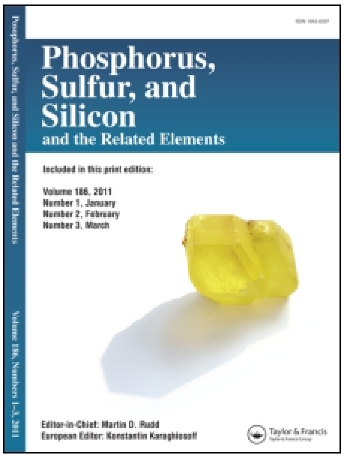
This article was downloaded by:
On: *29 January 2011*
Access details: *Access Details: Free Access*
Publisher *Taylor & Francis*
Informa Ltd Registered in England and Wales Registered Number: 1072954 Registered office: Mortimer House, 37-41 Mortimer Street, London W1T 3JH, UK



Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

STUDIES WITH 2-BENZIMIDAZOLYLACETONITRILE, SYNTHESIS OF NEW BENZIMIDAZO-2-YLTHIOPHENES ANDBENZO[g]IMIDAZO[1,2-a]PYRIDINES

Mohamed Hilmy Elnagdi[a]; Kamal Usef Sadek[b]; Mohamed Abdallah El-maghraby[c]; Maghraby Ali Selim[c]; Ali Kamel Khalafallah[c]; Mohamed Abd El Monem Reaslan[c]
[a] Chemistry Department, Faculty of Science, Kuwait University, Kuwait [b] Chemistry Department, Faculty of Science, Minia University, Minia, A.R. Egypt [c] Chemistry Department, Faculty of Science, Aswan, Assiut University, Egypt

To cite this Article Elnagdi, Mohamed Hilmy , Sadek, Kamal Usef , El-maghraby, Mohamed Abdallah , Selim, Maghraby Ali , Khalafallah, Ali Kamel and Reaslan, Mohamed Abd El Monem(1995) 'STUDIES WITH 2-BENZIMIDAZOLYLACETONITRILE, SYNTHESIS OF NEW BENZIMIDAZO-2-YLTHIOPHENES ANDBENZO[g]IMIDAZO[1,2-a]PYRIDINES', Phosphorus, Sulfur, and Silicon and the Related Elements, 105: 1, 51 — 55
To link to this Article: DOI: 10.1080/10426509508042045
URL: http://dx.doi.org/10.1080/10426509508042045

PLEASE SCROLL DOWN FOR ARTICLE

Full terms and conditions of use: http://www.informaworld.com/terms-and-conditions-of-access.pdf

This article may be used for research, teaching and private study purposes. Any substantial or systematic reproduction, re-distribution, re-selling, loan or sub-licensing, systematic supply or distribution in any form to anyone is expressly forbidden.

The publisher does not give any warranty express or implied or make any representation that the contents will be complete or accurate or up to date. The accuracy of any instructions, formulae and drug doses should be independently verified with primary sources. The publisher shall not be liable for any loss, actions, claims, proceedings, demand or costs or damages whatsoever or howsoever caused arising directly or indirectly in connection with or arising out of the use of this material.

Phosphorus, Sulfur, and Silicon, 1995, Vol. 105, pp. 51-55
Reprints available directly from the publisher
Photocopying permitted by license only

© 1995 OPA (Overseas Publishers Association)
Amsterdam B.V. Published under license by
Gordon and Breach Science Publishers SA
Printed in Malaysia

STUDIES WITH 2-BENZIMIDAZOLYLACETONITRILE, SYNTHESIS OF NEW BENZIMIDAZO-2-YLTHIOPHENES AND BENZO[g]IMIDAZO[1,2-a]PYRIDINES

MOHAMED HILMY ELNAGDI
Chemistry Department, Faculty of Science, Kuwait University, P.O. Box 5965, Kuwait

and

KAMAL USEF SADEK
Chemistry Department, Faculty of Science, Minia University, 61519, Minia, A.R. Egypt

and

MOHAMED ABDALLAH EL-MAGHRABY, MAGHRABY ALI SELIM, ALI KAMEL KHALAFALLAH and MOHAMED ABD EL MONEM REASLAN
Chemistry Department, Faculty of Science, Aswan, Assiut University, Egypt

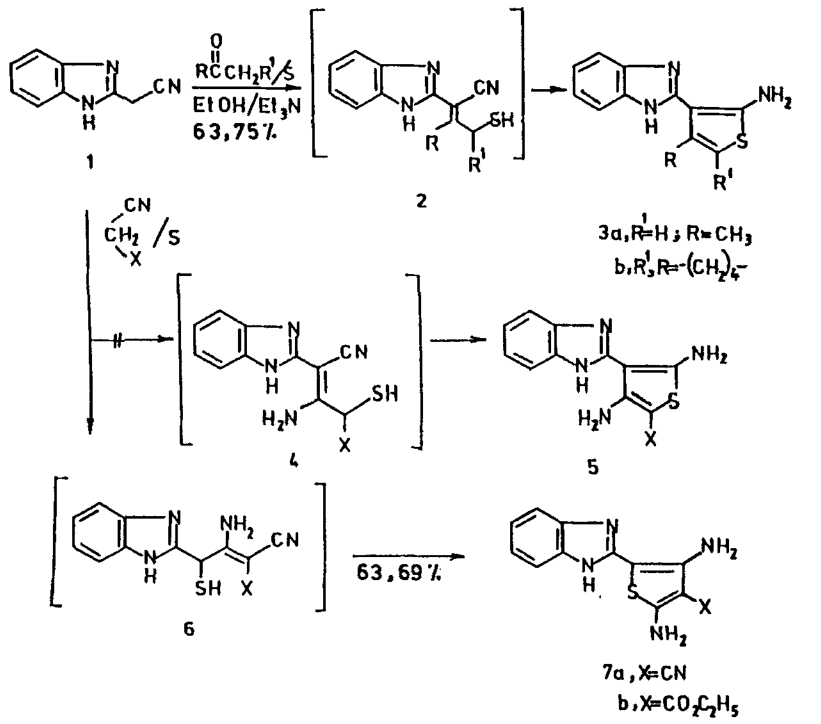
Downloaded At: 09:43 29 January 2011

(Received February 4, 1995; in final form April 8, 1995)

The synthesis of new benzimidazo-2-ylthiophenes, and benzo[g]imidazo[1,2-a]pyridines utilizing 2-benzimidazolylacetonitrile (**1**) as starting component is reported.

Key words: Thiophenes, pyridines, acetonitriles, azoles.

Azolylacetonitriles are readily obtainable compounds that have been extensively utilized as intermediates in heterocyclic synthesis.[1,2] In previous work from our laboratories we have shown that the cyanomethyl function in several azoles are active toward electrophilic reagents which enabled synthesis of several condensed azoles.[3,4] In conjunction of this work we report here the results of our further work exploring the synthetic potential of 2-(2-benzimidazolyl)acetonitrile (**1**). It is worth mentioning that the chemistry of benzimidazole derivatives has been of increasing interest since some of its derivatives have found applications as chemotherapeutics,[5] tuberculostatic agents[6] or potent antibacterial compounds.[7] Thus, it has been found that **1** reacts with acetone in the presence of sulfur and triethylamine in boiling ethanol solution to yield a product that is assigned the structure **3a** based on analytical and spectral data. The IR spectrum of this product revealed the absence of the CN signal and the appearance of the NH_2 signal as required by structure **3**. The formation of **3** is assumed to proceed via the intermediate mercapto derivative **2** that cyclizes readily to aromatic **3**. The behavior of **1** thus resembles other active methylene nitriles and to our knowledge this is the first reported use of azolyl-



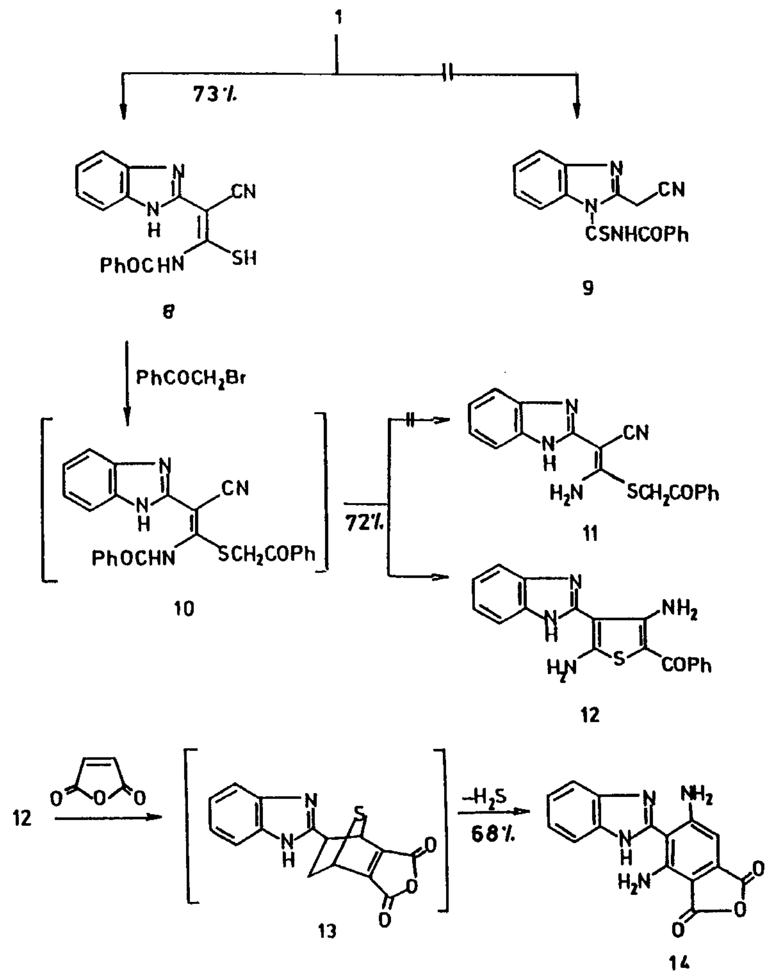
acetonitriles as active methylenes in the Gewald reaction. Compound **1** and cyclohexanone reacted similarly to yield the thienylbenzimidazole derivative **3b**.

In contrast to the reactivity of acetone, under a variety of conditions, acetophenone did not react with **1** under similar conditions. We believe that the thiophene that may result from such a reaction has a large steric interaction and a large energy barrier must be overcome for formation.

Malononitrile and sulfur reacted with compound **1** to yield either **5a** or **7a**. The formation of **7a** is assumed to proceed via addition of CH_2 group of the malononitrile to the CN function in **1** followed by reaction with sulfur to yield **6a** which was then cyclized into **7a**. Alternately, CH_2 of **1** may add to the CN of malononitrile, react with sulfur and then cyclize to **5**. Structure **7a** is preferred over possible **5a** based on the IR spectrum which showed a CN signal at $\nu = 2250\ cm^{-1}$. Alternative **5a** is expected to show a CN signal at a lower frequency.[8] Similar to malononitrile, ethyl cyanoacetate yields **7b**.

We have recently[9,10] shown that electron rich strained condensed thienopyridazines act as excellent dienes in 4 + 2 cycloaddition reactions. It seemed to us possible that the synthesized thiophenes may also react as dienes as they have an amino function and several other polyfunctional substituents that would raise the HOMO-LUMO energy. However, under a variety of conditions, compounds **3a, b** did not react with maleic anhydride or N-phenylmalemide. It was thus decided to prepare diaminothiophenes which may be more electron rich, thus raising further HOMO-LUMO energy. For this purpose **1** was treated with benzoylisothiocyanate to yield a 1:1 adduct which may be formulated as **8** or isomeric **9**. Structure **8** was

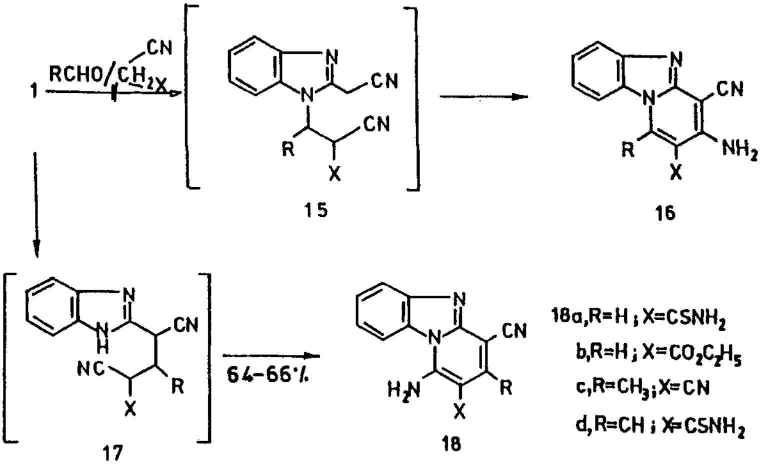
Downloaded At: 09:43 29 January 2011



Downloaded At: 09:43 29 January 2011

established for the reaction product based on ^{1}H NMR which revealed the absence of the CH_2 function and the presence of both 2NH as well as SH functions. Compound **8** reacted with phenacyl bromide to yield a product which was formulated as **12** rather than isomeric **11** based on the IR spectrum which showed the absence of a CN signal. ^{1}H NMR for **12** showed signals for 2 NH_2 groups and a multiplet for aromatic and NH protons. Compound **12** is believed to be formed via the intermediate **10** which undergoes cyclization and debenzoylation. Compound **12** reacted with maleic anhydride to yield **14** through intermediate **13**.

Cyanomethylazoles have been extensively utilized for the synthesis of condensed pyridines[11] by reaction with arylidenemalonitriles. Similar reaction with alkylidenemalononitriles has never been reported. In our laboratories trials to prepare alkylidenemalononitriles revealed that these compounds are only obtainable in very low overall yields. For this reason we thought of in situ formation of the required alkylidenemalononitrile derivatives. Thus, compound **1** reacts with a mixture of formaldehyde and cyanothioacetamide to yield either **16a** or isomeric **18a**. Structure **18a** was considered more likely based on the ^{1}H NMR spectrum which revealed



an amino function at δ = 8.3 ppm. If the reaction product was **16a**, this amino function would appear at a higher field. It is worth mentioning that the downfield shift of this signal was rationalized by the anisotropic effect of the ring nitrogen. Similarly, compound **1** reacts with a mixture of formaldehyde and ethyl cyanoacetate, acetaldehyde and malononitrile or cyanothioacetamide to afford **18b–d**.

Downloaded At: 09:43 29 January 2011

EXPERIMENTAL

All melting points are uncorrected. The IR spectra (KBr) were obtained on a Shimadzu 408 spectrophotometer. The ^{1}H NMR were measured in DMSO[d_6] on a Varian EM-390 90 MHz spectrometer using TMS as internal reference and chemical shifts are expressed as δ ppm. Analytical data were obtained from the Analytical Data Unit at Cairo University.

Synthesis of Benzimidazo-2-ylthiophene Derivatives (**3a–b**, **7a**,**b**) *(General Procedure)*: A solution of **1** (1.57 g, 0.01 mol, 1 eq) in ethanol (40 ml) was treated with the appropriate active methylene reagent (0.01 mol, 1 eq) and sulfur (0.01 mol, 1 eq) with catalytic amount of triethylamine (1 ml). The reaction mixture was heated under reflux for 3–6 h (TLC control). The solvent was removed under reduced pressure and the residue was triturated with water and neutralized with conc. HCl. The solid product, so formed, was collected by filtration and recrystallized from DMF.

3a (4.44 g, 63%); mp 300°C; Ir: 3400–3100 cm^{-1} (br, NH_2 and NH), 2990 (CH_3); 1600 (C=N). ^{1}H Nmr: δ = 2.2 (s, 3H, CH_3); 6.9–8.2 (m, 8H, aromatic, NH and NH_2). $C_{12}H_{11}N_3S$, Found C 62.8; H 4.7; N 18.3; S 13.9; requires C 62.6; H 4.8; N 18.3; S 14.0%.

3b (2.0 g, 75%); mp > 300°C; Ir: 3400–3100 cm^{-1} (br, NH_2 and NH); 1620 (C=N). ^{1}H Nmr: δ = 2.6 (t, 4H, 2CH_2 groups); 3.6 (m, 4H, 2CH_2); 6.9–8.3 (m, 8H, aromatic, NH and NH_2 protons). $C_{15}H_{15}N_3S$, Found C 66.9; H 5.5; N 15.6; S 11.9; requires C 66.9; H 5.6; N 15.6; S 11.9%.

7a (1.76 g, 69%); mp > 300°C. Ir: 3400–3150 cm^{-1} (br, NH_2 and NH); 2250 (CN); 1620 (C=N). ^{1}H Nmr: δ = 7.2–7.9 (m, aromatic, NH and 2NH_2 protons). $C_{12}H_9N_5S$, Found C 56.4; H 3.5; N 27.1; S 12.5; requires C 56.5; H 3.6; N 27.4; S 12.6%.

7b (1.9 g, 63%); mp > 300°C. Ir: 3450–3150 cm^{-1} (br, NH_2 and NH), 1700–1660 (CO). ^{1}H Nmr: δ = 1.3 (t, 3H, CH_3); 4.2 (q, 2H, CH_2); 7.1–7.5 (m, 9H, aromatic, NH and 2NH_2). $C_{14}H_{14}N_4O_2S$, Found C 55.6; H 4.6; N 18.5; S 10.6; requires C 55.6; H 4.7; N 18.5; S 10.6%.

The Reaction of Compound **1** *with Benzoylisothiocyanate*: A solution of benzoylisothiocyanate (0.01 mol) in acetone (40 ml) was treated with compound **1** (1.57 g, 0.01 mol). The reaction mixture was heated under reflux for 4 h. The solvent was removed under reduced pressure and the remnant was treated with ice water. The solid product, formed on standing, was collected by filtration and recrystallized from dioxane.

8 (2.33 g, 73%); mp 235°C. Ir: 3150 cm^{-1} (NH); 2200 (CN); 1680 (CO); 1610 (C=N). ^{1}H Nmr: δ = 7.3–8.3 (m, 11H, aromatic and 2NH); 10.6 (s, 1H, SH). $C_{17}H_{12}N_4SO$, Found C 63.8; H 3.7; N 17.4; S 9.9; requires C 63.7; H 3.8; N 17.5; S 10.0%.

Synthesis of Diaminothiophene Derivative (**12**): A solution of compound **8** (3.2 g, 0.01 mol) in dioxane (30 ml) was treated with phenacylbromide (1.99 g, 0.01 mol) and triethylamine (0.9 g, 0.012 mol). The reaction mixture was heated under reflux for 4 h. The solvent was then evaporated under reduced pressure and the residue was triturated with water. The solid product formed was collected by filtration and recrystallized from DMF.

12 (2.4 g, 72%); mp 275°C. Ir: 3300–3200 cm^{-1} (br, NH_2 and NH); 1680 (CO); 1600 (C=N). ^{1}H Nmr: δ = 7.3–7.9 (m, 10H, aromatic and NH); 8.2 (br, 4H, $2NH_2$). $C_{18}H_{14}N_4OS$, Found C 64.6; H 4.0; N 16.7; S 9.5; requires C 64.7; H 4.2; N 16.8; S 9.6%.

The Reaction of **12** *with Maleic Anhydride*: A solution of compound **12** (3.3 g, 0.01 mol) in DMF (30 ml) was treated with maleic anhydride (0.98 g, 0.01 mol) and the reaction mixture was heated under reflux for 6 h. The solvent was then evaporated in vacuo and the residue was treated with ice water. The solid product, formed on standing, was collected by filtration and recrystallized from DMF.

14 (2.7 g, 68%); mp > 300°C; Ir: 3300–3100 cm^{-1} (br, NH_2 and NH); 1680 (CO); 1600 (C=N). $C_{22}H_{14}N_4O_4$, Found C 66.3; H 3.5; N 14.0; requires C 66.3; H 3.5; N 14.1%.

Synthesis of Benzo[g]imidazo[1,2-a]pyridine Derivatives (**18a–d**): A solution of the appropriate alkylidenemalononitrile derivative (0.01 mol), prepared in situ from the reaction of the corresponding aldehyde and active methylene in ethanol in the presence of a catalytic amount of triethylamine) was added to compound **1** (1.57 g, 0.01 mol). The reaction mixture was heated under reflux for 4 h. The solvent was then evaporated under reduced pressure. The solid product, so formed, was collected by filtration and crystallized from DMF.

18a (1.7 g, 64%); mp > 300°C; Ir: 3400–3100 cm^{-1} (NH_2); 2200 (CN); 1600 (C=N). ^{1}H Nmr: δ = 4.2 (br, 2H, NH_2); 7.1–8.2 (m, 7H, aromatic, pyridine and NH_2 protons). $C_{13}H_9N_5S$, Found C 58.3; H 3.4; N 26.2; S 11.0; requires C 58.4; H 3.4; N 26.2; S 11.1%.

18b (1.84 g, 66%); mp 265°C. Ir: 3250 cm^{-1} (NH_2); 2200 (CN); 1700 (ester CO); 1620 (C=N). ^{1}H Nmr: δ = 1.3 (t, 3H, CH_3); 4.2 (q, 2H, CH_2); 7.1–8.2 (m, 7H, aromatic, pyridine and NH_2 protons). $C_{15}H_{12}N_4O_2$, Found C 64.1; H 4.2; N 20.2; requires C 64.3; H 4.3; N 20.0%.

18c (1.6 g, 66%); mp 270°C. Ir: 3100–3200 cm^{-1} (NH_2); 2200 (CN); 1630 (C=N). ^{1}H Nmr: δ = 3.4 (s, 3H, CH_3); 7.1–8.3 (m, 6H, aromatic and NH_2 protons). $C_{14}H_9N_5$, Found C 68.2; H 3.6; N 28.5; requires C 68.0; H 3.7; N 28.3%.

18d (2.0 g, 72%); mp > 300°C. Ir: 3200 cm^{-1} (NH_2); 2200 (CN); 1620 (C=N). $C_{14}H_{11}N_5S$, Found C 60.0; H 3.8; N 24.9; S 11.4; requires C 60.1; N 3.7; N 25.0; S 11.2%.

Downloaded At: 09:43 29 January 2011

REFERENCES

1. K. U. Sadek, A. E. Mourad, A. Elhafeez and M. H. Elnagdi, *Synthesis*, 739 (1983).
2. J. L. Soto, C. Seoane, P. Zamsrans and F. J. Cwadrado, *Synthesis*, 529 (1981).
3. M. R. H. Elmoghayar, M. K. A. Ibrahim, A. H. H. Elghandour and M. H. Elnagdi, *Synthesis*, 635 (1981).
4. K. U. Sadek, E. A. A. Hafez, A. E. Mourad and M. H. Elnagdi, *Z. Naturforsch.*, **39B,** 824 (1984).
5. H. W. Wagner and E. Winkelmann, *Arzneimittle-Forsch.*, **19,** 715 (1969).
6. A. Fujita, J. Arotomo, Sh. Minami and H. Takamotsu, *Yakugaku Zashi*, **86,** 427 (1966); *Chem. Abstr.*, **65,** 3870 (1966).
7. P. S. Rao and R. V. Venkataratnam, *Indian J. Chem., Sec. B*, **32,** 484 (1993).
8. L. J. Bellamy, "The Infra-red Spectra of Complex Organic Molecules," 2nd. Ed., John Wiley, New York, 1958.
9. M. H. Elnagdi, A. M. Negm and A. W. Erian, *Liebigs Ann. Chem.*, 1255 (1989).
10. M. H. Elnagdi, A. M. Negm, E. M. Hassan and A. El-Boreiy, *J. Chem. Res. (s)*, 130 (1993).
11. M. A. Hammad, J. A. M. Nawwar, G. E. H. Elgemeie and M. H. Elnagdi, *Heterocycles*, **23,** 2177 (1985).