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Rearrangement Studies on 1-Tetralylidenecyanothioacetamide: A Different Novel Synthetic Routes to Strong Fluorescent Phenanthridine and Phenanthrene Analogues

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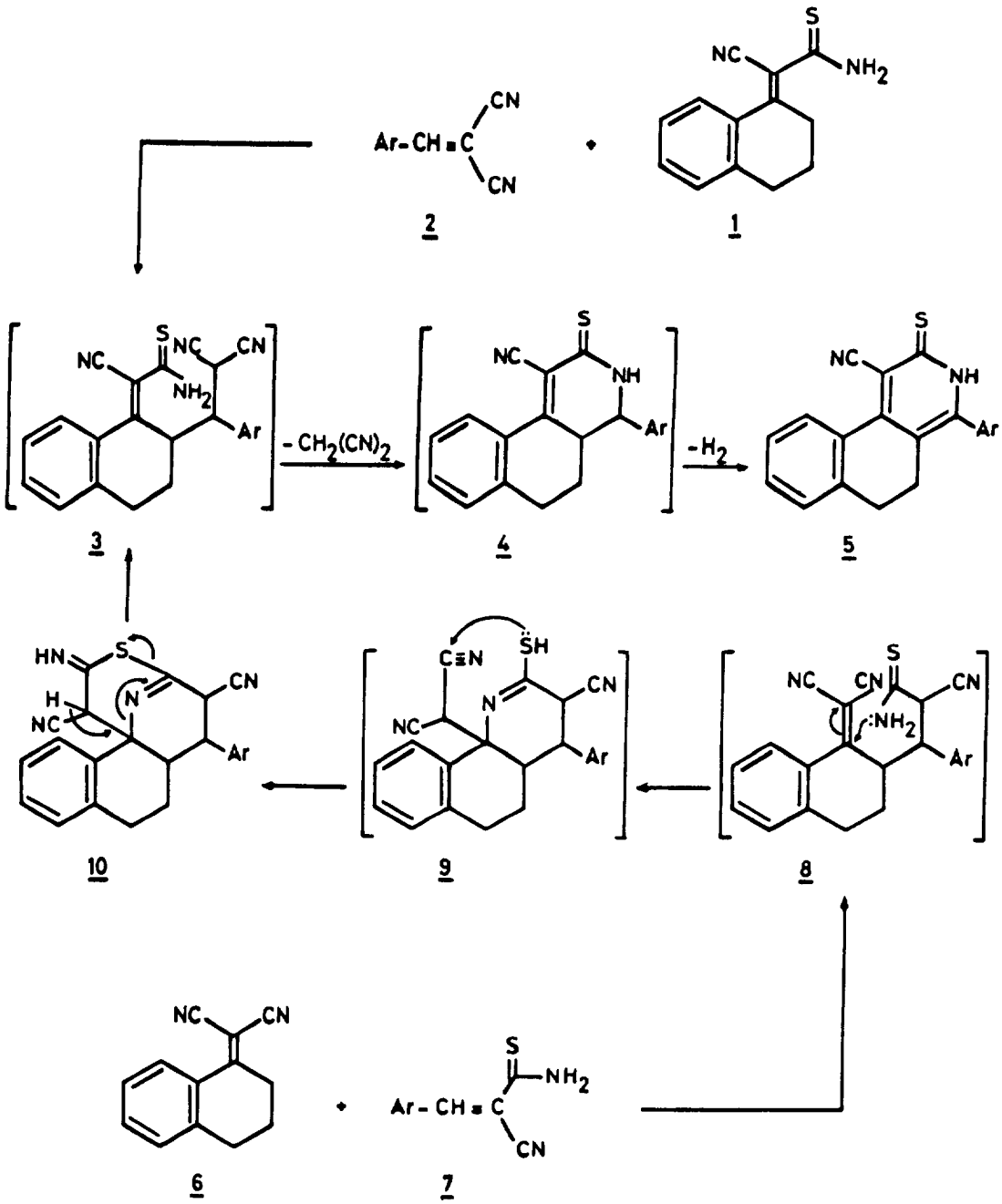
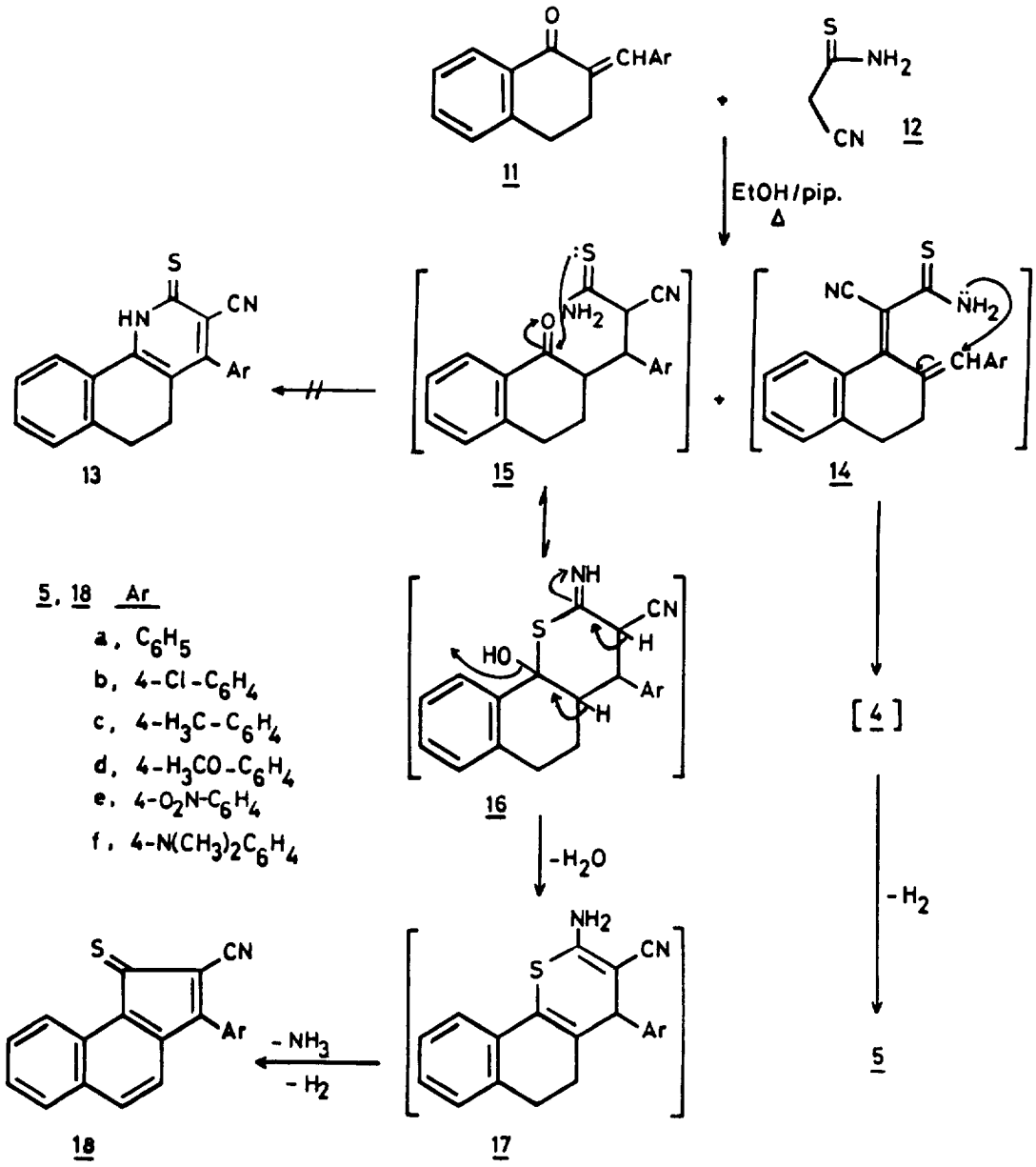
Abstract: A novel synthesis of strong fluorescent phenanthridine and phenanthrene analogues utilizing arylmethylenecyanothioacetamides and 1-tetralylidenemalononitrile or 1-tetralylidene-cyanothioacetamide and arylmethylenemalononitriles as starting components is described.

Continuing our interest in development of efficient and simple procedures for the synthesis of fused heterocyclic nitrogen compounds,[1,2] we have recently reported that arylmethylenecyanothioacetamides can be used for synthesis of pyridine-2(1H)-thiones via reaction with suitable active methylene reagents.[3,4] As a part of our development of new, simple, and efficient procedures for the synthesis of antimetabolites, we have recently reported that pyridine-2(1H)-thiones can be used as a building block units for synthesis of novel 3-deazapyrimidine nucleosides , thioguanine and folic acid analogues.[5-7] We report in this research the novel reaction of 1-tetralylidenemalononitrile with arylmethylenecyanothioacetamides, or 1-tetralylidenecyano-thioacetamide with arylmethylenemalononitriles.

Thus, it has been found that heating 1-tetralone with cyanothioacetamide and a catalytic amount of ammonium acetate-acetic acid in benzene for 3 h with azeotropic removal of water gave the corresponding 1-tetralylidenecyanothioacetamide **1** in good yield. The structure of compound **1** was established on the basis of its elemental analysis and spectral data (MS, IR, ^{1}H NMR). Compound **1** reacted with arylmethylenemalononitriles **2** in refluxing ethanol containing catalytic amounts of piperidine for 3 h to give the unexpected phenanthridine analogues **5**. The structure of compounds **5** was established on the basis of their elemental analysis and spectral data (MS, IR, ^{1}H NMR). Thus, the mass spectrum of **5a** was compatible with the molecular formula $C_{20}H_{14}N_2S$ (M^+ 314), and ^{1}H NMR spectrum had signals at δ 2.61 (s, CH_2), 2.83 (s,CH_2), 7.21-7.68 (m, ArH) and 14.2(br, NH). The formation of **5** from **1** and **2** is assumed to proceed via addition of the active methylene group of **1** to the double bond of **2** to give the intermediate **3**. This Michael adduct then cyclizes via malononitrile elimination to give the intermediate dihydropyridine derivative **4** which


Ar-CH=C(CN)CN
2
1
3
- CH2(CN)2
4
-H2
5
10
9
8
6
7


11
12
EtOH/pip.
Δ
13
15
14
16
17
18
5
[4]
-H2O
-NH3
-H2
-H2
5, 18 Ar
a, C6H5
b, 4-Cl-C6H4
c, 4-H3C-C6H4
d, 4-H3CO-C6H4
e, 4-O2N-C6H4
f, 4-N(CH3)2C6H4

is oxidized under the reaction conditions to yield **5**. The unexpected course of the reaction between the arylmethylenemalononitriles **2** and **1** prompted us to investigate the reaction between the 1-tetralylidenemalononitrile and arylmethylenecyanothioacetamides **7** under the same conditions. The products **5** obtained were shown to be the same as those obtained from the reaction of **1** with **2** by their melting points and spectral data. The mechanism of the reaction of **6** and **7** is assumed to proceed through the formation of the initial Michael adduct **8** which leads to the intermediate **3** and hence to the final product **5** as produced by the reaction of **1** with **2**.

In order to establish the structure of **5** further, we studied the reaction of 2-arylidene-1-tetralone **11** with cyanothioacetamide **12** for synthesizing the other phenanthridine analogues **13**. Compound **13b** was previously prepared from the reaction of **7** with 1-tetralone.[8] Thus, it has been found that **11** reacts with **12** in boiling ethanol containing a catalytic amount of piperidine to give not the expected phenanthridine analogues **13**, but two other products, the first was formulated as the phenanthridine analogues **5** and the second as the carbocyclic nitriles **18**. The products **5** obtained from this reaction were shown to be the same as those obtained from the reaction of **1** and **2** by their melting points and spectral data (MS, IR, ^{1}H NMR). The mechanism for the formation of **5** from the reaction of **11** and **12** is assumed to proceed through the formation of the initial adducts **14**, which leads to intermediate **4** and these are oxidised under the reaction conditions to yield **5**. The mechanism for the formation of **18** from the reaction of **11** and **12** is assumed to proceed via addition of the active methylene group of **12** to the double bond of **11** to give the intermediate **15**. This Michael adduct then cyclizes via water elimination to form a 1,4-dihydrothiopyran species, which undergo ring contraction and elimination of ammonia, followed by oxidation to give the phenanthrene analogues **18**. The structure of **18** was established on the basis of their elemental analysis and spectral data (MS, IR, ^{1}H NMR). Thus, the mass spectrum of **18d** was compatible with the molecular formula $C_{21}H_{13}NSO$ (M^+ 327) and the ^{1}H NMR spectrum had signals at δ 6.66-8.21 (ArH).

Solutions of compounds **18** in a variety of organic solvents showed a very strong luminescence evoked by daylight. Compound **18f** has strong blue fluoresence evoked by the 370 nm wave length. In summary, these results indicate that although addition of 1-tetralylidenemalononitrile or 1-tetralylidenecyanothioacetamide to the double bond of arylmethylenecyanothioacetamides or arylmethylenemalononitriles, respectively, leads to Michael adduct intermediates. However, the nature of the end products depends on thermodynamic and kinetic factors. The phenanthrene analogues **18** reveals promosing as fluorescent markers for nerve cells.

EXPERIMENTAL

All melting points are uncorrected. IR were obtained (KBr disc) on a Pye unicam Spectra-1000 or on a Shimadzu IR instrument. ^{1}H NMR spectra were measured on a Varian 400 MHz spectrometer for solutions in $(CD_3)_2SO$ using $SiMe_4$ as internal standard. Mass spectra were recorded on a Varian MAT 112 spectrometer. Analytical data were obtained from the Microanalytical Data Centre at Cairo University.

1-tetralylidenecyanothioacetamide 1

To a mixture of dry benzene (200 ml), 1-tetralone (0.1 mol), ammonium acetate (4.0 g), and glacial acetic acid (12 ml) was added cyanothioacetamide (0.1 mol). The mixture was heated under reflux for 4 h in a Dean-Stark apparatus. Evaporation of most of benzene left a residue which was crystallized from dioxane.

Yield (40%); m.p. 246 °C; IR (KBr) ν 3450, 3400 (NH_2); ^1H NMR (DMSO) δ 2.48 (s, 2H, CH_2), 2.50 (s, 2H, CH_2), 2.51 (s, 2H, CH_2), 5.1 (s, br, 2H, NH_2), 5.70-5.82 (m, 4H, C_6H_4); (Calcd for $C_{13}H_{12}N_2S$: C, 68.4; H, 5.3; N, 12.3. Found: C, 68.0; H, 5.0; N, 12.1%).

7,8-Dihydrobenzo[f]isoquinoline-3(2H)-thiones 5a-f

To a mixture of **1** and **2a-f** or **6** and **7a-f** (0.01 mol) in ethanol (50 ml), piperidine (0.5 ml) was added. The mixture was heated under reflux for 3 h, and then set aside overnight. The resultant precipitate was filtered off and crystallized from the appropriate solvent.

5a: Yield (30%); m.p. 197 °C; IR (KBr) ν 3400, 3485 (NH), 2225 (CN); ^1H NMR (DMSO) δ 2.61 (s, 2H, CH_2), 2.83 (s, 2H, CH_2), 7.21-7.68 (m, 9H, C_6H_5, C_6H_4), 14.20 (s, br, 1H, NH); MS, m/e 314; (Calcd for $C_{20}H_{14}N_2S$: C, 76.4; H, 4.5; N, 8.9. Found: C, 76.2; H, 4.2; N, 8.7%).

5b: Yield (20%); m.p. 291-93 °C; IR (KBr) ν 3510, 3480 (NH), 2220 (CN); ^1H NMR (DMSO) δ 2.58 (s, 2H, CH_2), 2.77 (s, 2H, CH_2), 7.12-8.00 (m, 8H, 2 C_6H_5), 13.95 (s, br, 1H, NH); MS, m/e 348; (Calcd for $C_{20}H_{13}ClN_2S$: C, 68.9; H, 3.8; N, 8.0. Found: C, 68.6; H, 3.6; N, 8.0%).

5c: Yield (25%); m.p. 280 °C; IR (KBr) ν 3450, 3330 (NH), 2225 (CN); ^1H NMR (DMSO) δ 2.52 (s, 3H, CH_3), 2.61 (s, 2H, CH_2), 2.78 (s, 2H, CH_2), 7.09 (m, 8H, 2 C_6H_4), 14.1 (s, br, 1H, NH); MS, m/e 328; (Calcd for $C_{21}H_{16}N_2S$: C, 76.8; H, 4.9; N, 8.5. Found: C, 76.5; H, 5.1; N, 8.3%).

5d: Yield (25%); m.p. 249-49 °C; IR (KBr) ν 3440, 3400 (NH), 2218 (CN); ^1H NMR (DMSO) δ 2.58 (s, 2H, CH_2), 2.75 (s, 2H, CH_2), 3.85 (s, 3H, OCH_3), 7.11 (m, 8H, 2 C_6H_4), 14.15 (s, br, 1H, NH); MS, m/e 344; (Calcd for $C_{21}H_{16}N_2SO$: C, 73.2; H, 4.7; N, 8.1. Found: C, 73.0; H, 4.5; N, 8.0%).

5e: Yield (50%); m.p. 335-37 °C; IR (KBr) ν 3450, 3430 (NH), 2220 (CN); ^1H NMR (DMSO) δ 2.64 (s, 2H, CH_2), 2.77 (s, 2H, CH_2), 7.15 (m, 8H, C_6H_4), 14.0 (s, br, 1H, NH); MS, m/e 359; (Calcd for $C_{20}H_{13}N_3SO_2$: C, 66.8; H, 3.6; N, 11.9. Found: C, 66.5; H, 4.0; N, 11.6%).

5f: Yield (40%); m.p. 259-60 °C; IR (KBr) ν 3400, 2280 (NH), 2225 (CN); MS, m/e 357; (Calcd for $C_{22}H_{19}N_3S$: C, 73.9; H, 5.4; N, 11.8. Found: C, 73.6; H, 5.5; N, 11.5%).

8-Cyano-9-thioxo-cyclopent-7-eno[h]naphthalene 18a-f

A solution of 2-arylmethylene-1-tetralone **11** (0.01 mol) and cyanothioacetamide **12** (0.01 mol) in ethanol (30 ml) and a few drops of piperidine was refluxed for 3 h, cooled, the precipitate was filtered off and crystallized from the appropriate solvent. The first fraction comprises compounds **5a-f**. Two ml of water were then added to the filtrate, the formed solid was filtered off and crystallized from the appropriate solvent to yield compounds **18a-f**.

18a: Yield (20%); m.p. 168 °C, IR (KBr) ν 2220 (CN); ^1H NMR (DMSO) δ 6.66 (s, 2H, C_6H_2), 7.12-8.07 (m, 9H, C_6H_5 and C_6H_4); MS, m/e 297; (Calcd for $C_{20}H_{11}NS$: C, 80.8; H, 3.7; N, 4.7. Found: C, 80.5; H, 4.0; N, 4.4%).

18b: Yield (35%); m.p. 210 °C; IR (KBr) ν 2218 (CN); ^1H NMR (DMSO) δ 6.85 (s, 2H, C_6H_2), 7.25-8.32 (m, 8H, 2 C_6H_4); MS, m/e 331; (Calcd for $C_{20}H_{10}ClNS$: C, 72.5; H, 3.0; N, 4.2. Found: C, 72.5; H, 3.4; N, 4.0%).

18c: Yield (15%); m.p. 170 °C; IR (KBr) ν 2225 (CN); ^1H NMR (DMSO) δ 2.45 (s, 3H, CH_3), 7.28-8.27 (m, 8H, 2 C_6H_4 and C_6H_2); (Calcd for $C_{21}H_{13}NS$: C, 81.0; H, 4.23; N, 4.5. Found: C, 81.2; H, 4.0; N, 4.2%).

18d: Yield (15%); m.p. 174 °C; IR (KBr) ν 2230 (CN); ^{1}H NMR (DMSO) δ 3.82 (s, 3H, OCH_3), 6.66 (s, 2H, C_6H_2), 6.96-8.21 (m, 8H, 2 C_6H_4); MS, m/e 327; (Calcd for $C_{21}H_{13}NSO$: C, 77.1; H, 4.0; N, 4.3. Found: C, 76.8; H, 4.4; N, 8.0%).

18e: Yield (15%), m.p. 238-40 °C; IR (KBr) ν 2220 (CN); ^{1}H NMR (DMSO) δ 6.95 (s, 2H, C_6H_2), 7.36-8.35 (m, 8H, 2 C_6H_4); MS, m/e 342; (Calcd for $C_{20}H_{10}N_2SO_2$: C, 70.2; H, 2.9; N, 8.2. Found: C, 70.0; H, 3.2; N, 8.0%).

18f: Yield (15%); m.p. 211 °C; IR (KBr) ν 2220 (CN); ^{1}H NMR (DMSO) δ 2.99 (s, 6H, 2 CH_3), 6.61 (s, 2H, C_6H_2), 6.80-8.18 (m, 8H, 2 C_6H_4); MS, m/e 340; (Calcd for $C_{22}H_{16}N_2S$: C, 77.6; H, 4.7; N, 8.2. Found: C, 77.4; H, 5.0; N, 8.0%).

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