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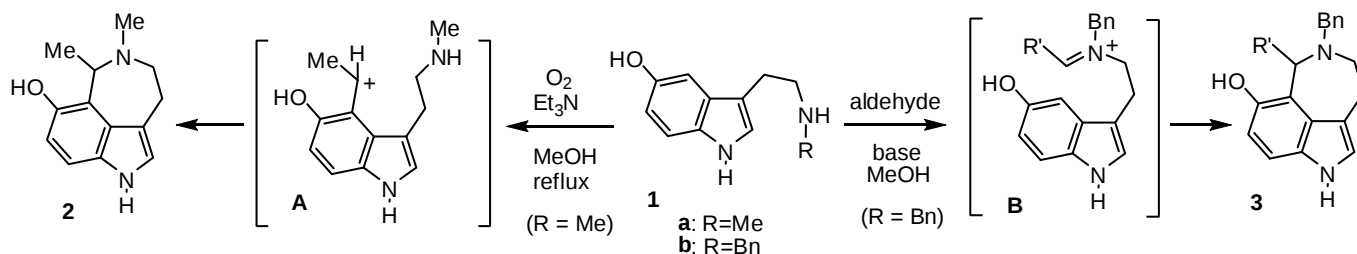
REACTION OF *N*_β-BENZYLSEROTONIN WITH α,β -UNSATURATED AND ARYL ALDEHYDES IN THE PRESENCE OF A BASE

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Abstract – The reaction of *N*_β-benzylserotonin with α,β -unsaturated and aryl aldehydes in the presence of a base produced 1*H*-azepino[5,4,3-*cd*]indoles.

Pictet-Spengler reaction is widely accepted as one of the most fundamental and versatile synthetic protocol in heterocyclic synthesis.¹ Generally, tryptamine derivatives are known to react with aldehydes under acidic or neutral conditions through an initial iminium ion formation, followed by cyclization onto the 2-position of the indole ring, leading to β -carboline.² On the other hand, it has been previously proved that heating of *N*_β-methylserotonin (**1a**) with large excess Et₃N under O₂ atmosphere in MeOH provided azepinoindole **2** in moderate yield, in which the intermediary formation of **A** from **1a** and acetaldehyde equivalent generated *in situ* from Et₃N and O₂ was speculated.³ Therein, ready availability of **2** from treatment of **1a** with acetaldehyde in the presence of Et₃N in high yield was also shown.³ Therefore, we have become interested in the applicability of other aldehydes to the cyclization reaction from the standpoint of synthetic potential. In this report, we describe the reaction of *N*_β-benzylserotonin **1b** with α,β -unsaturated and aryl aldehydes in the presence of a base.⁴



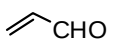
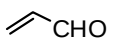
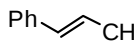
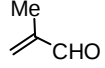
Scheme 1

The reaction was carried out simply by treating **1b** with aldehydes **4** and **6** (3 equiv.) in the presence of a base in MeOH, and products were separated by flash chromatography.⁵ At first, the reaction of **1b** with α,β -unsaturated aldehyde **4a** was undertaken, leading to **3a** in moderate yield (Table 1, runs 1 and 2).

This paper is dedicated to Professor Emeritus Keiichiro Fukumoto on the occasion of his 75th birthday.

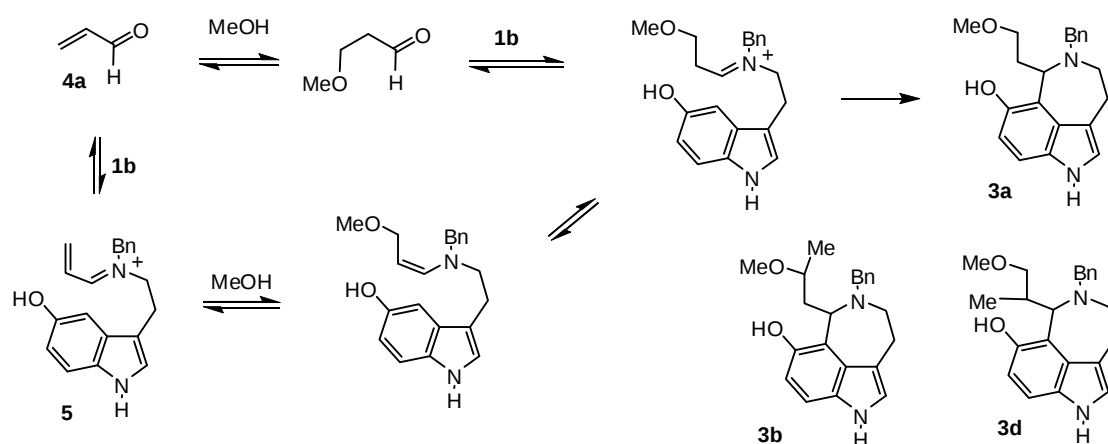
Reactions of **4b** and **4c** produced **3b** and **3c**, respectively, in good yields. Since the reactions of **4d** and **4e** equipped with an α -Me group were subject to steric hindrance (runs 5-7). On treating **4d** at room temperature for 7 days, only small amount of **3d** was isolated along with **3f** in 16% yield.⁶ Heating of **4e** under reflux for 5 days gave **3e** in 50% yield (run 7).

Table 1. Reaction of **1b** with α,β -unsaturated aldehydes **4**^a

run	aldehyde 4	conditions	yield (%) of 3 ^b
1	 4a	rt / 24 h	41 (3a) (R'=CH ₂ CH ₂ OMe)
2	 4a	reflux / 3 h	55 (3a)
3	 4b	rt / 24 h	75 (3b) ^c (R'=CH ₂ CHMeOMe)
4	 4c	rt / 6 h	84 (3c)
5	 4d	rt / 7 d	10 (3d) ^{c, d} (R'=CHMeCH ₂ OMe)
6	 4e	rt / 24 h	--- ^e
7	4e	reflux / 5 d	50 (3e)

^aTreatment of **1b** with aldehyde (3 equiv.) in Et₃N:MeOH (1:1). ^bIsolated yield based on **1b**. ^cTwo diastereoisomers in a 1:1 ratio. ^dIsolation of **3f** (R'=Et) in 16% yield.⁶ ^eNo reaction.

Scheme 2 depicts the outcome for the production of **3a** involving the facile addition of MeOH to **4a** and/or the addition of MeOH to iminium ion **5**, which is also illustrative of the generation of **3b** and **3d**.

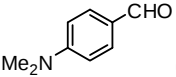
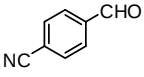
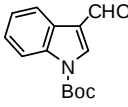
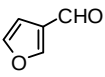


Scheme 2

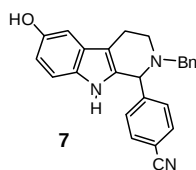
Next, aryl aldehydes **6** were subjected to the reaction with **1b** (Table 2). While the reaction with **6a** was completed in 24 h under reflux, substitution of large excess Et₃N for DABCO (3 equiv.) was, to our

delight, found to lead to a significant shortening of the reaction time in producing **3g** in high yield (runs 1 and 2). Aldehyde **6b** equipped with an electron donating group required elongation of the reaction time. In contrast, the reaction with **6c** having an electron withdrawing group produced moderate amount of **3i** accompanied by a small amount of β -carboline **7**. The treatment of indole-3-carbaldehyde with **1b** gave no identifiable products, whereas subjection of **6e** bearing the *N*-Boc group to the reaction was far more successful producing **3k** in high yield.

Table 2. Reaction of **1b** with aryl aldehydes **6**^a

run	aldehyde 6	conditions	yield (%) of 3 ^b
1	PhCHO 6a	Et ₃ N / 24 h	86 (3g)
2	PhCHO 6a	DABCO / 3 h	85 (3g)
3	 6b	DABCO / 12 h	74 (3h)
4	 6c	DABCO / 3.5 h	55 (3i) ^c
5	 6d	DABCO / 3 h	83 (3j)
6	 6e	DABCO / 3 h	86 (3k)
7	 6f	DABCO / 3 h	84 (3l)

^aTreatment of **1b** with aldehyde (3 equiv.) in the presence of Et₃N (large excess) or DABCO (3 equiv.) in MeOH under reflux. ^bIsolated yield based on **1b**. ^c β -Carboline **7** in 9% yield.



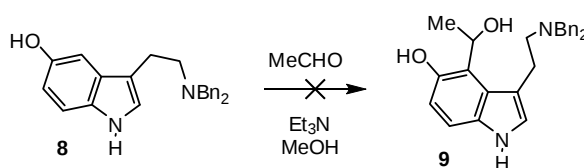
In summary, we have shown that the reaction of *N*_β-benzylserotonin (**1b**) with α,β -unsaturated and aryl aldehydes proceeded smoothly with the aid of a base, successfully providing azepinoindoles **3**. Further studies of the present cyclization reaction, including applications to natural product synthesis, are underway.

ACKNOWLEDGEMENTS

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3. M. Somei, S. Teranishi, K. Yamada, and F. Yamada, *Chem. Pharm. Bull.*, 2001, **49**, 1159.
4. Since we were unable to detect **9** on treating **8** with MeCHO, it seemed likely that the reaction proceeded through the formation of iminium ion **B**, followed by Pictet-Spengler type cyclization onto the 4-position of the indole ring.



5. Reaction of **1b** with **4c**: Typical procedure: A mixture of **1b** (100 mg, 0.4 mmol), **4c** (0.14 mL, 1.2 mmol), Et₃N (5 mL) and MeOH (5 mL) was stirred at rt for 6 h. The mixture was concentrated, and the residue was separated by flash chromatography (SiO₂/ hexane-AcOEt = 1:3) to give **3c** in 84% yield. ¹H-NMR (CDCl₃) δ: 2.85 (dt, 1H, *J* = 16.6, 2.4 Hz), 3.07 (ddd, 1H, *J* = 13.7, 3.2, 2.4 Hz), 3.20 (ddd, 1H, *J* = 16.6, 13.7, 3.2 Hz), 3.59 (td, 1H, *J* = 13.7, 3.2 Hz), 3.94 (d, 1H, *J* = 13.7 Hz), 4.10 (d, 1H, *J* = 13.7 Hz), 5.18 (d, 1H, *J* = 5.7 Hz), 6.16 (d, 1H, *J* = 16.0 Hz), 6.58 (dd, 1H, *J* = 16.0, 5.2 Hz), 6.78 (d, 1H, *J* = 8.6 Hz), 6.98 (s, 1H), 7.19 (d, 1H, *J* = 8.6 Hz), 7.24-7.27 (m, 5H), 7.30-7.34 (m, 3H), 7.41 (d, 2H, *J* = 7.4 Hz), 7.96 (s, 1H). ¹³C-NMR (CDCl₃) δ: 26.4, 46.2, 56.6, 63.3, 110.2, 113.0, 115.5, 119.9, 121.9, 126.6, 126.9, 127.4, 128.3, 128.4, 128.8, 130.5, 131.6, 132.4, 136.9, 140.0, 146.3. HR-MS *m/z*: Calcd for C₂₆H₂₄N₂O: 380.1889. Found: 380.1890.
6. It seemed likely that **3f** resulted from the reaction of **1b** with propionaldehyde generated *in situ* through the addition of H₂O to **4d** and the subsequent retro-aldol step.

