Tetrahedron Letters 51 (2010) 3062–3064

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Improved enamine-type addition of dehydroaporphine using microwave irradiation

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ARTICLE INFO

Article history:
Received 29 March 2010
Accepted 5 April 2010
Available online 13 April 2010

ABSTRACT

Previous report demonstrated that 7-substituted aporphine, possessing interesting biological aspects, could be synthesized via an enamine-type addition of dehydroaporphine reacted with an electrophile, but it has the drawbacks of a long reaction time, low yield, and limitation to reactive electrophiles. Here we found that the reaction time and yield could greatly be improved under microwave irradiation in the presence of 4 equiv of sodium iodide for the synthesis of 7-benzyl dehydroglaucine. The application of this finding for treating dehydroglaucine with a variety of alkyl bromides also gave corresponding 7-substituted dehydroglaucines (**2a**–**j**) with yields of 14–89%. Other enamines such as 1,10-dimethoxydehydroaporphine (**3a**), 2,9-diacetyldehydroboldine (**3b**), and 7,8-dihydroberberine (**5**) were found to react with benzyl bromide under similar conditions as described above to give corresponding products (**4a**–**b**, **6**) in satisfactory yields, indicating the versatility of this improved reaction condition.

Aporphines are naturally occurring isoquinoline alkaloids that are widely distributed in plants belonging to several families such as the Annonaceae, Lauraceae, Monimiaceae, Menispermaceae, Hernandiaceae, and Ranunculaceae.[1] Various biosynthetic reactions afforded versatile substitutions on rings A–D of the aporphine skeleton, leading to the diverse structures and bioactivities including serotonergic,[2] dopaminergic,[2] antiplatelet,[3] antimicrobial,[4] and anticancer activities.[5] Of these activities, structure–activity relationships (SARs) for binding affinity to either dopaminergic or serotonergic receptors are well documented. Previous efforts focused on introducing heteroatoms such as nitrogen,[6] oxygen,[7] halide[8] and sulfur,[9] and alkyl groups into the A- or D-ring,[10,11] and different chain-length alkyl groups into N-6[12,13] to improve their affinity and selectivity for receptors. We synthesized a series of aporphine analogues from the commercially available boldine for further pharmacological studies. Recently, the hypoglycemic effect of boldine derivatives was demonstrated.[14] To enrich the chemical bank for the SAR study on this aspect, we tried to prepare 7-substituted dehydroaporphines. The semi-synthesis of 7-substituted aporphines had been developed by Cava and co-workers[15] by reacting dehydroaporphines with an electrophile via an enamine-type addition. Such an approach, however, was limited to highly reactive electrophiles such as acyl halides, α,β-unsaturated carboxylate esters, and benzoquinones.[16,17]

During last decade, microwave activation has increasingly been used in pharmaceutical chemistry due to several advantages including improved yields, enhanced reaction rates, and efficient energy compared to conventional heating methods.[18,19] We found that microwave irradiation effectively improved yields and shortened the reaction time of this reaction. To our knowledge, no previous report mentioned the application of microwave-activation for the enamine-type addition of dehydroaporphine. The following describes the outcome of our efforts with this finding and the application of this method to synthesize a variety of 7-substituted dehydroglaucines (Fig. 1).

Dehydroglaucine (**1**) was prepared using boldine as the starting material via selective *O*,*O*-dimethylation[20] and C_{6a}–C_7 dehydrogenation.[21] The results of the reaction of dehydroglaucine (**1**) with benzyl bromide to afford 7-benzyl dehydroglaucine (**2c**) under dif-

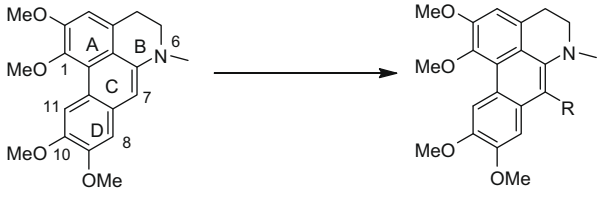

Figure 1. Synthesis of 7-substituted dehydroglaucines via an enamine-type addition.

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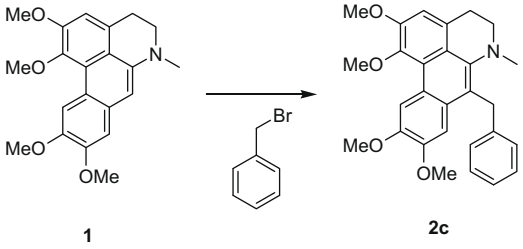
doi:10.1016/j.tetlet.2010.04.008

Table 1
Reaction conditions for the synthesis 7-benzyl dehydroglaucine (**2c**)



1 **2c**

Run	Solvent	Heating condition	Additive	Time	Yield[a] (%)
1	Dioxane	Reflux	None	72 h	Trace
2	MeCN	Reflux	None	72 h	Trace
3	DMF	Reflux	None	72 h	Trace
4	MeCN	Reflux	NaI	24 h	55
5	Toluene	Reflux	NaI	24 h	11
6	DMF	Reflux	NaI	24 h	15
7	MeCN	Microwave[b]	NaI	20 min	89
8	Toluene	Microwave[b]	NaI	20 min	12
9	DMF	Microwave[b]	NaI	20 min	51
10	MeCN	Microwave[b]	None	40 min	Trace

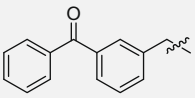
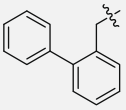
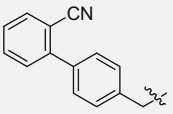
[a] Isolated yields.
[b] Reaction conditions: reaction temperature at 80 °C, irradiation time for 20 min and the maximal output at 100 W.

ferent conditions are summarized in Table 1. It was found that the reaction using dioxane, acetonitrile, or DMF as a solvent (Table 1, Runs 1–3) afforded only a trace amount of **2c**, even after 72 h.[22] An attempt to improve this reaction using 5 equiv of benzyl bromide in acetonitrile, however, yielded N^6,C-7-dibenzyldehydroglaucine. Evans et al.[23] synthesized a morphine skeleton via an intramolecular enamine alkylation by heating the chloroenamine in acetonitrile in the presence of 4 equiv of sodium iodide. Hence, we followed this reaction condition, and the yield increased to 55% after 24 h (Table 1, Run 4). The replacement of acetonitrile by either toluene or DMF, however, gave lower yields of 11% and 15%, respectively (Table 1, Runs 5 and 6). Owing to the reported advantages of microwave irradiation, it was used as a heating source, and we found that the reaction time was dramatically shortened and the yield was also significantly improved (Table 1, Run 7) compared to conventional heating. The solvent effect, which gave 12% and 51% yield, respectively, upon replacing acetonitrile with toluene or DMF (Table 1, Runs 8 and 9), was found to be similar to what was indicated above. It was also noted that the additive, NaI, is critical for this reaction since devoid of NaI in Run 7, the reaction did not work even with a prolonged reaction time (120 min) (Table 1, Run 10). This finding suggests that the microwave irradiation and the presence of sodium iodide play important roles in providing a satisfactory yield and rapid reaction time for the condensation of dehydroglaucine with benzyl bromide via an enamine-type addition.

The generality of the above-mentioned reaction conditions for the preparation of 7-alkyl-dehydroaporphines was verified by treating dehydroglaucine (**1**) with various alkyl halides in acetonitrile under microwave irradiation[24] with the additive of sodium iodide (4 equiv) (Table 2). It was found that more reactive halides such as benzyl bromide and allyl bromide gave better yields than the less active halides such as methyl iodide (Table 2, Runs 1–3). In spite of low yields while dehydroglaucine (**1**) reacted with either methyl iodide or allyl bromide, the yield was improved compared to that of a conventional heating condition, whose reaction was undertaken in our lab. In order to investigate the electronic effect on the enamine-type addition, it was carried out by reacting with benzyl bromides substituted with electron-withdrawing or electron-donating groups (Table 2, Runs 4–7). The result indicates that substituted benzyl

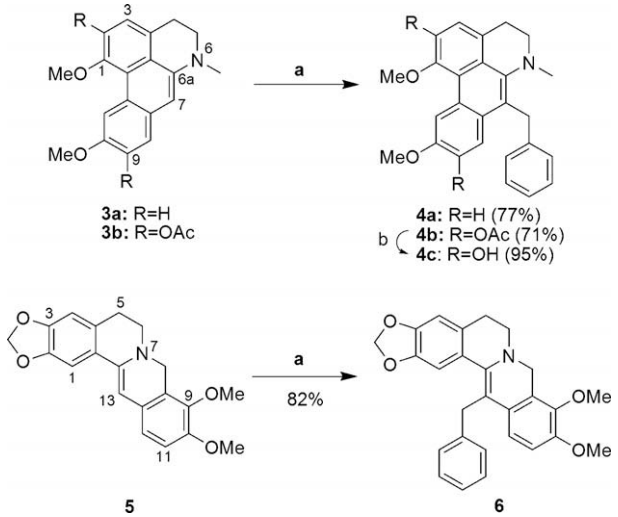
Table 2
Synthesis of 7-substituted dehydroglaucines (**2a–j**) under microwave irradiation

1 **2a-j**

Run	R	Product	Mp (lit. mp) (°C)	Yield[a] (%)
1	Me	**2a**	151–154 (148–150)[25]	14
2	Allyl	**2b**	—	31
3	Bn	**2c**	88–92	89
4	*p*-Br–Bn	**2d**	70–73	45
5	*p*-CF_3–Bn	**2e**	92–95	35
6	*p*-MeO–Bn	**2f**	—	25
7	*p*-NO_2–Bn	**2g**	50–54	72
8		**2h**	148–151	53
9		**2i**	160–162	51
10		**2j**	195–200	62

[a] Isolated yields.

bromides gave lower yields relative to the nonsubstituted one. Further analysis indicated that those substituted with electron-withdrawing groups (nitro-) afforded better yields than those substituted with electron-donating groups (methoxy-). This suggests that the electron-withdrawing effect has a positive contribution for the reaction. We finally treated dehydroglaucine (**1**) with *m*-benzoyl-, *p*-phenyl, and *o*-(2-cyanophenyl)-benzyl bromides (Table 2, Runs 8–10). It was shown that most of these had lower yields than **2c**, indicating that the steric effect of the N^6-Me group hampered the formation of the products to some extent.



Scheme 1. Reagents and conditions: (a) BnBr, NaI, MeCN, MW; (b) K_2CO_3, MeOH, N_2, rt.

To explore the versatility of this reaction for natural products with an enamine moiety, two dehydroaporphines (**3a** and **3b**) together with 7,8-dihydroberberine (**5**) were treated in the similar manner as described in Scheme 1. Compound **3a** was synthesized from boldine via three reaction steps: reaction with 5-chloro-1-phenyltetrazole,[26] hydrogenolysis,[26] and dehydrogenation.[21] Compound **3b** was prepared from boldine via acetylation followed by dehydrogenation.[21] The reaction of **3a** and **3b** with benzyl bromide under general microwave irradiation gave **4a** and **4b** in 77% and 71% yields, respectively. Similarly, the reaction of 7,8-dihydroberberine (**5**), prepared from sodium borohydride reduction of berberine,[27] gave 13-benzyl-7,8-dihydroberberine (**6**) in an 82% yield. In conclusion, this study provides a highly efficient method to prepare substituted enamine, in particular dehydroaporphine and 7,8-dihydroberberine, relative to the conventional method. This method not only accelerates the enamine-type addition, using microwave irradiation as a heating source, but also improves yields by the addition of sodium iodide.

Acknowledgment

We gratefully acknowledge the National Science Council, Taiwan, R. O. C., for the support of this work under Grants NSC97-2323-B-002-015 and NSC97-2320-B-038-010-MY3.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.04.008.

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24. The microwave reactor Discovery Benchmate (CEM) was used for microwave irradiation as a sealed vessel technique. The temperature of reaction mixture was measured and controlled to a constant level using an infrared temperature detector. The general condition for the synthesis of 7-substituted dehydroglaucines (**2a–j**, **3a–b**, **5**) is described as follows. The mixture of dehydroglaucine (100 mg, 0.28 mmol) of MeCN (2 mL) was added to NaI (166 mg, 1.12 mmol) and substituted alkyl halide (1.40 mmol), and the resulting suspension was heated to 80 °C under microwave irradiation for 20 min. The reaction mixture was condensed under reduced pressure. The residue was suspended in CH_2Cl_2 (50 mL), and partitioned against distillated H_2O (25 mL × 2) and brine (25 mL). The organic layer was dried over anhydrous Na_2SO_4 and condensed under reduced pressure. The residue was chromatographed over semi-preparative high-performance liquid chromatography (HPLC) (C_{18}), delivered with MeOH–H_2O (9:1), to give the desired products. The physical data of compounds **2a–j**, **4a–c**, and **6** are provided in the Supplementary data.
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