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5,7-Diaryl-4,4-dimethyl-4,5,6,7-tetrahydropyridino [3,4-d]-1,2,3-selenadiazoles의 손쉬운 One-pot 합성

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A Facile Entry for One-pot Synthesis of 5,7-Diaryl-4,4-dimethyl-4,5,6,7-tetrahydropyridino[3,4-d]-1,2,3-selenadiazoles

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요 약. 마이크로파의 조사 아래 불균일촉매 $NaHSO_4.SiO_2$의 존재하에서 5,7-diaryl-4,4-dimethyl-4,5,6,7-tetrahydropyridino [3,4-d]-1,2,3-selenadiazoles의 one-pot.

주제어: One-pot 합성, 3,3-Dimethyl-2,6-diarylpiperidin-4-one, 1,2,3-Selenadiazoles, Selenium dioxide; $NaHSO_4.SiO_2$ 불균일촉매

ABSTRACT. A simple synthetic strategy is described for one-pot synthesis of 5,7-diaryl-4,4-dimethyl-4,5,6,7-tetrahydropyridino[3,4-d]-1,2,3-selenadiazoles **(11-15)** in the presence of $NaHSO_4.SiO_2$ as a heterogeneous catalyst in dry media under microwave irradiation.

Key words: One-pot synthesis, 3,3-Dimethyl-2,6-diarylpiperidin-4-one; 1,2,3-Selenadiazoles; Selenium dioxide; $NaHSO_4.SiO_2$ Heterogeneous catalyst.

INTRODUCTION

Coupling of dry media synthesis with microwave activation is one of the novel approaches to eco-friendly chemistry. Reports about synthesizing selenium-containing heterocycles are relatively rare,[1,2] although some of them are used as chemotherapeutic agents.[3,4] In addition, organoselenium reagents[5,6] are now commonly used as a powerful tool for introducing new functional groups into organic substrates. Piperidin-4-one nucleus have received extensive attention in the past and recent years because of their diverse biological activities, including antiviral, antitumour,[7,8] central nervous system,[9] local anesthetic,[10] anticancer,[11] and antimicrobial activity[12] and their derivative piperidine are also biologically important and act as neurokinin receptor antagonists,[13] analgesic and anti-hypertensive agents.[14] In recent years there has been a great deal of interest in exploiting more than one proximal functional groups for designing novel structures capable of performing a variety of functions. One such functionality is α-keto methylene group, which has been used as a building block for 1,2,3-selenadiazoles.

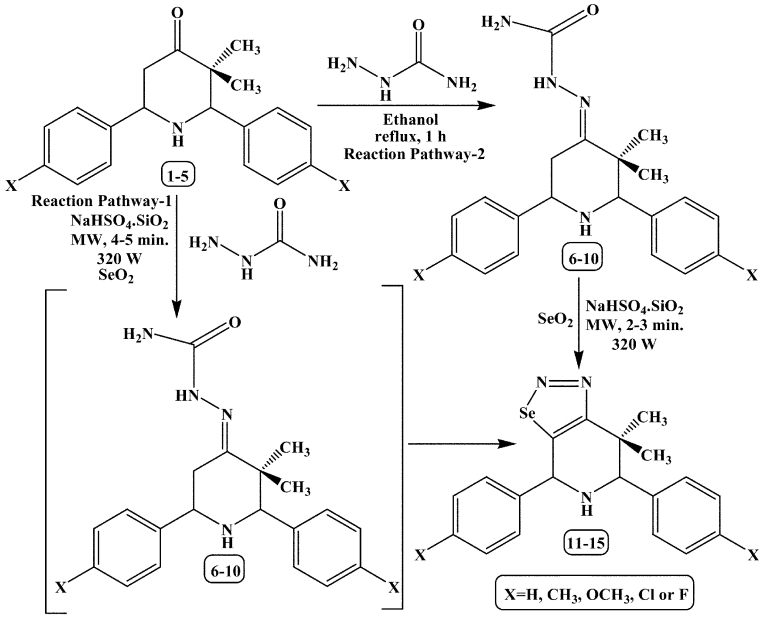
Microwave-induced rate acceleration technology[15-17] has become powerful tool in organic synthesis in view of the mild, clean, and convenient methodol-

ogy and the enhanced selectivity of the reaction processes in comparison to conventional solution reactions, and the associated ease of manipulation. Chemical reactions are accelerated essentially because of selective absorption of microwave energy by polar molecules, which are inert to the microwave dielectric loss. Among them, heterogeneous reactions[18,19] facilitated by supported reagents on various mineral oxides have received special attention in recent years.

Silica gel supported sodium hydrogen sulfate ($NaHSO_4.SiO_2$), a non-toxic and inexpensive catalyst, has been used for one-pot conversion of ketones to amides[18] and single-step synthesis of 4(3H)-quinazolinones.[20] Owing to our interest in synthesizing fascinating pharmacological and therapeutic important compounds under solid-state reactions,[21,22] we report now to use silica gel supported sodium hydrogen sulphate ($NaHSO_4.SiO_2$), as a heterogeneous catalyst for the one-pot conversion of 3,3,-dimethyl-2,6-diaryl-piperidin-4-ones **(1-5)** to 5,7-diaryl-4,4-dimethyl-4,5,6,7-tetrahydropyridino[3,4-d]-1,2,3-selenadiazoles **(11-15)** in dry media under microwave irradiation.

RESULTS AND DISCUSSION

The only classical method[23] available for the synthesis of 1,2,3-selenadiazoles is the conversion of semicarbazones of respective ketones by selenium dioxide in acetic acid medium. There are some problems associated with above synthesis, such as severe conditions, low to moderate yields for the reaction, difficulty in separating the products from the system, and serious environmental pollution. In the present procedure, treatment of 0.01 mole of 3,3-dimethyl-2,6-diaryl-piperidin-4-ones, 0.01 mole of semicarbazide and 0.01 mole of selenium dioxide along with a catalytic amount of $NaHSO_4.SiO_2$ afford the corresponding 5,7-diaryl-4,4-dimethyl-4,5,6,7-tetrahydropyridino[3,4-d]-1,2,3-selenadiazoles **(11-15)** (*Scheme* 1) in high yields with shorter time period in dry media under MW irradiation than the classical method and the results are shown in *Table* 1. Also, the present dry media procedure eliminates the usage of glacial acetic acid[23] solvent for the formation of respective 1,2,3-selenadiazoles. $NaHSO_4.SiO_2$ catalyst was shown to be one of the most efficient MW absorber with a very high specificity to MW heating. It was able to reach a



Scheme 1. One-pot synthesis of 5,7-diaryl-4,4-dimethyl-4,5,6,7-tetrahydropyridino[3,4-d]-1,2,3-selenadiazoles.

Table 1. Reaction time and yields of compounds 11-15

X	Microwave Conditions		Classical Conditions	
	Time (min)	Yield (%)	Time (min)	Yield (%)
H	5	70	60	40
CH_3	4	65	50	46
OCH_3	4	68	40	38
Cl	5	70	60	40
F	4	74	50	44

temperature of 110 ºC after 3 minutes of irradiation in a domestic oven (320 W). Mere 100 mg of $NaHSO_4.SiO_2$ catalyst to 0.01 moles of substrates is the most acceptable ratio in terms of efficiency and safety; a power level of 320 watts is the most suitable one.

The conversion of 3,3-dimethyl-2,6-diaryl-piperidin-4-ones **(1-5)** into 5,7-diaryl-4,4-dimethyl-4,5,6,7-tetrahydropyridino[3,4-d]-1,2,3-selenadiazoles **(11-15)** by this method is believed to be followed *via* the 3,3-dimethyl-2,6-diaryl-piperidin-4-one semicarbazones derivative **(6-10)**. In the first step, 3,3-dimethyl-2,6-diarylpiperidin-4-ones are converted to their respective semicarbazones and rapidly rearrange to give 5,7-diaryl-4,4-dimethyl-4,5,6,7-tetrahydropyridino[3,4-d]-1,2,3-selenadiazoles in the second step. The attempt to isolate the respective semicarbazones from the reaction mixture is unsuccessful.

The formations of 5,7-diaryl-4,4-dimethyl-4,5,6,7-tetrahydropyridino[3,4-d]-1,2,3-selenadiazoles *via* the semicarbazones are confirmed by the same kind of reactions carried out using $NaHSO_4.SiO_2$ catalyst and 3,3-dimethyl-2,6-diarylpiperidin-4-one semicarbazones **(6-10)** and under microwave irradiation for 2-3 min. The products formed from the above two methods are found to be the same.

CONCLUSION

In conclusion, we have developed an efficient, environmentally friendly, one-pot microwave-assisted synthesis of 5,7-diaryl-4,4-dimethyl-4,5,6,7-tetrahydropyridino[3,4-d]-1,2,3-selenadiazoles in good yields under short reaction time.

General remarks

Performing TLC assessed the reactions and the purity of the products. All the reported melting points were taken in open capillaries and were uncorrected. IR spectra were recorded in KBr (pellet forms) on a Nicolet-Avatar-330 FT-IR spectrophotometer and note worthy absorption values (cm^{-1}) alone are listed. ^1H and ^{13}C NMR spectra were recorded at 400 MHz and 100 MHz respectively on Bruker AMX 400 NMR spectrometer using $CDCl_3$ as solvent. The ESI +ve MS spectra were recorded on a Bruker Daltonics LC-MS spectrometer. Satisfactory microanalysis was obtained on Carlo Erba 1106 CHN analyzer. A conventional (*unmodified*) domestic microwave oven equipped with a turntable (LG, MG-395 WA, 230V~50Hz, 760 W) was used for the irradiation.

Experimental procedure for the preparation of $NaHSO_4.SiO_2$: To a solution of 0.01 mole of $NaHSO_4.H_2O$ in 10 mL of water in a 50 mL beaker containing a stir bar was added 4 g of SiO_2. The mixture was stirred for 15 min. and then gently heated on a hot plate with intermittent swirling, until a free flowing white solid was obtained. The catalyst was further dried by placing the beaker in an oven maintained at 120 ºC for 24 h prior to use.

By adopting the literature precedent[24], 3,3-dimethyl-2,6-diarylpiperidin-4-ones **(1-5)** and its semicarbazones were prepared.

*Typical procedure for the synthesis of 5,7-diphenyl-4,4-dimethyl-4,5,6,7-tetrahydropyridino[3,4-d]-1,2,3-selenadiazoles **11***: A mixture containing 0.01 mole of 3,3-dimethyl-2,6-diphenylpiperidin-4-one, 0.01 mole of semicarbazide, and 0.01 mole of selenium dioxide and $NaHSO_4.SiO_2$ (100 mg) was added in an alumina bath and mixed properly with the aid of glass rod (10s) and then irradiated in a microwave oven for 5 min. at 320W (monitored by TLC). After completion of the reaction, the reaction mixture was extracted with ethyl acetate (3×5 mL). The catalyst and other solid wastes were removed by filtration. The combined organic layer was washed with water three times and then dried over anhydrous $MgSO_4$. The organic layer was concentrated *in vacuo* to furnish the products, which were purified by column chromatography using ethyl acetate: petroleum ether (bp 40:60) in the ratio 2:8 as

eluent. Yield: 70%; m.p. 97-99 °C; MS: m/z 369, $M^{+\cdot}$; Molecular formula: $C_{19}H_{19}N_3Se$; Elemental analysis: Carbon 61.91_{found} ($61.96_{cal.}$); Hydrogen 5.17_{found} ($5.20_{cal.}$); Nitrogen 11.38_{found} ($11.41_{cal.}$); IR (KBr) (cm^{-1}): 3306, 3065, 3033, 2969, 2927, 2880, 2798, 1585, 682, 765, 700; ^{1}H NMR (δ ppm): 1.25 (s, 3H, CH_3 at C-4), 1.70 (s, 3H, CH_3 at C-4), 1.94 (s, 1H, H_6); 4.80 (s, 1H, H_5), 5.39 (s, 1H, H_7), 7.22-7.60 (m, 10H, H_{arom}); ^{13}C NMR (δ ppm): 26.5 CH_3 at C-4, 28.1 CH_3 at C-4, 37.5 C-4, 69.5 C-5, 73.9 C-7, 140.4, 142.8 *ipso*-C, 159.1 C-8, 170.5 C-9, 126.9-128.8 -C_{arom}.

The compounds ***7-10*** *were synthesized similarly.*

5,7-Bis(p-methylphenyl)-4,4-dimethyl-4,5,6,7-tetrahydropyridino[3,4-d]-1,2,3-selenadiazoles ***12***: Irradiation reaction time = 5 min.; Yield: 65%; m.p. 100-101 °C; MS: m/z 397, $M^{+\cdot}$; Molecular formula: $C_{21}H_{23}N_3Se$; Elemental analysis: Carbon 63.60_{found} ($63.63_{cal.}$); Hydrogen 5.81_{found} ($5.85_{cal.}$); Nitrogen 10.58_{found} ($10.60_{cal.}$); IR (KBr) (cm^{-1}): 3300, 3022, 2965, 2923, 2854, 1580, 818,670; ^{1}H NMR (δ ppm): 1.20 (s, 3H, CH_3 at C-4), 1.71 (s, 3H, CH_3 at C-4), 2.27 (s, 1H, H_6); 2.35 (s, 6H, CH_3 at Arom. ring), 4.83 (s, 1H, H_5), 5.41 (s, 1H, H_7), 7.14-7.28 (m, 8H, H_{arom}); ^{13}C NMR (δ ppm): 21.1 CH_3 at Arom. ring, 26.8 CH_3 at C-4, 28.1 CH_3 at C-4, 37.5 C-4, 68.2 C-5, 73.5 C-7, 134.9, 137.2, 141.5, 142.6 *ipso*-C, 158.9 C-8, 170.5 C-9, 127.0-129.4 -C_{arom}.

5,7-Bis(p-methoxylphenyl)-4,4-dimethyl-4,5,6,7-tetrahydropyridino[3,4-d]-1,2,3-selenadiazoles ***13***: Irradiation reaction time = 4 min.; Yield: 68%; m.p. 106-108 °C; MS: m/z 429, $M^{+\cdot}$; Molecular formula: $C_{21}H_{23}N_3O_2Se$; Elemental analysis: Carbon 58.85_{found} ($58.88_{cal.}$); Hydrogen 5.37_{found} ($5.41_{cal.}$); Nitrogen 9.79_{found} ($9.81_{cal.}$); IR (KBr) (cm^{-1}):3315, 2959, 2925, 2923, 1578, 831, 668; ^{1}H NMR (δ ppm): 1.38 (s, 3H, CH_3 at C-4), 1.54 (s, 3H, CH_3 at C-4), 2.35 (s, 1H, H_6); 3.81 (s, 6H, OCH_3 at Arom. ring), 4.79 (s, 1H, H_5), 5.34 (s, 1H, H_7), 7.22-7.44 (m, 8H, H_{arom}); ^{13}C NMR (δ ppm): 24.5 CH_3 at C-4, 25.6 CH_3 at C-4, 37.7 C-4, 55.2, 55.5 -OCH_3 at Arom. ring, 68.0 C-5, 73.2 C-7, 130.2, 131.9, 159.1, 159.7 *ipso*-C, 158.5 C-8, 170.5 C-9, 113.8-129.7 -C_{arom}.

5,7-Bis(p-chlorophenyl)-4,4-dimethyl-4,5,6,7-tetrahydropyridino[3,4-d]-1,2,3-selenadiazoles ***14***: Irradiation reaction time = 4 min.; Yield: 70%; m.p. 110-112 °C; MS: m/z 438, $M^{+\cdot}$; Molecular formula: $C_{19}H_{17}Cl_2N_3Se$; Elemental analysis: Carbon 52.13_{found} ($52.19_{cal.}$); Hydrogen 3.90_{found} ($3.92_{cal.}$); Nitrogen 9.57_{found} ($9.61_{cal.}$); IR (KBr) (cm^{-1}): 3322, 3297, 2929, 2863, 1588, 834, 676; ^{1}H NMR (δ ppm): 1.20 (s, 3H, CH_3 at C-4), 1.72 (s, 3H, CH_3 at C-4), 2.16 (s, 1H, H_6), 4.49 (s, 1H, H_5), 5.06 (s, 1H, H_7), 7.22-7.48 (m, 8H, H_{arom}); ^{13}C NMR (δ ppm): 26.1 CH_3 at C-4, 28.2 CH_3 at C-4, 37.5 C-4, 68.8 C-5, 73.2 C-7, 133.4, 136.6, 137.2, 138.5 *ipso*-C, 158.5 C-8, 170.8 C-9, 128.1-130.7 -C_{arom}.

5,7-Bis(p-fluorophenyl)-4,4-dimethyl-4,5,6,7-tetrahydropyridino[3,4-d]-1,2,3-selenadiazoles ***15***: Irradiation reaction time = 4 min.; Yield: 74%; m.p. 119-120 °C; MS: m/z 405, $M^{+\cdot}$; Molecular formula: $C_{19}H_{17}F_2N_3Se$; Elemental analysis: Carbon 56.41_{found} ($56.44_{cal.}$); Hydrogen 4.21_{found} ($4.24_{cal.}$); Nitrogen 10.35_{found} ($10.39_{cal.}$); IR (KBr) (cm^{-1}): 3320, 3293, 2924, 2859, 1579, 1201, 823, 671; ^{1}H NMR (δ ppm): 1.23 (s, 3H, CH_3 at C-4), 1.77 (s, 3H, CH_3 at C-4), 2.19 (s, 1H, H_6), 4.51 (s, 1H, H_5), 5.09 (s, 1H, H_7), 7.28-7.51 (m, 8H, H_{arom}); ^{13}C NMR (δ ppm): 26.7 CH_3 at C-4, 28.4 CH_3 at C-4, 37.9 C-4, 69.1 C-5, 73.5 C-7, 134.4, 137.1, 138.7, 139.5 *ipso*-C, 159.3 C-8, 171.3 C-9, 129.5-131.6 -C_{arom}.

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