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Some Transformations of 1-(1,2,3,4-Tetrahydronaphthylidene)-Malononitrile or Cyanoacetate**

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Summary. Syntheses of 11-amino-5,6-dihydronaphtho[1′,2′:4,5]thieno[2,3-d]pyrimidine (**8**) and its 10-oxide **7** from 2-amino-1-cyano-4,5-dihydronaphtho[2,1-b]thiophene and its derivatives are described. Several open chain tetrahydronaphthylidene derivatives and a substituted pyrimidine derivative **9** were also prepared.

Keywords. Tetracyclic pyrimidines and naphthothiophene derivatives.

Über einige Umwandlungen von 1-(1,2,3,4-Tetrahydronaphthyliden)malononitril und Cyanessigsäureester

Zusammenfassung. Synthesen von 11-Amino-5,6-dihydronaphtho[1′,2′:4,5]thieno[2,3-d]pyrimidin (**8**) und seinem 10-Oxid **7** aus 2-Amino-1-Cyano-4,5-dihydronaphtho[2,1-b]thiophen und Derivaten werden beschrieben. Einige offenkettige Tetrahydronaphthyliden Derivate und ein substituiertes Pyrimidin **9** wurden dargestellt.

Introduction

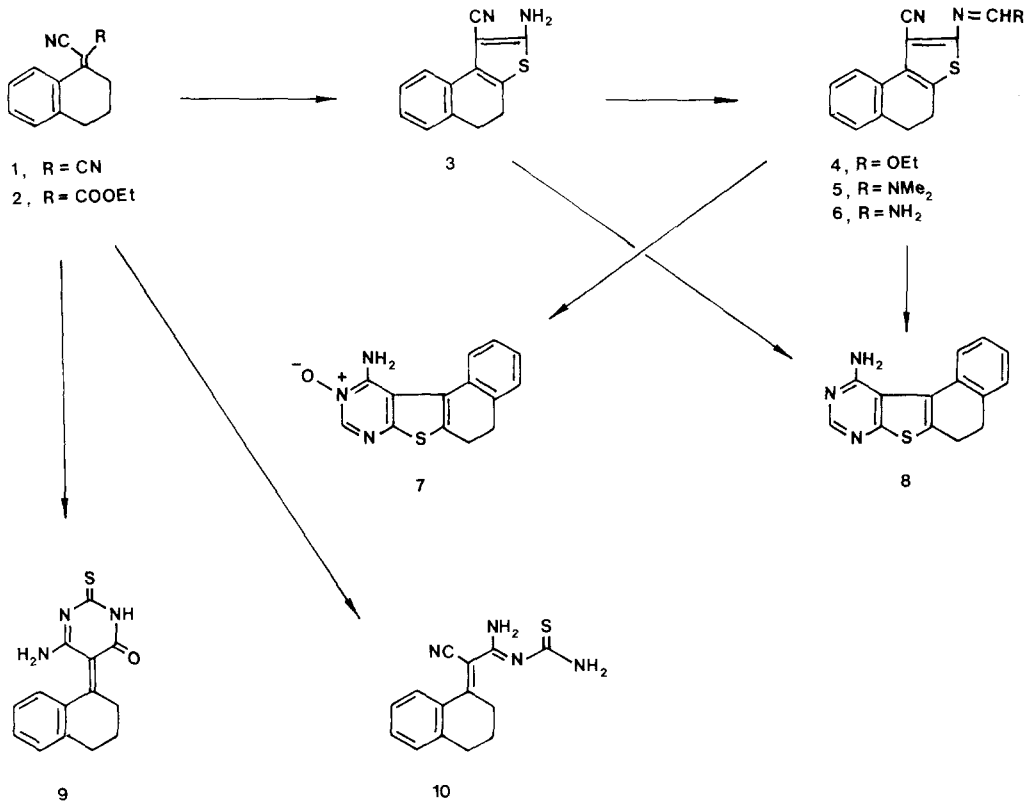
As a continuation of our studies on the reactivity of heterocyclic cyano compounds [1] we were interested in the syntheses of condensed pyrimidines from 1-(1,2,3,4-tetrahydronaphthylidene)malononitrile or the related ylidenecyanoacetate. So far, only few compounds of the naphtho[1′,2′:4,5]thieno[2,3-d]pyrimidine and the isomeric naphtho[2′,1′:4,5]thieno[2,3-d]pyrimidine ring systems are known [2–4].

Results and Discussion

In addition to the chemical synthesis [2] the naphtho[2,1-b]thiophene ring was synthesized also by photooxidative cyclization of naphthylthienylethylene [5]. We have found that 1-(1,2,3,4-tetrahydronaphthylidene)malononitrile (**1**), when heated

** Dedicated to Professor Dr. K. Gewald on the occasion of his 60th birthday

in the presence of sulfur afforded the corresponding thiophene derivative **3**. This method proved to be advantageous over the synthesis based on the Gewald method of thiophene derivatives, the reaction taking place at higher temperature and in the presence of a base [2, 6].



Several attempts to transform the cyano group of **3** into an amidoxime group were unsuccessful whereas the 2-amino functional group of **3** could be modified when reacting with triethyl orthoformate to give the corresponding ethoxymethylene derivative **4**, or with N,N-dimethylformamide dimethyl acetal to give the amidine **5**. Moreover, the ethoxymethylene compound reacted with an ethanolic solution of ammonia to give the amidine **6**. All aforementioned compounds served as starting material for the synthesis of an annelated pyrimidine ring. The tetracyclic N-oxide **7** was prepared either from compounds **4** or **5** and hydroxylamine. The N-oxide **7** could be deoxygenated with phosphorus trichloride to give the tetracyclic derivative **8**. This is otherwise accessible either from the amine **3** and formamide in high yield or from the amidine **6** in low yield and accompanied with several by-products as judged from tlc examination of the reaction mixture.

Several attempts to transform the ylidenecyanoacetate group of **2** into a pyrimidine ring were not successful and with thiourea, for example, the corresponding open chain compound **10** was formed. If, however, an equivalent amount of sodium methylate was used and after prolonged heating and leaving the reaction mixture at room temperature, the pyrimidine derivative **9** could be prepared in reasonable yield.

Aromatization of the tetrahydronaphthalene ring of **1** or **2** appeared unexpectedly difficult. Dehydrogenation with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (*DDQ*) failed, whereas dehydrogenation in the presence of palladized carbon at elevated temperature afforded 1-naphthylcyanoacetate or 1-naphthylmalonodinitrile in very low yield. It appears, that these compounds are prepared advantageously by palladium-catalyzed coupling reaction between the corresponding aryl halide and malonodinitrile [7] or alkyl cyanoacetate [8].

Finally, it should be mentioned that the starting ylidene compounds **1** and **2** are not stable in the presence of such nucleophiles as hydrazine or hydroxylamine since they are converted into the corresponding hydrazone or oxime of 1-tetralone.

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Experimental

Melting points were taken on a Kofler micro hot stage. ^{1}H NMR spectra were obtained on JEOL-C60-HL or JEOL JNM FX 90Q spectrometers with *TMS* as internal standard. IR spectra were obtained on a Perkin-Elmer 727 B spectrometer. Elemental analyses for C, H, and N were performed on a Perkin-Elmer CHN Analyzer 240 C.

1-Tetralone was converted into its ylidene derivative **1** with malonodinitrile in 88% yield [9, 10] and ethyl 1-(1,2,3,4-tetrahydronaphthylidene)cyanoacetate was prepared according to the published procedure [11] in 58% yield, b.p. 170–174°C/1 mm Hg (Ref. [11] gives b.p. 164–168°C/0.3 mm Hg).

2-Amino-1-cyano-4,5-dihydronaphtho[2,1-b]thiophene (**3**)

A mixture of 1.0 g (5.15 mmol) of **1** and 1.65 g of sulfur (5.15 mmol) was heated on an oil bath at 150–160°C for 2.5 h. Upon cooling and addition of few ml of ethanol the mixture crystallized. The reaction mixture was filtered, the solid residue (0.85 g) was heated in 15 ml of ethanol and after filtration, the filtrate was evaporated to dryness. The obtained product was crystallized from ethanol with addition of charcoal (0.56 g, 48%). M.p. 165–168°C (Ref. [2] gives m.p. 165–168°C). IR: 2210 cm^{-1} (CN). ^{1}H NMR ($CDCl_3$) δ: 2.5–3.1 (m, 4 H_2 and 5 H_2), 4.52 (s, NH_2), 7.12–8.08 (m, H6, H7, H8, H9). Elemental analysis calculated for $C_{13}H_{10}N_2S$: C 69.01, H 4.46, N 12.38. Found: C 69.49, H 4.51, N 11.99.

The amino compound **3** was transformed with formic acid into the formylamino derivative in 71% yield. M.p. 305–308°C. IR: 2200 cm^{-1} (CN). Elemental analysis calculated for $C_{14}H_{10}N_2OS$: C 66.13, H 3.96, N 11.02. Found: C 66.12, H 3.98, N 11.09.

1-Cyano-2-ethoxymethyleneamino-4,5-dihydronaphtho(2,1-b)thiophene (**4**)

The above compound **3** (80 mg, 0.28 mmol) and triethyl orthoformate (2 ml) were heated under reflux for 2 h. The reaction mixture was evaporated, the residue was treated with cyclohexane and cooled. The precipitated solid was filtered and crystallized from absolute ethanol (45 mg, 45%). M.p. 120–125°C. IR: 2235 cm^{-1} (CN). Elemental analysis calculated for $C_{16}H_{14}N_2OS$: C 68.07, H 5.00, N 9.92. Found: C 67.97, H 4.98, N 9.89.

1-Cyano-2(N,N-dimethylaminomethyleneamino)-4,5-dihydronaphtho[2,1-b]thiophene (**5**)

A mixture of 0.295 g (1.05 mmol) of compound **3** and 3 ml of N,N-dimethylformamide dimethyl acetal was heated under reflux for 2 h. Excess of the reagent was distilled in vacuo and the solid

residue was treated with some methanol and filtered (0.312 g, 83%). The compound is enough pure to be used for further transformations. For analysis it was crystallized from a mixture of toluene and chloroform, m.p. 206–208°C. IR: 2225 cm^{-1}. ^1H NMR (*DMSO-d_6*) δ: 2.81 (s, *Me*), 3.03 (s, *Me*), 2.7–3.0 (m, 4 H_2 and 5 H_2), 6.95–8.0 (m, CH, H6, H7, H8, H9). Elemental analysis calculated for $C_{16}H_{15}N_3S$: C 68.31, H 5.38, N 14.94. Found: C 68.58, H 5.39, N 15.05.

2-Aminomethyleneamino-4,5-dihydronaphtho(2,1-b)thiophene (**6**)

To 2 ml of an ice-cold saturated solution of ammonia in ethanol 45 mg (0.16 mmol) of the ethoxymethylene compound **4** was added, the mixture was stirred for 15 min and left for 1 h at room temperature. The product was filtered, washed with some ethanol (28 mg, 70%), m.p. 200–210°C. IR: 2225 cm^{-1} (CN). ^1H NMR (*DMSO-d_6*) δ: 2.65–2.95 (m, 4 H_2 and 5 H_2), 7.05–8.0 (m, CH and H6, H7, H8, H9). Elemental analysis calculated for $C_{14}H_{11}N_3S$: C 66.39, H 4.38, N 16.59. Found: C 66.52, H 4.39, N 16.48.

11-Amino-5,6-dihydronaphtho(1',2':4,5)thieno[2,3-d]pyrimidine-10-oxide (**7**)

(a) A mixture of 50 mg (0.18 mmol) of compound **4**, 30 mg of hydroxylammonium chloride (0.43 mmol) and 5 ml of methanol was heated under reflux for 8 h. After standing overnight at room temperature, 3 ml of water were added and the precipitate was filtered (0.23 mg, 46%). M.p. 221–224°C. In some experiments the yield was higher, but the product contained some starting material and the amino compound **3**. These impurities could be removed by column chromatography on silica and the product had m.p. 245–246°C. IR: 1205 cm^{-1} (N–O). ^1H NMR (*DMSO-d_6*) δ: 2.75–3.0 (m, 5 H_2 and 6 H_2), 7.0–8.1 (m, H1, H2, H3, H4), 8.74 (s, H9). Elemental analysis calculated for $C_{14}H_{11}N_3OS$: C 62.45, H 4.12, N 15.61. Found: C 62.61, H 4.37, N 15.80.

(b) A mixture of 0.125 g (0.44 mmol) of the ethoxymethylene compound **4** and 0.2 g of hydroxylamine (5 mmol) (prepared from its hydrochloride) in 2 ml of methanol was stirred at room temperature for 5 days. After addition of water the precipitate was filtered (90 mg, 80%). M.p. 220–225°C, and mixed m.p. with the compound obtained as described under (a) was undepressed.

11-Amino-5,6-dihydronaphtho(1',2':4,5)thieno[2,3-d]pyrimidine (**8**)

(a) A mixture of 95 mg (0.42 mmol) of the amino compound **3** and 2 ml of formamide was heated under reflux for 2 h and thereafter poured into 20 ml of water. The solid material was filtered, washed with water and dried in vacuo (100 mg, 94%). For analysis the compound was crystallized from a mixture of N,N-dimethylformamide and ethanol. M.p. 196–198°C. ^1H NMR ($CDCl_3$) δ: 2.95–2.93 (m, 5 H_2 and 6 H_2), 7.84–7.19 (m, H1, H2, H3 and H4), 8.39 (s, H9). MS (*m/e*): 253 (M^+). Elemental analysis calculated for $C_{14}H_{11}N_3S$: C 66.39, H 4.38, N 16.59. Found: C 66.34, H 4.52, N 16.40.

(b) A mixture of 0.1 g (0.4 mmol) of the N-oxide **7** in 5 ml of chloroform and 1 ml of phosphorus trichloride was stirred for 3 h and heated under reflux. The chloroform solution was washed twice with aqueous sodium bicarbonate and water, dried and evaporated to dryness. The residue was found to be identical with the compound obtained as described above under (a). Yield 73 mg (78%).

(c) 0.35 g (1.39 mmol) of compound **6** was dissolved in N,N-dimethylformamide and treated with sodium methylate according to the procedure described for an isomeric system [3]. The resulting product (0.31 g) was heated in N,N-dimethylformamide, filtered and the solution evaporated. The oily residue consisted of a mixture of three compounds as revealed by TLC and among them the amino compound **8** could be identified.

6-Amino-4-oxo-5-(1',2',3',4'-tetrahydronaphthylidene-1')-2-thioxo-2,3,4,5-tetrahydropyrimidine (**9**)

To a solution of sodium ethylate, prepared from 79 mg of sodium and 5 ml of absolute ethanol, 0.83 g (3.4 mmol) of compound **2** and 0.261 g (3.4 mmol) of thiourea were added and the mixture was heated

under reflux for 2.5 h. After standing at room temperature for two days the mixture was again heated under reflux for 2.5 h. Upon cooling the solid material was filtered (0.8 g), dissolved in water and acidified with 5% hydrochloric acid. The obtained solid material was filtered, washed with water, dried and crystallized from ethanol (0.41 g, 45%). M.p. 130–135°C. ^{1}H NMR (*DMSO-d_6*) δ: 1.65–2.20 (m) and 2.6–2.95 (m, 2′H_2, 3′H_2, 4′H_2), 7.05–7.68 (m, $H_{5'}$, $H_{6'}$, $H_{7'}$, $H_{8'}$), 10.23 and 11.70 (s, NH). Elemental analysis calculated for $C_{14}H_{13}N_3OS$: C 61.98, H 4.83, N 15.49. Found: C 61.89, H 5.06, N 15.36.

Reaction Between Compound **1** *and Thiourea*

A mixture of ethanolic sodium ethoxide, prepared from 0.237 g of sodium and 15 ml of absolute ethanol, 1 g (5.15 mmol) of compound **1** and 0.392 g (5.15 mmol) of thiourea was heated under reflux for 5.5 h and left overnight at room temperature in a closed flask. The reaction mixture was filtered and evaporated to dryness, water was added and the resulting solution was extracted with 3 portions of 30 ml of diethyl ether. The aqueous solution was neutralized with 5% hydrochloric acid to *pH* 7 and extracted with 3 portions of 30 ml of diethyl ether. The combined extracts were washed with water, dried over sodium sulfate and after filtration and evaporation of the solvent the residue was crystallized from a mixture of cyclohexane and acetone (0.1 g, 16%). M.p. of compound **10**: 247–248°C. IR: 2195 cm^{-1} (CN). ^{1}H NMR ($CDCl_3$) (*DMSO-d_6*) δ: 1.93–2.54 (m, 2H_2, 3H_2, 4H_2), 6.95–7.30 (m, H_5, H_6, H_7, H_8), 5.91 and 9.44 (s, NH_2 groups). Elemental analysis calculated for $C_{14}H_{14}N_4S$: C 62.21, H 5.22, N 20.73. Found: C 62.20, H 5.26, N 20.45.

References

[1] For pertinent references see review article: Tišler M. (1989) Revs. Heteroatom Chem. **2**: 211
[2] Elslager E. F., Jacob P., Werbel L. M. (1972) J. Heterocycl. Chem. **9**: 775
[3] Taylor E. C., Berger J. G. (1967) J. Org. Chem. **32**: 2376
[4] Rosowsky A., Chen K. K. N., Lin M. (1973) J. Med. Chem. **16**: 191
[5] Das B. P., Campbell J. A., Samples F. B., Wallace R. A., Whisenant L. K., Woodard R. W., Boykin D. W. (1972) J. Med. Chem. **15**: 370
[6] Gewald K., Schinke E., Böttcher H. (1966) Ber. Dtsch. Chem. Ges. **99**: 94
[7] Uno M., Seto K., Takahashi S. (1984) J. Chem. Soc., Chem. Commun: 932
[8] Uno M., Seto K., Ueda W., Masuda M., Takahashi S. (1985) Synthesis: 506
[9] Cope A. C., Hofmann C. M., Wyckoff C., Hardenbergh E. (1941) J. Amer. Chem. Soc. **63**: 3452
[10] Campaigne, Bulbenko T. (1962) J. Org. Chem. **27**: 4224
[11] Crooks P. A., Szyndler R. (1980) J. Med. Chem. **23**: 679

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