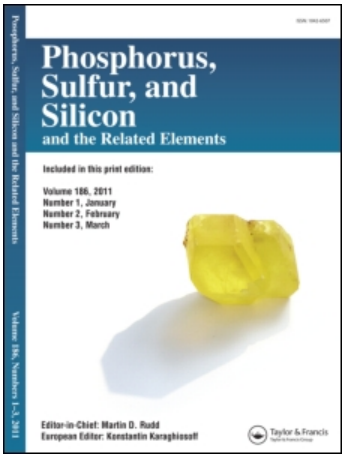

Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

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Online publication date: 11 August 2010

To cite this Article Latif, Fawi M. Abd El and Rady, Eman A. El(2004) 'FACILE ONE-POT SYNTHESIS OF 4-ARYL-3-METHYL-1-PHENYLPYRAZOLO[3,4-b]-[1,5]BENZOTHIAZEPINE DERIVATIVES VIA A REGIOSELECTIVE NUCLEOPHILIC ADDITION', Phosphorus, Sulfur, and Silicon and the Related Elements, 179: 2, 215 — 219
To link to this Article: DOI: 10.1080/10426500490274646
URL: http://dx.doi.org/10.1080/10426500490274646

Phosphorus, Sulfur, and Silicon, 179:215–219, 2004

ISSN: 1042-6507 print / 1563-5325 online
DOI: 10.1080/10426500490274646

FACILE ONE-POT SYNTHESIS OF 4-ARYL-3-METHYL-1-PHENYLPYRAZOLO[3,4-b]-[1,5]BENZOTHIAZEPINE DERIVATIVES VIA A REGIOSELECTIVE NUCLEOPHILIC ADDITION

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(Received March 2, 2003; accepted July 26, 2003)

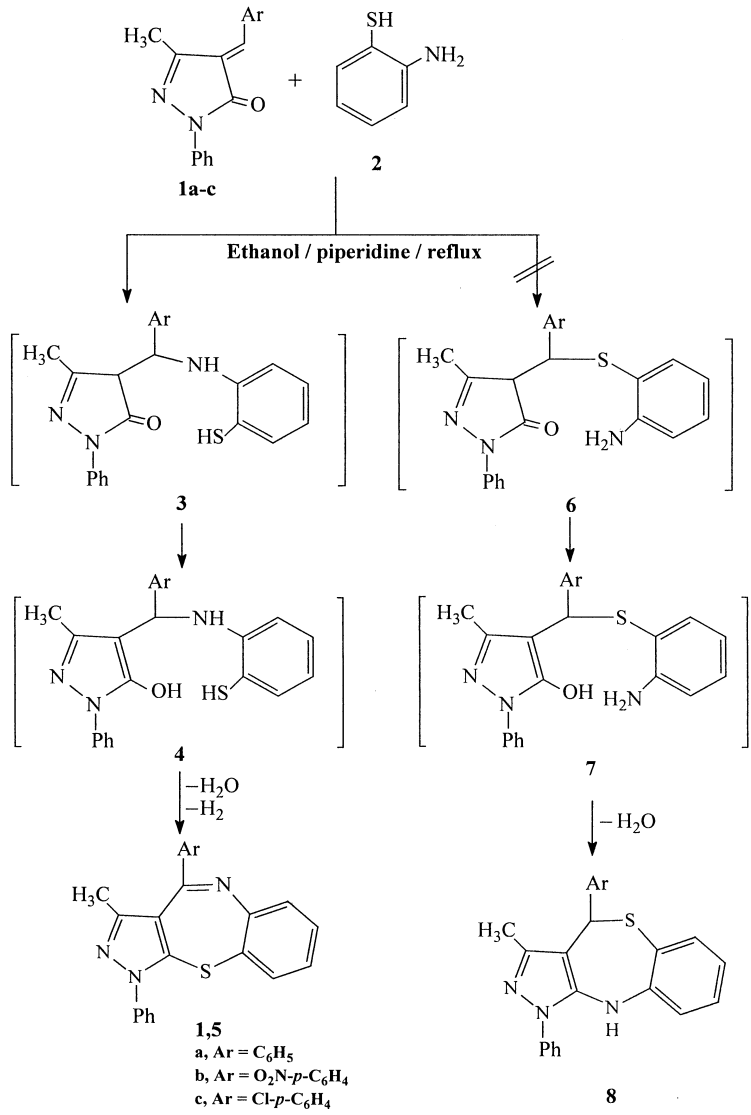
4-Arylidene-3-methyl-1-phenylpyrazole-5-one reacts with 2-aminobenzenethiol in ethanol-acetic acid solution to produce a mixture of 4-aryl-3-methyl-1-phenylpyrazolo[3,4-b][1,5]benzothiazepines, 2-arylbenzothiazoles and 3-methyl-1-phenylpyrazole-5-one.

Keywords: 2-Arylbenzothiazoles; pyrazolo[1,5]benzothiazepine; spectral characterization

Previously we have shown that 2-aminobenzenethiol **2** and its analogues are useful precursor for the synthesis of seven-membered ring.[1–4] Most of the reactions lead to the formation of a seven-membered ring based on condensation of 2-aminophenol derivatives followed by cyclization.[5–8] However, the azepine derivatives are of importance in medicinal chemistry because of their remarkable effect.[9,10] In this sequence, this article describes a convenient and simple route for the preparation of pyrazolo[3,4-b][1,5]benzothiazepine derivatives.

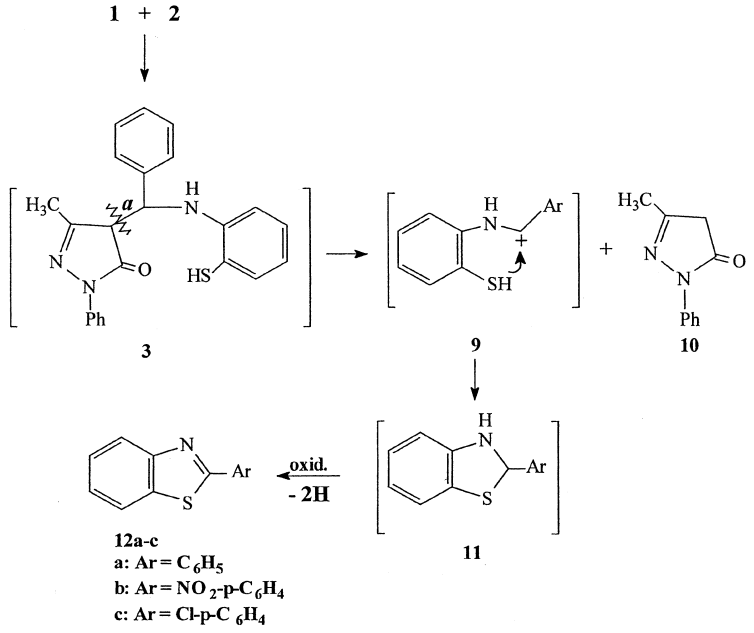
RESULTS AND DISCUSSION

2-Aminobenzenethiol **2** reacts directly with arylidenes **1** in ethanol solution in the presence of a catalytic amount of acetic acid to give 4-aryl-3-methyl-1-phenylpyrazolo[3,4-b][1,5]benzothiazepines **5** predominantly, concomitant with a minor amount of 3-methyl-1-phenylpyrazole-5-one **10** and 2-arylbenzthiazoles **12** (c.f. Schemes 1 and 2). Formation of the products seems to be formed through a nucleophilic addition of the amine function of **2** to **1** resulting in formation of the intermediate **3**, which may present in its enol form **4**, which subsequently loses water to give the target compound **5**. However, if the addition starts from



SCHEME 1

the thiol function to yield the intermediates **6** and **7**, the final product would be **8** which is ruled out based on spectral data. ^{1}H NMR spectra (DMSO-d_6,) of **5** showed one singlet at $\delta = 2.1$ ppm due to the protons of the methyl group. However, ^{13}C NMR spectra of **5** showed absorption at 14.20 ppm assigned for methyl carbon. The lack of absorption due to



SCHEME 2

the NH as the lake of any singlet signal at δ <7.0 and at <90 ppm in their ^{1}H and ^{13}C NMR spectra which would appear for C-4 of structure **8** demonstrates the assumption of regioselectivity of this addition.

On the other hand, it is worthy to mention that the minor amount of colorless crystals that formed during reflux were identified as 3-methyl-1-phenylpyrazol-5-one **10** by both spectroscopic analysis and comparison with an authentic sample. Meanwhile, isolation of 2-phenylbenzothiazole **12a** from the reaction mixture prompt us to suggest a plausible pathway forming both **10** and **12**. Formation of 2-arylbenzthiazoles **12** seems possible to proceed from the intermediate **3** which loses pyrazolone moiety **10** via broken the bond **a** to yield the intermediate cation **9**. Intramolecular nucleophilic attack by lone pair electrons of the sulfur atom on the electrophilic carbon leads to the dihydro intermediate **11** which is readily oxidized under an aerobic conditions to give **12** (c.f. Scheme 2).

EXPERIMENTAL

All melting points were measured on a Gallen-Kamp melting point apparatus and are uncorrected. IR spectra were recorded (potassium

bromide, $\nu = cm^{-1}$) were run on a Shimadzu 408 and a Pye Unicam Spectrophotometer. The ^1H, ^{13}C NMR spectra (DMSO-d_6, $CDCl_3$, δ = ppm) were recorded on a Bruker WM 300 MH_z Spectrometer and TMS was used as internal standard. Mass spectra were recorded on a mass spectrometer MS 9 (AET) EI Mode at 70 ev. All the Microanalysis were carried out at Microanalytical Center, Cairo University, Egypt.

Preparation of 4-Aryl-3-methyl-1-phenylpyrazolo[3,4-b]-[1,5]benzothiazepine Derivatives 5

General Procedure

To ethanol solution (20 ml) of **1a** (1.04 g, 4 mmol) an equimoluar amount of **2** (0.52 g, 4 mmol) was added. The mixture was boiled under reflux in presence of 0.1 ml of acetic acid for 3 h. The pyrazolone **10** that crystallized after cooling at room temperature was filtered and washed with ethanol. The residue was concentrated in vacuum whereupon 2-phenylbenzothiazole **12a** was isolated after addition of 5 ml of methanol, filtered, and washed with cold methanol. The remainder solution was diluted with a mixture of 3 ml of water acidified by 0.1 ml of concentrated hydrochloric acid. The solid formed was filtered, washed well with cold water, dried, and crystallized. In analogy, **1b**,**c** reacted with **2** (4 mmol each) under the same reaction conditions to give the corresponding **5b**,**c** **12b**,**c**, and pyrazolone **10**. The reactions were monitored by tlc using toluene/ethyl acetate (3:1, v : v).

4-Phenyl-3-methyl-1-phenylpyrazolo[3,4-b][1,5]benzothiazepine (5a): m.p.: 325°C (MeOH). Yield: 55%. ^1H NMR: 2.1(*s*, 3H, CH_3), 7.1–7.9 (*m*, 14H, Ar-H). ^{13}C NMR: 14.20 (CH_3), 117.2–128.3 (benzene), 138.5 (C-3), 140.5 (C-4), 148.4 (C-10a). MS, m/e = 369 (M^+, 80%). Anal Calcd. for $C_{23}H_{19}N_3S$ (369.49): C, 74.77; H, 5.18; N, 11.37. S, 8.68. Found: C, 74.87; H, 5.10; N, 11.30; S, 8.49.

4-(4-Nitrophenyl)-3-methyl-1-phenylpyrazolo[3,4-b][1,5]benzothiazepine (5b): m.p.: 235°C (EtOH). Yield: 45%. ^1H NMR: 2.11 (*s*, 3H, CH_3), 7.0–7.8 (*m*, 13H, Ar-H). ^{13}C NMR: 14.21 (CH_3), 118.1–129.3 (benzene), 138.9 (C-3), 141.5 (C-4), 148.8 (C-10a). MS: m/e = 414 (M^+, 65%). Anal Calcd. for $C_{23}H_{18}N_4O_2S$ (414.48): C, 66.65; H, 4.38; N, 13.52. S, 7.73. Found: C, 66.77; H, 4.10; N, 13.30; S, 7.59.

4-(4-Chlorophenyl)-3-methyl-1-phenylpyrazolo[3,4-b][1,5]-benzothiazepine (5c): m.p.: 298°C (MeOH). Yield: 50%. ^1H NMR: 2.10 (*s*, 3H, CH_3), 7.0–7.9 (*m*, 13H, Ar-H). ^{13}C NMR: 14.12 (CH_3), 117.2–129.4 (benzene), 138.2 (C-3), 141.5 (C-4), 148.9 (C-10a). MS: m/e = 404 (M + 1, 75%). Anal Calcd. for $C_{23}H_{18}ClN_3S$ (403.93): C, 68.37; H, 4.49; N, 10.40. S, 7.94. Found: C, 68.57; H, 4.30; N, 10.30; S, 7.79.

2-Phenylbenzothiazole (12a): m.p.: 110°C (EtOH). Yield: 25%. ^{1}H NMR: ($CDCl_3$, δ = ppm): 7.0–7.9 (*m*, 9H, Ar-H). MS; m/e = 211 (M^+, 90%). Anal Calcd. for $C_{13}H_9NS$ (211.28): C, 73.90; H, 4.29; N, 6.63. S, 15.17. Found: C, 73.72; H,4.38; N, 6.53; S, 15.10.

2-(4-Nitrophenyl)benzothiazole (12b): m.p.: 105°C (EtOH). Yield: 15%. ^{1}H NMR: ($CDCl_3$, δ = ppm): 7.0–7.9 (*m*, 8H, Ar-H). MS; m/e = 257 (M + 1, 85%). Anal. Calcd. for $C_{13}H_8N_2O_2S$ (256.28): C, 60.93; H, 3.15; N, 10.93. S, 12.51. Found: C, 60.99; H, 3.25; N, 10.73; S, 12.75.

2-(4-Chlorophenyl)benzothiazole (12c): m.p.: 220°C (EtOH). Yield: 20%. ^{1}H NMR: ($CDCl_3$, δ = ppm): 7.1–7.9 (*m*, 8H, Ar-H). MS; m/e = 246 (M + 1, 90%). Anal Calcd. for $C_{13}H_8NclS$ (245.73): C, 63.54; H, 3.28; N, 5.70. S, 13.05. Found: C, 63.82; H, 3.15; N, 5.53; S, 12.99.

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