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REACTION OF FENCHONE HYDRAZONE WITH DISELENIUM DIBROMIDE: NOVEL FORMATION OF BICYCLIC DISELENIDE

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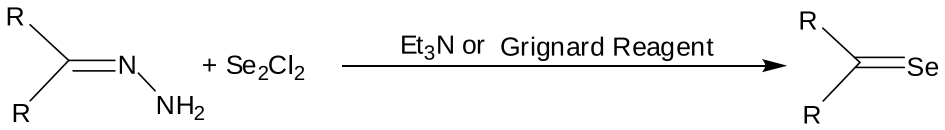
Abstract – Bicyclic diselenide containing a norbornane skeleton was synthesized by the reaction of fenchone hydrazone with Se_2Br_2. Initially formed selenofenchone further reacted with another molar amount of Se_2Br_2 to afford Wagner-Meerwein rearranged diselenide. Camphor hydrazone also reacted with Se_2Br_2 to afford the corresponding diselenide, whereas no rearranged product was formed.

It is well known that sterically crowded selones were synthesized by the reaction of triphenylphosphoranilidene hydrazone with elemental selenium in high temperature.[1] Lately, Okazaki *et al*. reported the improved synthesis of selones, in which ketone hydrazones reacted with Se_2Cl_2 at rt (Scheme 1).[2] They applied this methodology to the synthesis of 1,1,3,3-tetramethylindan-2-tellone.[3] Guziec also reported the synthesis of selones by using ketone hydrazones and Se_2Br_2 under basic conditions.[4] Although cyclic polyselenides were obtained by these methods,[5] there is no report on the synthesis of diselenides from ketone hydrazones.

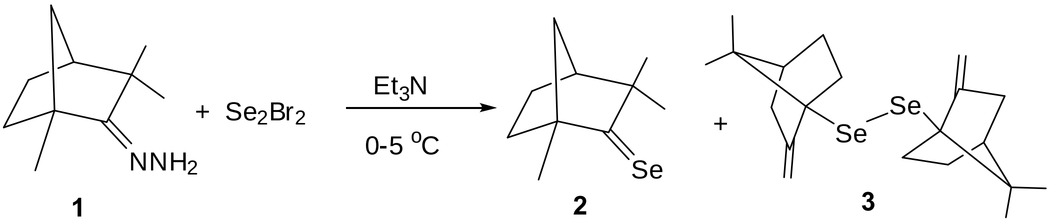


Scheme 1

While 1,1,3,3-tetramethylindan-2-selone was synthesized in 82% yield by this method, reaction of fenchone hydrazone with Se_2Cl_2 or Se_2Br_2 under basic conditions gave selenofenchone in 24% or 76% yields, respectively.[2] Recently, we have communicated that thiofenchone reacted with S_2Cl_2 in reluxing dichloroethane to afford the corresponding tricyclic tetrasulfides and selenofenchone reacted with Se_2Br_2 to give Wagner-Meerwein rearranged diselenide[6] and selenofenchone-propiolic acid adduct rearranged to give maleic acid derivative.[7] These results prompted us to investigate the precise reaction of fenchone hydrazone with Se_2Br_2 whether the Wagner-Meerwein rearrangement occurs or not. Herein, we would like to show full details of the synthesis of diselenanes by the reaction of fenchone or camphor hydrazone with Se_2Br_2.

We first tried the reaction of fenchone hydrazone **1** with Se_2Br_2 at 0 °C. Treatment of fenchone hydrazone **1** with 1 eq. of diselenium dibromide and triethylamine (2 eq.) in dichloromethane at 0 °C resulted in the formation of selenofenchone **2** in 50% yield (Table 1, Entry 1), which is almost similar as the reported ones.[3,4] However, when 1.2 eq. of Se_2Br_2 was used, 1,2-bis(7,7-dimethyl-2-methylene-bicyclo[2.2.1]heptan-1-yl)diselenide (**3**) was obtained in 38% yield (Entry 2). When 2 eq. of Se_2Br_2 was used, yield of diselenide **3** was improved to 76% (Entry 4).

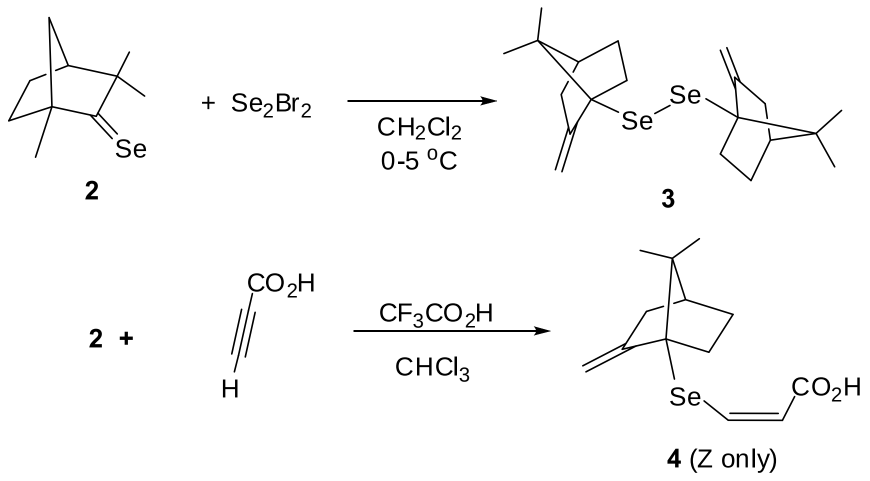
Table 1. Reaction of Fenchone Hydrazone **1** with Se_2Br_2.



Entry	Se_2Br_2/eq	Et_3N/eq.	**2** yield/%	**3** yield/%
1	1.0	2.0	50	0
2	1.2	2.0	0	38
3	2.0	3.0	0	57*
4	2.0	4.0	0	76*

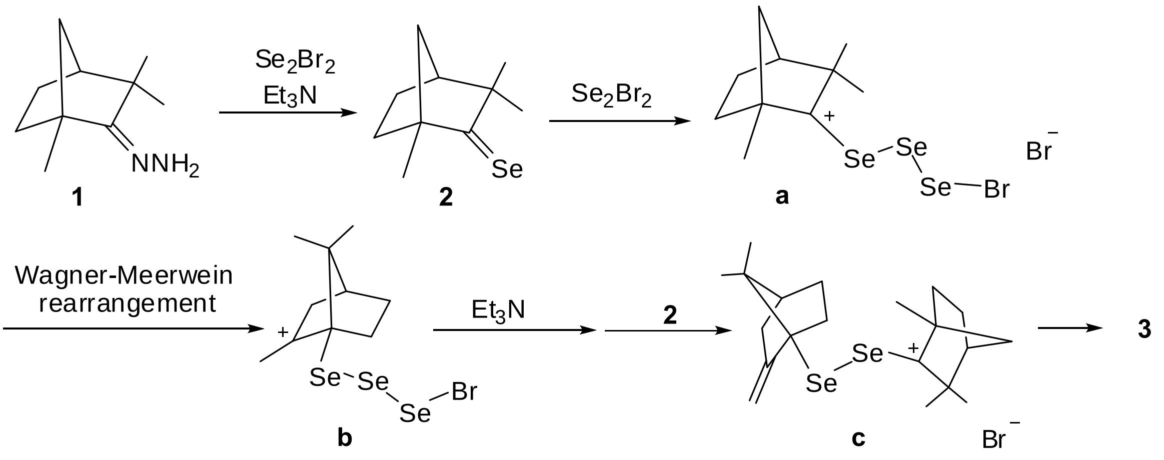
*Less than 3% of triselenide was formed, which easily decomposed to give diselenide **3**.

Structure of diselenide **3** was determined by spectroscopic and elemental analysis. ^1H NMR of compound **3** shows two methyl protons at 0.84 and 1.00 ppm and two exo-methylene protons at 4.85 and 5.16 ppm. To confirm whether excess amount of Se_2Br_2 played as a selenation reagent or an acid, we then tried the following two reaction. First, the reaction of isolated selenofenchone **2** with diselenium dibromide was carried out. Treatment of selenofenchone **2** with Se_2Br_2 (1 eq.) resulted in the formation of diselenide in 88% yield. Next, we tried the reaction of **2** with methyl propiolate in the presence of trifluoroacetic acid (1eq.), which resulted in the formation of rearranged adduct **4** in almost quantitatively, the structure of which was confirmed by the spectroscopic analysis (Scheme 2). Thus, Se_2Br_2 and trifluoroacetic acid play as a Lewis acid toward initially formed selenofenchone **2**.



Scheme 2

Thus, the reaction might proceed as follows: reaction of hydrazone **1** with 1 eq. of Se_2Br_2 gave selenofenchone **2**. Selenofenchone **2** reacted with additional Se_2Br_2 to give carbocation intermediate **a**, which rearranged via Wagener-Meerwein manner to afford the corresponding selenium bromide **b**. Further addition of **2** gave another carbocation **c**, which rearranged via Wagner-Meerwein manner to give diselenide **3** (Scheme 3).

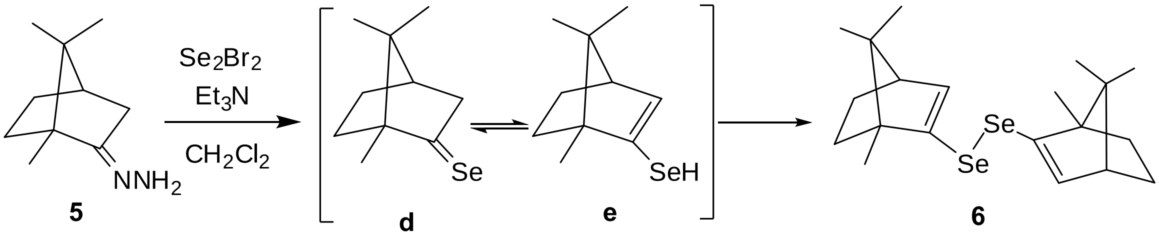


Scheme 3. Plausible Reaction Mechanism

We then tried the reaction of camphor hydrazone **5** with Se_2Br_2 whether the corresponding Wagner-Meerwein rearranged product would be formed. Treatment of hydrazone **5** with Se_2Br_2 (1 eq.) and Et_3N (2 eq.) at 0 °C resulted in the formation of 1,2-bis(1,7,7-trimethylbicyclo[2.2.1]hept-2-enyl)diselenide **5** in 46% yield (Table 2, Entry 1). When 2 eq. of Se_2Br_2 was used, not Wagner-Meerwein product but diselenide **6** was obtained in high yield (Entry 3 and 4). Initially formed selenocamphor **d** tautomerized to afford eneselenol **e**, which readily oxidized to give diselenide **6**.

When 3 eq. of Se_2Br_2 was used, complex mixture of unidentified products was obtained, which suggested that clear Wagner-Meerwein rearrangement reaction, as seen in the reaction with fenchone hydrazone, did not proceed.

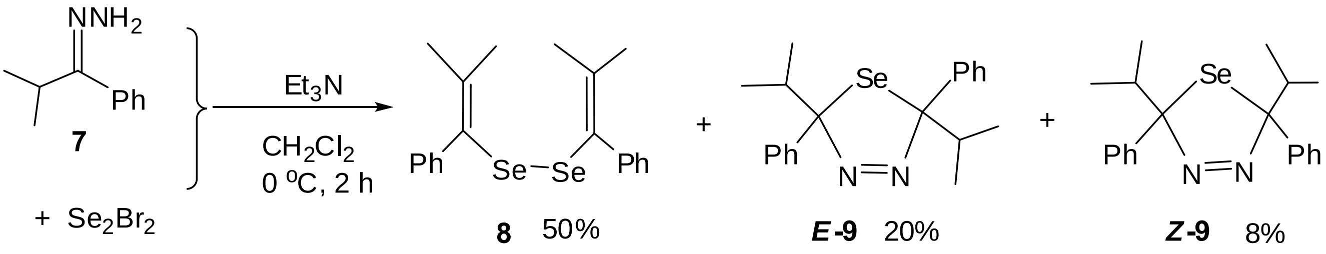
Table 2. Reaction of Camphor Hydrazone **5** with Se_2Br_2.



Entry	Se_2Br_2/eq	Et_3N/eq.	Temp.	**6** yield/%
1	1.0	2.0	0	46
2	1.5	3.0	rt	42
3	2.0	4.0	0	67
4	2.0	4.0	rt	80
5	3.0	6.0	0	-*

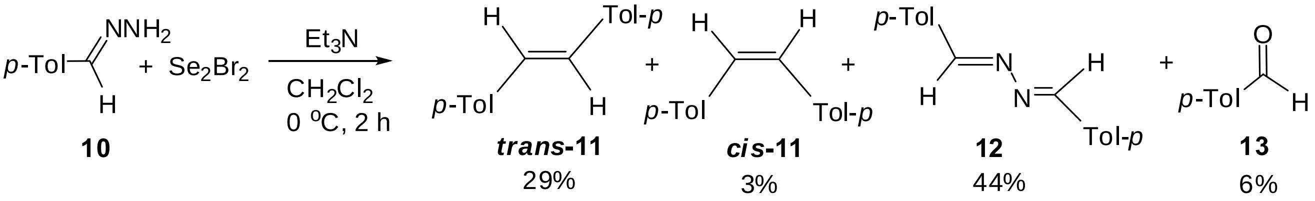
*Unidentified mixture was obtained.

Previously, Shimada et al. reported that the reaction of camphor tosylhydrazone with elemental selenium at 120 °C resulted in the formation of diselenide **6**.[8] Comparing with the present method, it requires high temperature and the yield of **6** was low. Thus, present method provides another formation of dialkenyl diselenides from ketone hydrazones having α-methine hydrogen. We have reported that the reaction of isobutyrophenone hydrazone **7** with diselenium dibromide in refluxing benzene gave bis(2-methyl-1-phenylpropenyl)diselenide **8** and a mixture of *E*- and *Z*-dimethyl-3,4-diphenyl-3-hexene.[9] We then tried this reaction in dichloromethane at 0 °C, which resulted in the formation of diselenide **8** and *E*- and *Z*-phenylisopropyl-1,3,4-selenadiazoline **9** in 50%, 20%, and 8%, respectively (Scheme 4). This result confirms the formation of dialkenyl selenide from α-hydrogen containing ketone hydrazone and Se_2Br_2 under basic conditions.



Scheme 4

When *p*-tolualdehyde hydrazone **10**, which has no α-hydrogen, was used as a substrate under these conditions (2 eq. Se_2Br_2, 4 eq. Et_3N, 0 °C, 2h), the corresponding stilbenes (*trans*-**11** and *cis*-**11**) were obtained in 33% (*trans*:*cis* = 10:1) along with *p*-toluadehyde azine **12** (44%), indicating that the intermediate would be 1,3,4-selendiazoline (Scheme 5).



Scheme 5

Thus, we have found that the reaction of fenchone hydrazone with Se_2Br_2 in the presence of triethylamine gave a new method for the synthesis of bicyclic diselenide via Wagner-Meerwein rearrangement. On the other hand, the reaction of camphor and other ketone hydrazones having α-hydrogen gave the corresponding alkenyl diselenides in moderate to good yields. α-Hydrogen plays an important role for the synthesis of diselenide. The present method provides a novel efficient route to bicyclic diselenides and alkenyl diselenides without isolating selones under very mild conditions.

EXPERIMENTAL

GENERAL: All solvents were distilled. Analytical TLC was carried out on precoated plates (Merck silica gel 60, F254) and flash column chromatography was performed with silica (Merck, 70-230 mesh). NMR spectra (^1H at 400 MHz; ^{13}C at 100 MHz) were recorded in $CDCl_3$, and chemical shifts are expressed in ppm relative to internal TMS ($\delta = 0.00$) and $CDCl_3$ ($\delta = 77.00$) for ^1H- and ^{13}C-NMR. Melting points were uncorrected.

MATERIAL: Fenchone hydrazone and camphor hydrazone were prepared by the reaction of ketones with hydrazine hydrate (EtOH reflux).[3,4] Se_2Br_2 was synthesized by the method reported by Guziec and Mustakis.[4]

REACTION OF FENCHONE HYDRAZONE WITH Se_2Br_2

To a solution of fenchone hydrazone **2** (162 mg, 1.0 mmol) and triethylamine (404 mg, 4.0 mmol) in CH_2Cl_2 (10 mL) was added a solution of Se_2Br_2 (634 mg, 2.0 mmol) in CH_2Cl_2 (10 mL) at 0 °C. After stirring for 2 h, the reaction mixture was washed with water (30 mL), dried over magnesium sulfate, filtered, and evaporated to give brown oil, which was chromatographed over silica gel by elution with hexane to afford diselenide **3** (163 mg, 0.38 mmol) and unstable 1,2-bis(7,7-dimethyl-2-methylene-bicyclo[2.2.1]heptan-1-yl)triselenide (9 mg, 0.02 mmol).

1,2-Bis(7,7-dimethyl-2-methylene-bicyclo[2.2.1]heptan-1-yl)diselenide **3**: yellow needles. Mp 78-79 °C. ^{1}H NMR ($CDCl_3$) δ = 0.84 (s, 3H, Me), 1.00 (s, 3H, Me), 1.35 (m, 2H, CH_2), 1.80-1.96 (m¸ 2H, CHH), 2.04 (d, 1H, *J* = 14 Hz, CHH), 2.41-2.52 (m, 2H, CHH and CH), 4.85 (s, 1H, =CH), 5.16 (s, 1H, =CH). ^{13}C NMR ($CDCl_3$) δ= 20.37 (Me), 20.57 (Me), 28.84 (CH_2), 35.59 (CH_2), 37.45 (CH_2), 43.27 (CH), 50.95 (q-C), 61.82 (q-C), 106.39 (=CH_2), 155.73 (=C). Anal. Calcd for $C_{20}H_{30}Se_2$: C, 56.08; H, 7.06. Found: C, 55.71; H, 6.98. Triselenide could not be isolated due to its instability, which easily extruded selenium to give diselenide **3**.

REACTION OF SELENOFENCHONE 2 WITH PROPIOLIC ACID UNDER ACIDIC CONDITIONS

To a solution of selenofenchone **2** (145 mg, 0.68 mmol) and trifluoroacetic acid (78 mg, 0.68 mmmol) in $CHCl_3$ (5 mL) was added propiolic acid (71 mg, 1.0 mmol) in one portion. After being stirred for 2 days at rt, the reaction mixture was evaporated to give pale brown oily crystals, which was chromatographed over silica gel by elution with CH_2Cl_2-EtOAc (2:1) to give *Z*-adduct **4** (188 mg, 0.66 mmol). Compound **4**[7]: Pale yellow crystals. Mp 156-158 °C. ^{1}H NMR ($CDCl_3$) δ = 0.93 (s, 3H, Me), 1.03 (s, 3H, Me), 1.35-1.42 (m, 1H, CHH), 1.70-1.78 (m, 1H, CHH), 1.84-1.98 (m, 2H, CH and CHH), 2.00-2.14 (m, 2H, CHH), 2.56 (br d, 1H, *J* = 16 Hz, CHH), 4.94 (dd, 1H, *J* = 1 and 2 Hz, =CHH), 5.02 (dd, 1H, *J* = 1 and 2Hz, =CHH), 6.34 (d, 1H, *J* =10 Hz, =CH), 8.04 (d, 1H, *J* = 10 Hz, =CH). ^{13}C NMR ($CDCl_3$) δ = 20.16 (Me), 20.97 (Me), 28.62 (CH_2), 35.51 (CH_2), 37.36 (CH_2), 43.79 (CH), 50.70 (q-C), 63.38 (q-C, $J_{\text{Se-C}}$ = 43 Hz), 107.33 (=CH_2), 116.11 (=CH), 149.84 (=CH, $J_{\text{Se-C}}$ = 80 Hz), 154.08 (=C), 172.49 (C=O). Anal. Calcd for $C_{13}H_{18}O_2Se$: C; 54.74; H, 6.36. Found: C, 55.04; H, 6.41.

REACTION OF CAMPHOR HYDRAZONES WITH Se_2Br_2

To a solution of camphor hydrazone **5** (156 mg, 1.0 mmol) and triethylamine (404 mg, 4.0 mmol) in CH_2Cl_2 (15 mL) was added a solution of Se_2Br_2 (634 mg, 2.0 mmol) in CH_2Cl_2 (10 mL) at rt. After stirring for 2 h, the reaction mixture was washed with water, dried over magnesium sulfate, filtered, and evaporated to give brown oil, which was chromatographed over silica gel by elution with hexane to afford 1,2-bis(1,7,7-trimethylbicyclo[2.2.1]hept-2-enyl)diselenide **6** (171 mg, 0.40 mmol).

Dilselenide **6**: pale yellow oil. ^{1}H NMR ($CDCl_3$) δ = 0.79 (s, 3H, Me), 0.82 (s, 3H, Me), 0.085-1.15 (m, 2H, CH_2), 1.08 (s, 3H, Me), 1.43-1.50 (m, 1H, CHH), 1.82-1.93 (m, 1H, CHH), 2.36 (t, 1H, *J* = 3.0 Hz, CH), 6.14 (d, 1H, *J* =3.0 Hz, =CH). ^{13}C NMR ($CDCl_3$) δ = 11.52 (Me), 18.42 (Me), 18.95 (Me), 24.62 (CH_2), 30.43 (CH_2), 52.07 (CH), 55.70 (q-C), 56.83 (q-C), 136.75 (q-C), 138.07 (=CH). Anal. Calcd for $C_{20}H_{30}Se_2$: C, 56.08; H, 7.06. Found C, 56.39; H, 6.87.

REACTION OF ISOPROPIOPHENONE HYDRAZONE WITH Se_2Br_2

To a solution of isopropiophenone hydrazone **7** (162 mg, 1.0 mmol) and triethylamine (404 mg, 4.0 mmol) in CH_2Cl_2 (10 mL) was added a solution of Se_2Br_2 (634 mg, 2.0 mmol) in CH_2Cl_2 (6 mL) at 0 °C. After stirring for 2 h, the reaction mixture was washed with water, dried over magnesium sulfate, filtered, and evaporated to give brown oil, which was chromatographed over silica gel by elution with hexane to afford 1,2-bis(2-methyl-1-phenyl-1-propenyl)diselenide **8** (105 mg, 0.25 mmol), *E*-selenadiazoline *E*-**9** (37 mg, 0.10 mmol) and *Z*-selenadiazoline *Z*-**9** (14 mg, 0.04 mmol). Diselenide **8**: pale yellow oil. ^{1}H NMR ($CDCl_3$) δ = 1.56 (s, 6H, Me), 2.00 (s, 6H, Me), 6.79 (d, 4H, *J* = 7.2 Hz, Ph), 7.09-7.12 (m, 6H, Ph). ^{13}C NMR ($CDCl_3$) δ = 23.36 (Me), 25.50 (Me), 126.61, 126.84, 127.67, 130.14, 138.24, 142.37 (alkene and Ph). HRMS (*m/z*): Calcd for $C_{10}H_{22}Se_2$ 422.0052 (M^+). Found: 422.0053 (M^+).

Selenadiazoline *E*-**9**: colorless solid: mp 92 °C (dec). ^{1}H NMR ($CDCl_3$) δ = 0.61 (d, 6H. *J* = 7.2 Hz, Me), 0.76 (d, 6H, *J* = 7.2 Hz, Me), 2.59 (sep, 2H, *J* = 7.2 Hz, CH), 7.27 (t, 2H, *J* = 7.6 Hz, 2H, Ph), 7.33 (t, 4H, *J* = 7.6 Hz, Ph), 7.65 (d, 4H, *J* = 7.6 Hz, Ph). ^{13}C NMR ($CDCl_3$) δ = 19.39 (Me), 19.59 (Me), 41.36 (CH), 124.78 (q-C), 127.83, 127.86, 128.18, 143.17 (Ar). Anal. Calcd for $C_{20}H_{26}N_2OSe$ •1/2H_2O: C, 63.15; H, 6.62; N, 7.36. Found: C, 63.37; H, 6.46; N, 6.91. GC-MS of *E*-**9** showed a mixture of (*E*)- and (*Z*)-2,5-dimethyl-3,4-diphenyl-3-hexene (*m/z* = 264.2 and 264.2), selenoisopropiophenone (*m/z* = 212.0), and isopropiofenone azine (292.1).

Selenadiazoline *Z*-**9**: colorless solid: mp 82 °C (dec). ^{1}H NMR ($CDCl_3$) δ = 0.99 (d, 6H, *J* = 6.8 Hz, Me), 1.08 (d, 1H, *J* = 6.8 Hz, Me), 2.89 (hep, 2H, *J* = 6.8 Hz, CH), 7.05-7.13 (m. 6H, Ph), 7.34-7.42 (m, 4H, Ph). ^{13}C NMR ($CDCl_3$) δ = 20.36 (Me), 20.50 (Me), 40.77 (CH), 122.72 (q-C), 127.59 (Ph), 127.78 (Ph), 127.80 (Ph), 141.51 (Ph). Anal. Nitrogen's percentage of *Z*-**9** was little bit off. Anal. Calcd for $C_{20}H_{26}N_2OSe$: C, 64.68; H, 6.51; N, 7.54. Found: C, 64.33; H, 6.59; N, 6.54. GC-MS of *E*-8 showed a mixture of (*E*)- and (*Z*)-2,5-dimethyl-3,4-diphenyl-3-hexene (*m/z* = 264.2 and 264.2), selenoisopropiophenone (*m/z* = 212.0), and isopropiofenone azine (292.1).

REACTION OF *p*-TOLUALDEHYDE HYDRAZONE WITH Se_2Br_2

To a solution of *p*-tolualdehyde hydrazone **10** (134 mg, 1.0 mmol) and triethylamine (440 mg, 4.4 mmol) in CH_2Cl_2 (5 mL) was added a solution of Se_2Br_2 (634 mg, 2.0 mmol) in CH_2Cl_2 (7 mL) at 0 °C. After stirring for 2h, the reaction mixture was filtered by celite, washed with water (10 mL x 3), dried over $MgSO_4$, filtered, and evaporated to give brown oil, which was chromatographed over silica gel by elution with hexane-CH_2Cl_2 (3:1) to give a mixture of *trans*- and *cis*-4,4'-dimethylstilbene **11** (33 mg, 0.16 mmol, *trans:cis* = 10:1), *p*-toluadehyde azine **12** (52 mg, 0.22 mmol), and *p*-tolualdehyde **13** (4 mg, 0.03 mmol). *trans*-4,4'-dimethylstilbene **11**: colorless crystals, mp 179-181 °C (lit.,[10] 179-181 °C). ^{1}H-NMR (400Hz,

$CDCl_3$) δ = 2.36 (s, 3H, CH_3), 7.04 (s, 2H, =CH), 7.16 (d, *J* = 8.0 Hz, 4H, *p*-Tol), 7.40 (d, *J* = 8.0 Hz, 4H, *p*-Tol). *cis*-4,4'-Dimethylstilbene **11'**: colorless oily crystals, mp 32-33 °C, (lit.,[11] mp 31-32 °C). ^{1}H-NMR (400Hz, $CDCl_3$) δ = 2.32 (s, 3H, CH_3), 6.52 (s, 2H, =CH), 7.16 (d, *J* = 8.0 Hz, 4H, *p*-Tol), 7.26 (d, *J* = 8.0 Hz, 4H, *p*-Tol). *p*-Toluadehyde azine **12**: orange crystals, mp 157-159 °C, (lit.,[12] mp 159-160 °C). ^{1}H-NMR (400Hz, $CDCl_3$) δ = 2.35 (s, 6H, Me), 7.30 (d, 4H, *J* = 8.0 Hz, *p*-Tol), 7.65 (d, 4H, *J* = 8.0 Hz, *p*-Tol), 8.60 (s, 2H, =CH).

REFERENCES

1. T. G. Back, D. H. R. Barton, M. R. Britten-Kelly, and F. S. Guziec, Jr., *J. Chem. Soc., Chem. Commun.*, 1975, 539; T. G. Back, D. H. R. Barton, M. R. Britten-Kelly, and F. S. Guziec, Jr., *J. Chem. Soc., Perkin Trans. 1*, 1976, 2079.
2. R. Okazaki, A. Ishii, and N. Inamoto, *Chem. Commun.*, 1983, 1429; A. Ishii, R. Okazaki, and N. Inamoto, *Bull. Chem. Soc. Jpn.*, 1988, **61**, 861.
3. R. Okazaki, M. Minoura, and T. Kawashima, *Chem. Lett.*, 1993, 1047; M. Minoura, T. Kawashima, and R. Okazaki, *J. Am. Chem. Soc.*, 1993, **115**, 7019; M. Minoura, T. Kawashima, N. Tokitoh, and R. Okazaki, *Tetrahedron*, 1997, **53**, 8137.
4. F. S. Guziec, Jr. and C. A. Mustakis, *J. Org. Chem.*, 1984, **49**, 189.
5. A. Ishii, M. Ding, J. Nakayama, and M. Hoshino, *J. Chem. Soc., Chem. Commun.*, 1992, 7; A. Ishii, M. Ding, J. Nakayama, and M. Hshino, *Chem. Lett.*, 1992, 2289; Y. Jin, A. Ishii, Y. Sugihara, and J. Nakayama, *Heterocycles*, 1997, **44**, 255.
6. K. Okuma and K. Munakata, *Phosphorus, Sulfur Silicon Relat. Elem.*, 2011, **186**, 1196.
7. K. Okuma, Y. Mori, T. Shigetomi, M. Tabuchi, K. Shioji, and Y. Yokomori, *Tetrahedron Lett.*, 2007, **48**, 8311.
8. K. Shimada, M.Asahida, K. Takahashi, Y. Sato, S. Aoyagi, Y. Takikawa, and C. Kabuto, *Chem. Lett.*, 1998, 513.
9. K. Okuma, T. Izaki, K. Kubo, K. Shioji, and Y. Yokomori, *Bull. Chem. Soc. Jpn.*, 2005, **78**, 1121.
10. D. J. Cram and R. H. Bauer, *J. Am. Chem. Soc.*, 1959, **81**, 5983.
11. T. Tanabe and T. Nagai, *Bull. Chem. Soc. Jpn.*, 1978, **51**, 1459.
12. K. Okuma, K. Nagakura, Y. Nakajima, K. Kubo, and K. Shioji, *Synthesis*, 2004, 1929.