-H), 7.90-7.96 (m, 2 H, Ar-H), 8.11 (s, 1 H, H-6); ^{13}C-nmr (DMSO-d_6) 111.3, 126.3, 127.4, 129.5, 130.0, 151.0, 160.6, 170.7, 179.2; ms (m/z) 229 (M^+, 100), 228 (30), 159 (39), 126 (22), 77 (22). Anal. Calcd for $C_{11}H_7N_3OS$: C, 57.63; H, 3.08; N, 18.33. Found: C, 57.37; H, 3.06; N, 18.33.

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