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A Facile Synthesis of 2-Amino-1,3-selenazole by Reaction of *N,N*-Unsubstituted Selenourea with Ketone

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ABSTRACT: *2-Dialkylamino-1,3-selenazoles were yielded by the reaction of N,N-unsubstituted selenoureas with ketones in the presence of ferric chloride.* © 2006 Wiley Periodicals, Inc. Heteroatom Chem 17:88–92, 2006; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.20180

INTRODUCTION

There are many selenium-containing heterocyclic compounds found in the literature [1]. Of these many are potential pharmaceutical and dye agents [2]. The use of selenourea as the precursor is one of the most efficient methods for the synthesis of heterocyclic compounds containing selenium [3]. Recently, 2-dialkylamino-1,3-selenazole has become of interest as a starting material for preparing dyes. They are prepared according to the well-known method [4] from selenoureas and have been converted successfully into corresponding azo dye and squarylium dyes [5]. This result stimulates us to prepare these compound derivatives. We describe here the syntheses of 2-dialkylamino-1,3-selenazoles by the reaction of selenoureas with ketones. This method would provide a new route to selenazoles without the use of lachrymatory halo carbonyl compounds.

RESULTS AND DISCUSSION

Various reactions were investigated to establish optimal conditions for the synthesis of 4-methyl-2-piperidino-1,3-selenazoles **3f**. The reaction of 1-selenocarbamoylpiperidine **1e** with acetone **2b** was carried out under an argon atmosphere. When reaction was carried out at reflux with acid or base such as $BF_3{\cdot}Et_2O$, HCl, acetic acid, triethylamine, or di-isopropylethylamine, unidentifiable mixtures resulted. The reaction with ferric chloride yielded **3f** after a shorter time in higher yield. Next, the optimal solvent was investigated in the presence of ferric chloride. When ethanol, dichloromethane, and THF were used as a reaction solvent, the reaction using ethanol gave **3f** exclusively after a shorter time in high yields.

Using the optimal reaction conditions, several 2-amino-1,3-selenazoles **3a–l** were prepared from the reaction of corresponding *N,N*-unsubstituted selenoureas **1** with ketones **2** in the presence of ferric chloride (Scheme 1). The reaction gave **3** in moderate to high yields in the present study (Table 1). The reactions using aromatic ketone (**3h** in 32% yield)

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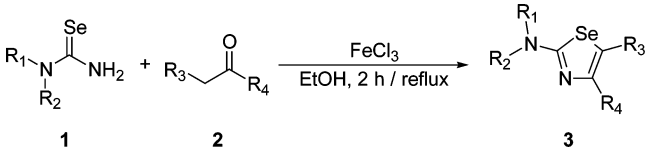


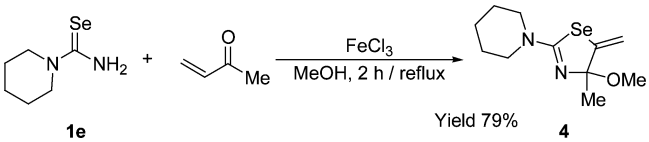
1 **2** **3**

SCHEME 1

and ketones-bearing bulky groups (in the case of tertiary butyl group, 5% yield, data not shown) all gave **3** in low yields. The existence of ferrous chloride, $FeCl_2$, in the reaction mixture was confirmed by the addition of potassium ferricyanide. The ^1J (^{77}Se–^{13}C) values (in the case of **3f**, $J = 93.6$ Hz) at the C5 carbon and the ^2J (^{77}Se–^{1}H) values (in the case of **3f**, $J = 52.1$ Hz) at the C5 proton of **3** were clearly observed on the proton-decoupled ^{13}C NMR and ^{1}H NMR spectra. Although in the case of **3f** the isomeric 5-methyl-1,3-selenazole is a possible product, the possibility of its formation was ruled out by the observation of the ^2J (^{77}Se–^{1}H) values and ^1J(^{77}Se–^{13}C) values at the C5 carbon of **3**.

In order to elucidate the reaction mechanism for the formation of compound **3**, the reaction of selenourea, 1-selenocarbamoylpiperidine **1e**, with methyl vinyl ketone in methanol was attempted under similar conditions. This reaction afforded 4-methoxy-4-methyl-5-methylene-2-piperidino-4,5-dihydro-1,3-selenazole **4** in 79% yield (Scheme 2). In the case of compound **4**, elimination of alcohol from the selenazole ring could not proceed due to the lack of a proton at the C5 carbon. The formation of **4** was initiated by the nucleophilic addition of the nitrogen atom of selenourea **1** on the carbonyl carbon, affording the 4-methoxy-4,5-dihydro-1,3-selenazole **4**.

The formation of **3** could be explained by the following mechanism: the reaction of *N,N*-unsubstituted selenourea **1** with ketone **2** is initiated by the nucleophilic addition of the nitrogen of the selenourea to the carbonyl carbon, affording 2-amino-1,3-selenazole **3** (Scheme 3). Previously, it was reported that the reaction of *N,N*-unsubstituted selenoureas with α-halocarboxylic acid led to the formation of 2-amino-1,3-selenazol-4-ones under reflux conditions [6], and 2-amino-1,3-selenazole was prepared by allowing the ketone to react with iodine (or hypervalent iodine) and selenourea ($H_2N{-}C(=Se){-}NH_2$) [7]. In the present study, it was confirmed that reacting *N,N*-unsubstituted selenourea **1** with ketone **2** in the presence of ferric chloride gives easily the corresponding 2-dialkylamino-1,3-selenazole **3**.



1e **4**

SCHEME 2

EXPERIMENTAL

General

Selenoureas were synthesized according to previously described procedures [8]. The ^{77}Se chemical shifts are expressed in ppm deshielded with respect to near Me_2Se in $CDCl_3$. ^2J (^{77}Se–^{1}H) values and ^1J (^{77}Se–^{13}C) values are of the ^{77}Se satellites of the ^{1}H NMR spectra and proton-decoupled ^{13}C NMR spectra.

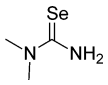
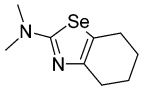
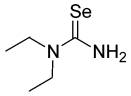
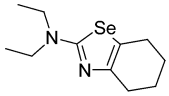
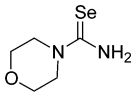
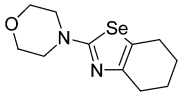
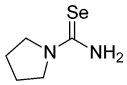
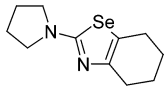
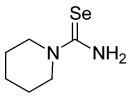
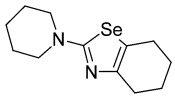
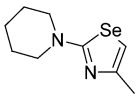
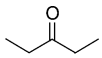
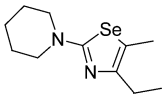
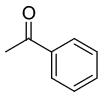
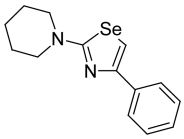
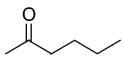
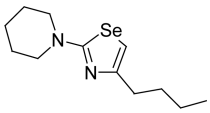
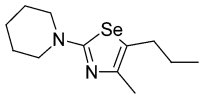
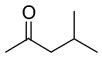
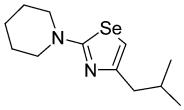
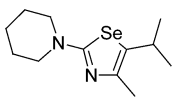
General Procedure for Synthesis of 2-Dimethylamino-4,5,6,7-tetrahydrobenzo-1,3-selenazole **3a**

Cyclohexanone **2a** (0.10 mL, 0.9 mmol) was added to a stirred solution of *N,N*-dimethylselenourea **1a** (45 mg, 0.3 mmol) in dry ethanol (3 mL) under an argon atmosphere. Ferric chloride (0.19 g, 1.2 mmol) was added into the reaction mixture. The reaction mixture was refluxed for 2 h. The mixture was extracted with diethyl ether and washed with H_2O. The organic layer was dried over sodium sulfate and evaporated to dryness. The residue was purified by flash chromatography on silica gel with dichloromethane: *n*-hexane (2:1) to give **3a** (70 mg, quantitative) as yellow liquid. IR (neat): 2928, 1558 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.75–1.83 (4H, m, CH_2), 2.56–2.59 (2H, m, CH_2), 2.67–2.69 (2H, m, CH_2), 3.04 (6H, s, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 23.1, 23.9, 25.4, 27.9, 41.0, 121.1, 147.1, 170.5; ^{77}Se NMR (95 MHz, $CDCl_3$) δ 554.2; MS (FAB): $m/z = 230$ [M$^+$].

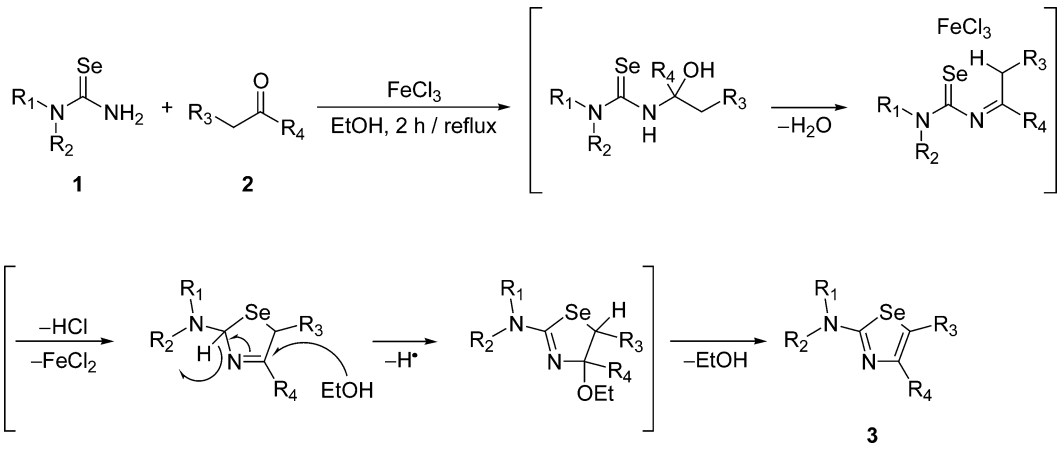
2-Diethylamino-4,5,6,7-tetrahydrobenzo-1,3-selenazole **3b**

Yellow liquid. IR (neat): 2930, 1544 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.21 (6H, t, $J = 7.2$ Hz, CH_3), 1.76–1.81 (4H, m, CH_2), 2.54–2.57 (2H, m, CH_2), 2.65–2.68 (2H, m, CH_2), 3.42 (4H, q, $J = 7.2$ Hz, CH_2); ^{13}C NMR (125 MHz, $CDCl_3$): δ 12.7, 23.2, 23.9, 25.4, 27.9, 46.0, 119.7, 146.9, 168.7; ^{77}Se NMR (95 MHz, $CDCl_3$): δ 550.5; MS (CI): $m/z = 259$ [M$^+ + 1$].

TABLE 1 Synthesis of 2-Amino-1,3-selenazoles **3**

		2-Amino-1,3-selenazole **3**	
Selenourea **1**	*Ketone* **2**	*Product*	*Yield (%)*[a]
 **1a**	 **2a**	 **3a**	Quant.
 **1b**	**2a**	 **3b**	87
 **1c**	**2a**	 **3c**	83
 **1d**	**2a**	 **3d**	Quant.
 **1e**	**2a**	 **3e**	97
1e	 **2b**	 **3f**	85
1e	 **2c**	 **3g**	73
1e	 **2d**	 **3h**	32
1e	 **2e**	 **3i**	20
		 **3j**	52
1e	 **2f**	 **3k**	45
		 **3l**	19

[a]Isolated yield. Reaction conditions: ketone **2** (3 equiv.), selenourea **1** (1 equiv.), dry ethanol, ferric chloride (4 equiv.), reflux, 2 h.



1 **2** **3**

SCHEME 3

2-Morpholino-4,5,6,7-tetrahydrobenzo-1,3-selenazole **3c**

Pink solid. mp: 52.0–54.0°C; IR (KBr): 2922, 2857, 1547 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 1.77–1.83 (4H, m, CH_2), 2.55–2.58 (2H, m, CH_2), 2.68–2.70 (2H, m, CH_2), 3.38 (4H, t, $J = 4.9$ Hz, CH_2), 3.77 (4H, t, $J = 4.9$ Hz, CH_2); ^{13}C NMR (125 MHz, $CDCl_3$): δ 23.0, 23.8, 25.4, 27.8, 49.5, 66.2, 122.4, 146.8, 171.5; ^{77}Se NMR (95 MHz, $CDCl_3$): δ 562.5; MS (CI): $m/z = 273$ $[M^+ + 1]$.

2-Pyrrolidino-4,5,6,7-tetrahydrobenzo-1,3-selenazole **3d**

Yellow solid. mp 75.0–78.5°C; IR (KBr): 2924, 1540 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 1.76–1.83 (4H, m, CH_2), 1.98–2.03 (4H, m, CH_2), 2.58–2.60 (2H, m, CH_2), 2.67–2.70 (2H, m, CH_2), 3.38–3.41 (4H, m, CH_2); ^{13}C NMR (125 MHz, $CDCl_3$): δ 23.1, 23.9, 25.46, 25.51, 27.9, 50.1, 120.1, 147.0, 166.7; ^{77}Se NMR (95 MHz, $CDCl_3$): δ 551.1; MS (CI): $m/z = 257$ $[M^+ + 1]$.

2-Piperidino-4,5,6,7-tetrahydrobenzo-1,3-selenazole **3e**

Yellow liquid. IR (neat): 2931, 2939, 1535 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 1.63–1.66 (6H, m, CH_2), 1.75–1.82 (4H, m, CH_2), 2.53–2.57 (2H, m, CH_2), 2.66–2.68 (2H, m, CH_2), 3.34–3.39 (4H, m, CH_2); ^{13}C NMR (125 MHz, $CDCl_3$): δ 23.1, 23.8, 24.2, 25.1, 25.4, 27.8, 50.5, 120.9, 146.6, 171.1; ^{77}Se NMR (95 MHz, $CDCl_3$): δ 556.7; MS (CI): $m/z = 271$ $[M^+ + 1]$.

4-Methyl-2-piperidino-1,3-selenazole **3f** *[4]*

Yellow liquid. IR (neat): 2936, 2853, 1534 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 1.64–1.68 (6H, m, CH_2), 2.21 (3H, s, CH_3), 3.40–3.42 (4H, m, CH_2), 6.56 (1H, s, CH) (^2J (^{77}Se–^1H) = 52.1 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 18.7, 24.2, 25.2, 50.7, 103.9, 150.2 (^1J (^{77}Se–^{13}C) = 93.6 Hz), 173.5; ^{77}Se NMR (95 MHz, $CDCl_3$): δ 549.4; MS (CI): $m/z = 231$ $[M^+ + 1]$.

4-Ethyl-5-methyl-2-piperidino-1,3-selenazole **3g**

Yellow liquid. IR (neat): 2935, 2855, 1540 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 1.16 (3H, t, $J = 7.7$ Hz, CH_3), 1.59–1.67 (6H, m, CH_2), 2.28 (3H, s, CH_3), 2.44 (2H, q, $J = 7.7$ Hz, CH_3), 3.32–3.37 (4H, m, CH_2); ^{13}C NMR (125 MHz, $CDCl_3$): δ 12.9, 13.9, 22.6, 24.3, 25.2, 50.5, 117.9, 150.5, 170.2; ^{77}Se NMR (95 MHz, $CDCl_3$): δ 580.6; MS (CI): $m/z = 259$ $[M^+ + 1]$.

4-Phenyl-2-piperidino-1,3-selenazole **3h** *[4]*

Yellow liquid. IR (neat): 2935, 2847, 1543 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 1.63–1.71 (6H, m, CH_2), 3.51 (4H, t, $J = 5.2$ Hz, CH_2), 7.25 (1H, t, $J = 7.5$ Hz, CH), 7.28 (1H, s, CH), 7.34 (2H, dd, $J = 7.5$, 8.3 Hz, CH), 7.85 (2H, d, $J = 8.3$ Hz, CH); ^{13}C NMR (125 MHz, $CDCl_3$): δ 24.3, 25.3, 50.8, 104.9 (^1J (^{77}Se–^{13}C) = 97.2 Hz), 126.3, 127.2, 128.4, 136.1, 152.8, 172.8; ^{77}Se NMR (95 MHz, $CDCl_3$): δ 575.9; MS (CI): $m/z = 293$ $[M^+ + 1]$.

4-Butyl-2-piperidino-1,3-selenazole **3i**

Orange liquid. IR (neat): 2934, 2856, 1534 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 0.92 (3H, t, $J = 7.5$ Hz, CH_3), 1.33–1.39 (2H, m, CH_2), 1.59–1.66 (10H, m, CH_2), 2.52 (2H, t, $J = 7.5$ Hz, CH_2), 3.40–3.43 (4H, m, CH_2), 6.57 (1H, s, CH) (^2J (^{77}Se–^1H) = 52.1 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 14.0, 22.5, 24.3, 25.3, 30.8, 32.9, 50.7, 103.1, 155.4, 173.5; ^{77}Se NMR (95 MHz, $CDCl_3$): δ 544.4; MS (CI): $m/z = 273$ $[M^+ + 1]$.

4-Methyl-2-piperidino-5-propyl-1,3-selenazole **3j**

Orange liquid. IR (neat): 2933, 2855, 1535 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 0.95 (3H, t, $J = 7.5$ Hz, CH_3), 1.54–1.68 (8H, m, CH_2), 2.10 (3H, s, CH_3), 2.59 (2H, t, $J = 7.5$ Hz, CH_2), 3.34–3.36 (4H, m, CH_2); ^{13}C NMR (125 MHz, $CDCl_3$): δ 13.5, 15.5, 24.2, 25.2, 26.0, 30.4, 50.4, 125.3 (^1J (^{77}Se–^{13}C) = 92.4 Hz), 143.9, 170.2; ^{77}Se NMR (95 MHz, $CDCl_3$): δ 561.5; MS (CI): $m/z = 273$ [$M^+ + 1$].

4-(2-Methylpropyl)-2-piperidino-1,3-selenazole **3k**

Orange liquid. IR (neat): 2937, 2864, 1534 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 0.91 (6H, d, $J = 6.9$ Hz, CH_3), 1.62–1.67 (6H, m, CH_2), 1.96–2.07 (1H, m, CH), 2.36 (2H, d, $J = 7.5$ Hz, CH_2), 3.39–3.41 (4H, m, CH_2), 6.56 (1H, s, CH) (^2J (^{77}Se–^1H) = 52.1 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 22.5, 24.3, 25.2, 27.7, 42.5, 50.7, 104.3 (^1J (^{77}Se–^{13}C) = 93.6 Hz), 154.3, 173.4; ^{77}Se NMR (95 MHz, $CDCl_3$): δ 542.6; MS (CI): $m/z = 273$ [$M^+ + 1$].

4-Methyl-5-(2-methylethyl)-2-piperidino-1,3-selenazole **3l**

Yellow solid. mp: 38.0–40.0°C; IR (KBr): 2934, 2853, 1541 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 1.20 (6H, d, $J = 6.9$ Hz, CH_3), 1.59–1.67 (6H, m, CH_2), 2.12 (3H, s, CH_3), 3.00–3.07 (1H, m, $J = 6.9$ Hz, CH), 3.37 (4H, t, $J = 5.2$ Hz CH_2); ^{13}C NMR (125 MHz, $CDCl_3$): δ 15.7, 24.3, 25.3, 26.1, 29.2, 50.4, 134.3, 142.0, 170.0; ^{77}Se NMR (95 MHz, $CDCl_3$): δ 528.9; MS (CI): $m/z = 273$ [$M^+ + 1$].

4-Methoxy-4-methyl-5-methylene-2-piperidino-4,5-dihydro-1,3-selenazole **4**

^1H NMR (500 MHz, $CDCl_3$): δ 1.60–1.68 (6H, m, CH_2), 2.17 (3H, s, CH_3), 3.33 (3H, s, CH_3), 3.38–3.43 (4H, m, CH_2), 3.00–3.07 (1H, m, $J = 6.9$ Hz, CH), 4.46 (2H, S, CH_2); ^{13}C NMR (125 MHz, $CDCl_3$): δ 15.7, 24.1, 25.1, 50.4, 56.9, 67.9, 120.22 (^1J (^{77}Se–^{13}C) = 91.2 Hz), 147.6, 171.9; ^{77}Se NMR (95 MHz, $CDCl_3$): δ 564.5; MS (CI): $m/z = 274$ [$M^+ + 1$].

REFERENCES

[1] (a) Katritzky, A. R.; Rees, C. W.; Scriven, E. F. V. Comprehensive Heterocyclic Chemistry II; Pergamon Press: New York, 1996; Vols. 1–11; (b) Back, T. G. Organoselenium Chemistry: A Practical Approach; Oxford University Press: New York, 1999; (c) Wirth, T. Organoselenium Chemistry. Modern Developments in Organic Synthesis; Springer: New York, 2000; (d) Murai, T.; Kato, S. Top Curr Chem 2000, 208, 177; (e) Ishihara, H.; Koketsu, M.; Fukuta, Y.; Nada, F. J Am Chem Soc 2001, 123, 8408.

[2] (a) Koketsu, M.; Ishihara, H.; Wu, W.; Murakami, K.; Saiki, I. Eur J Pharm Sci 1999, 9, 157; (b) Wu, W.; Murakami, K.; Koketsu, M.; Yamada, Y.; Saiki, I. Anticancer Res 1999, 19, 5375; (c) Cho, S. I.; Koketsu, M.; Ishihara, H.; Matsushita, M.; Nairn, A. C.; Fukazawa, H.; Uehara, Y. Biochim Biophys Acta 2000, 1475, 207; (d) Koketsu, M.; Yang, H. O.; Kim, Y. M.; Ichihashi, M.; Ishihara, H. Org Lett 2001, 3, 1705; (e) Koketsu, M.; Choi, S. Y.; Ishihara, H.; Lim, B. O.; Kim, H.; Kim, S. Y. Chem Pharm Bull 2002, 50, 1594; (f) Gutzkow, K. B.; Låhne, H. U.; Naderi, S.; Torgersen, K. M.; Skålhegg, B.; Koketsu, M.; Uehara, Y.; Blomhoff, H. K. Cell Signal 2003, 15, 871; (g) Park, Y.-J.; Koketsu, M.; Kim, J. M.; Yeo, J.-H.; Ishihara, H.; Lee, K.-G.; Kim, S. Y.; Kim, C.-K. Biol Pharm Bull 2003, 26, 1657.

[3] (a) Takahashi, M.; Watanabe, S.; Kasai, T. Heterocycles 1980, 14, 1921; (b) Kristian, P.; Koscik, D.; Gonda, J. Collect Czech Chem Commun 1983, 48, 3567; (c) Maslankiewicz, A.; Skrzypek, L.; Niedbala, A. Pol J Chem 1996, 70, 54; (d) Keil, D.; Hartmann, H. Phosphorus Sulfur Silicon Relat Elem 1999, 152, 169; (e) Shafiee, A.; Ebrahimzadeh, M. A.; Maleki, A. J Heterocycl Chem 1999, 36, 901; (f) Koketsu, M.; Suzuki, N.; Ishihara, H. J Org Chem 1999, 64, 6473; (g) Zhou, Y.; Linden, A.; Heimgartner, H. Helv Chim Acta 2000, 83, 1576; (h) Attanasi, O. A.; Filippone, P.; Guidi, B.; Perrulli, F. R.; Santeusanio, S. Synlett 2001, 144.

[4] Keil, D.; Hartmann, H. Phosphorus Sulfur Silicon Relat Elem 1999, 152, 169.

[5] (a) Keil, D.; Hartmann. H. Dyes and Pigments 2000, 44, 149; (b) Keil, D.; Hartmann. H.; Zug, I.; Schroder, A. J Prakt Chem 2000, 42, 169.

[6] (a) Geisler, K.; Künzler, A.; Below, H.; Bulka, E.; Pfeiffer, W.-D.; Langer, P. Synthesis 2004, 97; (b) Geisler, K.; Pfeiffer, W.-D.; Künzler, A.; Below, H.; Bulka, E.; Langer, P. Synthesis 2004, 875.

[7] (a) King, L. C.; Hlavacek, R. J. J Am Chem Soc 1951, 73, 1864; (b) Moriarty, R. M.; Vaid, B. K.; Duncan, M. P.; Levy, S. G.; Prakash, O.; Goyal, S. Synthesis 1992, 845; (c) Zhang, P.-F.; Chen, Z.-C. Synthesis 2000, 1219.

[8] (a) Koketsu, M.; Fukuta, Y.; Ishihara, H.; Tetrahedron Lett 2001, 42, 6333; (b) Koketsu, M.; Takakura, N.; Ishihara, H. Synth Commun 2002, 32, 3075.