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一种利用酰胺基转移反应脱除酰基保护基的实用方法

韩 群 徐 坤* 田发宁 黄胜阳* 曾程初*
(北京工业大学环境与生命学部 北京 100124)

摘要 酰胺化合物中的酰基脱除是有机合成化学的重要研究方向之一. 但是, 由于酰胺键较为惰性, 在温和条件下脱除酰基保护基的报道较少. 为了解决上述问题, 发展了一种使用氨水脱除酰基保护基的新方法. 该方法不但条件温和, 而且可以放大规模反应(10 mmol). 一系列药物分子或者药物分子衍生物, 例如吲哚美辛、*N*-乙酰基褪黑素及 *N*-乙酰基卡布洛芬中的酰基都可以采用此方法高产率脱除. 该方法具有较好的官能团容忍性、操作简便、条件温和、产率高以及所用的试剂廉价易得等优势. 因此, 该方法有望成为 *N*-酰基脱保护的实用方法之一.

关键词 脱酰基; 酰胺基转移; 绿色合成; 酰胺

A Practical Transamidation Strategy for the N-Deacylation of Amides

Han, Qun Xu, Kun* Tian, Faning Huang, Shengyang* Zeng, Chengchu*
(*Faculty of Environment and Life*, *Beijing University of Technology*, *Beijing 100124*)

Abstract The N-deacylation of amides under mild conditions is highly desirable in organic synthesis, but it remains challenging due to the chemically robust nature of amide bond. A general solution to the N-deacylation of amides with NH_3•H_2O under mild and scalable conditions (10 mmol) was developed. A range of drugs and drug derivatives including indomethacin, *N*-acetyl melatonin and *N*-acetyl carprofen could be deacylated to release free amines in excellent yields. The good functional group compatibility, combined with operational simplicity, excellent yield and cost effectiveness of all reagents, makes this protocol a prime candidate for N-deacylation of amide.

Keywords deacylation; transamidation; green synthesis; amide

1 Introduction

Amines are not only widespread in pharmaceuticals and natural products, but also represent a class of particularly valuable synthon in organic synthesis.[1] However, due to their basicity, remarkable nucleophilicity and susceptibility to oxidation, amines are necessarily to be protected in many instances to furnish synthesis with an increased level of predictability and security. Acyl group has been widely popularized in amine protection to alter the reactivity of amines. The resulting acylated amines have wide applications in total synthesis,[2] asymmetric hydrogenation of enamides[3] and site-selective C—H functionalizations, serving as important directing groups.[4] Although the application of acylated amines has gained increased attention in recent years, the N-deacylation of amides under mild conditions is underdeveloped because of the chemically robust nature of amide bond.

The traditional methods for N-deacylation of amides relied on the use of strong bases or acids at high reaction temperatures (Scheme 1, a).[5] Such hash hydrolysis conditions would lead to functional group compatibility issues, and thus detract from the synthetic potential of acylated amines. To overcome this limitation, new strategies employing phosphate-chlorine complex or oxalyl chloride to activate the amides at lower temperatures have been developed (Scheme 1, b).[6-7] However, anhydrous conditions are necessary in these transformations. Recently, Zr- or Ce-based organometallic reagents[8-9] or the combination of $Sc(OTf)_3$/boronic ester[10] have been utilized to enable the cleavage of acylated amines under mild conditions (Scheme 1, c). Despite their high efficiencies, the use of metal salts would cause various environmental issues. Transamidation provides an attractive alternative for the deprotection of amides with the assistance of suitable amine nucleophiles. In this context, Ohshima *et al*.[11] re-

* Corresponding authors. E-mail: kunxu@bjut.edu.cn; hsy@bjut.edu.cn; zengcc@bjut.edu.cn
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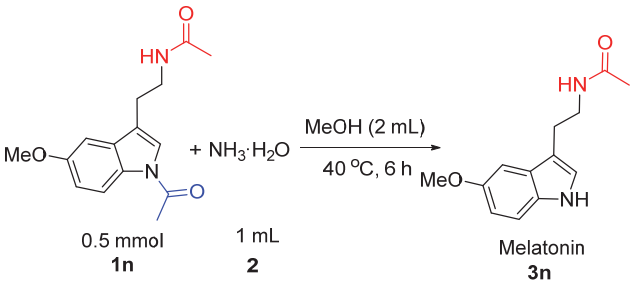
ported an elegant transamidation process promoted by the combination of ethylenediamine and NH_4Br under microwave irradiation conditions (Scheme 1, d). To realize a user-friendly deprotection of acylated amines, and in continuation of our interest in green synthesis,[12] we herein describe a general solution to the problem of deacylation of amides by exploiting a transamidation strategy with NH_3•H_2O as the amine nucleophiles (Scheme 1, e). A variety of acylated amines and amides including indoles, oxindole, isatin and benzamide could be deprotected with high efficiencies. Since the nucleophilic nature of NH_3 is stronger than that of water, the deprotection of acylated amine can be carried out under semi-aqueous conditions. In most cases, the isolation of the free amines can be realized with an extractive workup because the excess NH_3•H_2O and the side product formamide are soluble in water.

2 Results and discussion

The diacylation of acylated melatonin (**1n**) was chosen as a model reaction for the reaction condition optimization (Table 1). The deacylated product melatonin (**3n**) is an endogenous hormone and plays a significant role in the regulation of sleep-wake cycle.[13] When **1n** was treated with NH_3•H_2O in MeOH at 40 ℃, the desired product **3n** was obtained in 91% yield (Entry 1). Decreasing the reaction temperature to room temperature led to a much lower yield of **3n** (Entry 2). Increasing the reaction temperature to 60 ℃ could not improve the yield (Entry 3). Then, a series of solvents were examined (Entries 4～8). When MeOH was replaced by dichloromethane (DCM), dichloroethane (DCE) or tetrahydrofuran (THF), only trace amount of desired product **3n** was observed (Entries 4～6). When MeOH was replaced by MeCN or EtOH, the yield of **3n** was isolated in 47% and 67% yields, respectively (Entries 7, 8). Decreasing the amount of MeOH or NH_3•H_2O led to lower yields of **3n** (Entries 9, 10). Replacing NH_3•H_2O with CH_3NH_2 gave deacylated product **3n** in 63% yield (Entry 11).

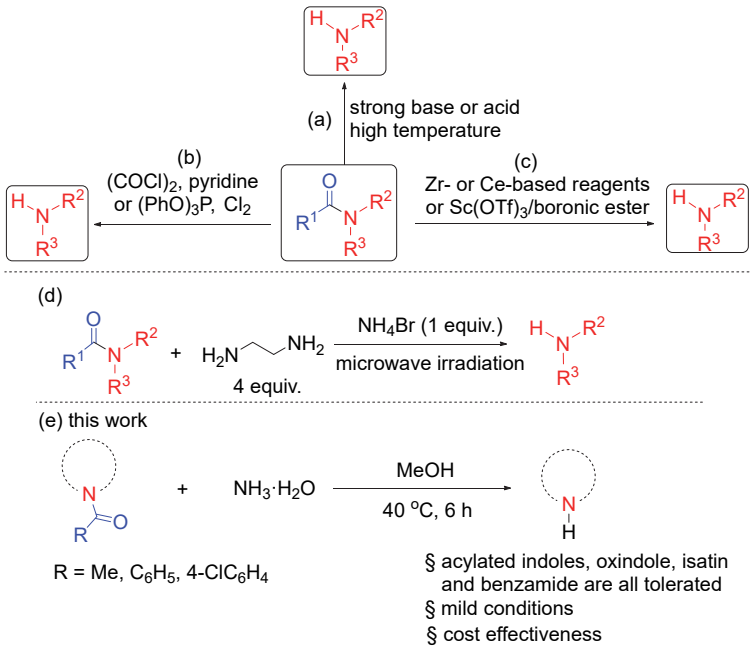
Table 1 Reaction optimization[a]



Entry	Deviation from standard conditions	Yield/%
1	None	91
2	r.t.	68
3	60 ℃	90
4	DCM instead of MeOH	Trace
5	DCE instead of MeOH	Trace
6	THF instead of MeOH	Trace
7	MeCN instead of MeOH	47
8	EtOH instead of MeOH	67
9	1 mL MeOH	56
10	0.8 mL NH_3•H_2O	77
11	CH_3NH_2 instead of NH_3•H_2O	63

[a] Reaction conditions: **1n** (0.5 mmol), NH_3•H_2O (1 mL, 6.5 mmol), MeOH (2 mL), sealed tube, 40 ℃, 6 h; isolated yield.

Having established the optimal conditions for deacylation, the substrate scope was examined (Table 2). First, a variety of *N*-acylated indoles were tested under the optimized conditions (**3a**～**3p**). The results showed that electron-donating and electron-withdrawing groups including



Scheme 1 Typical methods for the deacylation of amides

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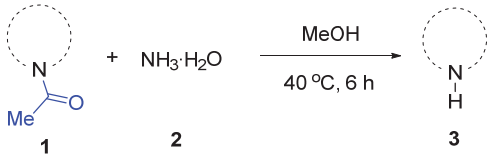
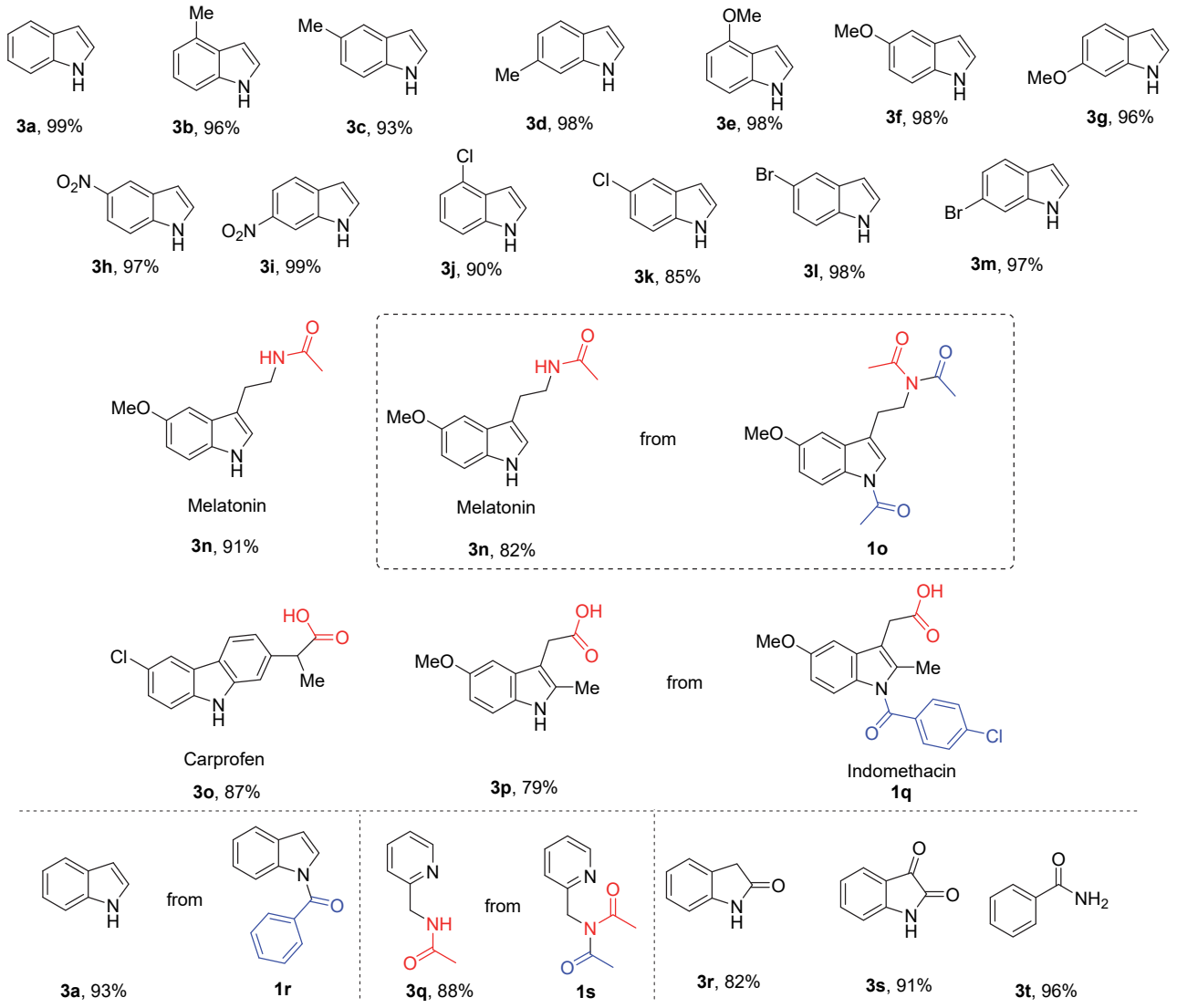
Table 2 Substrate scope





[a] Reaction conditions: **1** (0.5 mmol), NH_3•H_2O (1 mL, 6.5 mmol), MeOH (2 mL), sealed tube, 40 ℃, 6 h; isolated yield.

OMe (**3e**～**3g**) and NO_2 groups (**3h**～**3i**) were all well tolerated under the optimal conditions. Changing the substituents in the benzene ring of indoles from 4-, 5- to 6-position had little effect on the yields (**3b**～**3d**). A range of drugs and drug derivatives including *N*-acetyl melatonin, *N*-acetyl carprofen and indomethacin could be deacylated to release free amines **3n**～**3p** with up to 91% yield. The unprotected carboxylic acid moiety was well tolerated in these examples. It is noteworthy that this diacylation protocol features excellent selectivity. For example, di-acetylated melatonin (**1o**) underwent double deacetylation to give the desired amine **3n** in 82% yield, while di-acylated 2-picolylamine (**1s**) underwent the diacylation reaction to give acylated 2-picolylamine (**3q**) in 88% yield. In addition to acetyl group, the benzoyl group (**1q**～**1r**) could also be deprotected to give the corresponding amines in excellent yields. Next, other types of acetylated amines were tested under the optimal conditions. To our delight, *N*-acetyl oxindole, *N*-acetyl isatin and *N*-acetyl benzamide were all suitable substrates, affording the desired products **3r**～**3t** with up to 96% yield.

To demonstrate the synthetic potential of this deacylation reaction, a scale-up experiment was carried out. As shown in Scheme 2, when the reaction was performed on 10 mmol scale, the corresponding melatonin (**3n**) was obtained in 88% yield.

A plausible reaction pathway for the formation of **3n** is shown in Scheme 3. The nucleophilic addition between **1o**

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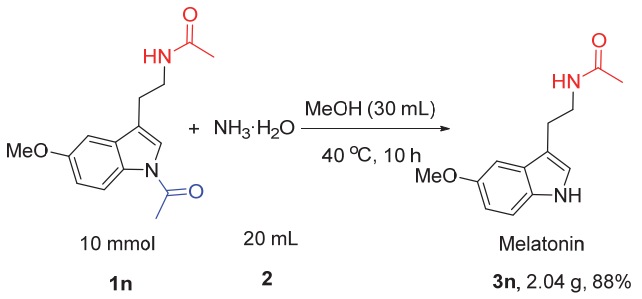
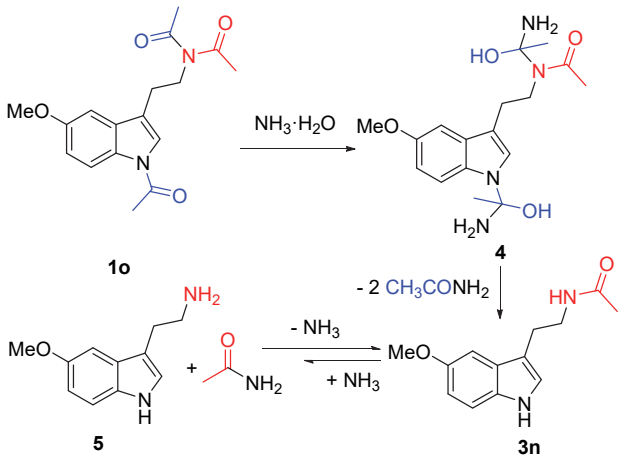


Scheme 2 Gram scale synthesis

and NH_3•H_2O gives intermediate **4**, which loses two molecules of acetamide to afford **3n**. In the presence of NH_3•H_2O, **3n** has the possibility to undergo another transamidation reaction to give **5**. However, due to the more nucleophilic nature of **5** than that of NH_3•H_2O, compound **5** would have a reverse transamidation with acetamide to give **3n**. Therefore, the transamidation of **1o** with NH_3•H_2O ends with the formation of product **3n** instead of **5**.



Scheme 3 A possible pathway for the formation of **3n**

3 Conclusions

In conclusion, a transamidation strategy for the deprotection of *N*-acyl amides with NH_3•H_2O under mild and scalable conditions was developed. A diverse range of acylated indoles, oxindole, isatin, benzamide and drugs could be deacylated to release free amines in excellent yields. Since the nucleophilic nature of NH_3 is stronger than that of water, the deprotection of acylated amine can be carried out under semi-aqueous conditions. The good functional group compatibility, combined with operational simplicity, excellent yield and cost effectiveness of all reagents, makes this protocol a prime candidate for *N*-deacylation of amides.

4 Experimental section

4.1 General information

Unless otherwise special indicated, all the reagents were purchased from commercial supplies. All the solvents were purchased from Energy Chemical. Thin-layer chromatography (TLC) was performed on plastic plates coated with silica gel GF254. Flash column chromatography was performed using silica gel (200～300 mesh). NMR spectra were recorded on a Bruker spectrometer operating at 400 MHz (^{1}H NMR) and 100 MHz (^{13}C NMR).

4.2 General procedure for the synthesis of acylated Amine **1**

N-Acyl amides except **1n** and **1o** were known compounds and were synthesized according to the literatures with the condensation of corresponding amines with acyl chlorides.[14-16]

4.2.1 General procedure for the synthesis of acylated amine **1n**

To a flask charged with melatonin (929 mg, 4 mmol), sodium hydroxide (400 mg, 10 mmol) and tetrabutylammonium hydrogen sulfate (29 mg, 0.08 mmol), DCM (11 mL) was added. A solution of acetyl chloride (276 μL, 3.5 mmol) in DCM (6 mL) was then added dropwise. The reaction mixture was stirred at room temperature for 16 h, filtered through a plug of silica and concentrated *in vacuo*. The resulting crude was purified by column chromatography on silica gel (petroleum ether/EtOAc, V∶V=3∶1～1∶1) to afford **1n** as a white foam (835 mg, 75% yield). m.p. 127～128 ℃; ^{1}H NMR (400 MHz, Chloroform-*d*) δ: 8.32 (s, 1H), 7.24 (s, 1H), 7.00 (d, J=2.5 Hz, 1H), 6.96 (dd, J=8.9, 2.5 Hz, 1H), 5.83 (s, 1H), 3.88 (s, 3H), 3.61 (q, J=6.6 Hz, 2H), 2.90 (td, J=6.9, 1.1 Hz, 2H), 2.55 (s, 4H), 1.99 (s, 3H); ^{3}C NMR (100 MHz, Chloroform-*d*) δ: 170.3, 168.0, 156.5, 131.5, 130.6, 123.2, 119.5, 117.6, 113.5, 101.8, 55.7, 38.9, 25.3, 23.7, 23.4; HRMS (APCI) calcd for $C_{15}H_{19}N_2O_3$ [M+H$^+$] 275.1390, found 275.1391.

4.2.2 General procedure for the synthesis of acylated amine **1o**

To a flask charged with melatonin (929 mg, 4 mmol), sodium hydroxide (400 mg, 10 mmol), and tetrabutylammonium hydrogen sulfate (29 mg, 0.08 mmol), DCM (11 mL) was added. A solution of acetyl chloride (460 μL, 6.45 mmol) in DCM (6 mL) was then added dropwise. The reaction mixture was stirred at room temperature for 16 h, filtered through a plug of silica and concentrated *in vacuo*. The resulting crude was purified by column chromatography on silica gel (petroleum ether/EtOAc, V∶V=1∶1) to afford **1o** as a white foam (908 mg, 70% yield). m.p. 134～135 ℃; ^{1}H NMR (400 MHz, Chloroform-*d*) δ: 8.33 (s, 1H), 7.23 (s, 1H), 7.14 (d, J=2.6 Hz, 1H), 6.98 (dd, J=9.0, 2.5 Hz, 1H), 4.12～3.93 (m, 2H), 3.91 (s, 3H), 3.12～2.83 (m, 2H), 2.60 (s, 3H), 2.42 (s, 6H); ^{13}C NMR (100 MHz, Chloroform-*d*) δ: 173.2, 168.0, 156.6, 131.1, 130.5, 123.5, 118.6, 117.6, 113.7, 101.7, 55.7, 44.9, 26.5, 24.8, 23.8; HRMS (APCI) calcd for $C_{17}H_{21}N_2O_4$ [M+H$^+$] 317.1496, found 317.1496.

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4.3 General procedure for the deacylation

To a sealed tube (10 mL) were added acylated amine (0.5 mmol), NH_3•H_2O (1 mL) and MeOH (2 mL). Then, the tube was sealed and placed in an oil bathe (40 ℃), and reacted at the same temperature for 6 h. After the reaction, the mixture was extracted with EtOAc (15 mL×3), and then the combined organic layer was washed with brine. The resulting organic layer was dried with Na_2SO_4 and the solvent was removed by distillation. The residue was purified by column chromatography on silica gel (etroleum ether/EtOAc, V∶V 10∶1～1∶1) to afford the desired pure product **3**.

1*H*-Indole (**3a**): White solid, 58.1 mg, 99% yield. m.p. 55～56 ℃ (lit.[17] 53～54 ℃); ^{1}H NMR (400 MHz, Chloroform-*d*) *δ*: 8.15 (s, 1H), 7.70 (dd, *J*=7.9, 1.2 Hz, 1H), 7.43 (dd, *J*=8.1, 1.1 Hz, 1H), 7.27～7.12 (m, 3H), 6.64～6.57 (m, 1H).

4-Methyl-1*H*-indole (**3b**):[18] White foam, 62.9 mg, 96% yield. ^{1}H NMR (400 MHz, Chloroform-*d*) *δ*: 8.14 (s, 1H), 7.36～7.26 (m, 1H), 7.23 (dd, *J*=3.3, 2.4 Hz, 1H), 7.16 (dd, *J*=8.2, 7.1 Hz, 1H), 6.98 (dt, *J*=7.1, 1.0 Hz, 1H), 6.62 (d, *J*=1.2 Hz, 1H), 2.63 (s, 3H).

5-Methyl-1*H*-indole (**3c**): White solid, 60.9 mg, 93% yield. m.p. 60～61 ℃ (lit.[18] 63～65 ℃); ^{1}H NMR (400 MHz, Chloroform-*d*) *δ*: 8.04 (s, 1H), 7.48 (d, *J*=1.7 Hz, 1H), 7.32 (d, *J*=8.3 Hz, 1H), 7.20 (t, *J*=2.9 Hz, 1H), 7.07 (dd, *J*=8.3, 1.7 Hz, 1H), 6.52 (t, *J*=2.6 Hz, 1H), 2.50 (s, 3H).

6-Methyl-1*H*-indole (**3d**): White solid, 64.2 mg, 98% yield. m.p. 26～28 ℃(lit.[18] 30～32 ℃); ^{1}H NMR (400 MHz, Chloroform-*d*) *δ*: 8.00 (s, 1H), 7.58 (dd, *J*=8.2, 3.6 Hz, 1H), 7.22 (s, 1H), 7.16 (t, *J*=2.8 Hz, 1H), 7.01 (d, *J*=8.0 Hz, 1H), 6.55 (d, *J*=3.1 Hz, 1H), 2.51 (s, 3H).

4-Methoxy-1*H*-indole (**3e**): White solid, 72.1 mg, 98% yield. m.p. 62～63 ℃ (lit.[19] 66～67 ℃); ^{1}H NMR (400 MHz, Chloroform-*d*) *δ*: 8.18 (s, 1H), 7.18～7.11 (m, 2H), 7.06 (dd, *J*=8.2, 0.9 Hz, 1H), 6.70 (t, *J*=2.7 Hz, 1H), 6.57 (d, *J*=7.7 Hz, 1H), 4.00 (s, 3H).

5-Methoxy-1*H*-indole (**3f**): White solid, 72.0 mg, 98% yield. m.p. 52～53 ℃(lit.[20] 56～58 ℃); ^{1}H NMR (400 MHz, Chloroform-*d*) *δ*: 8.08 (s, 1H), 7.35～7.30 (m, 1H), 7.21 (t, *J*=2.8 Hz, 1H), 7.15 (d, *J*=2.5 Hz, 1H), 6.90 (dd, *J*=8.8, 2.4 Hz, 1H), 6.52 (dq, *J*=2.2, 1.0 Hz, 1H), 3.89 (s, 3H).

6-Methoxy-1*H*-indole (**3g**): Yellow solid, 70.6 mg, 96% yield. m.p. 88～89 ℃ (lit.[21] 90～92 ℃); ^{1}H NMR (400 MHz, Chloroform-*d*) *δ*: 8.05 (s, 1H), 7.55 (d, *J*=8.6 Hz, 1H), 7.12 (dd, *J*=3.3, 2.3 Hz, 1H), 6.91 (d, *J*=2.2 Hz, 1H), 6.84 (dd, *J*=8.6, 2.3 Hz, 1H), 6.52 (d, *J*=1.1 Hz, 1H), 3.88 (s, 3H).

5-Nitro-1*H*-indole (**3h**): Brown solid, 78.7 mg, 97% yield. m.p. 135～136 ℃ (lit.[22] 142～144 ℃); ^{1}H NMR (400 MHz, Chloroform-*d*) *δ*: 8.64 (d, *J*=2.3 Hz, 1H), 8.15 (dd, *J*=9.0, 2.3 Hz, 1H), 7.47 (d, *J*=9.0 Hz, 1H), 7.41 (t, *J*=2.7 Hz, 1H), 6.77 (d, *J*=2.5 Hz, 1H).

6-Nitro-1*H*-indole (**3i**): Brown solid, 80.1 mg, 99% yield. m.p. 136～137 ℃ (lit.[22] 140～142 ℃); ^{1}H NMR (400 MHz, Chloroform-*d*) *δ*: 8.72 (s, 1H), 8.43 (d, *J*=2.0 Hz, 1H), 8.06 (dd, *J*=8.8, 2.1 Hz, 1H), 7.72 (d, *J*=8.8 Hz, 1H), 7.55 (t, *J*=2.9 Hz, 1H), 6.74～6.63 (m, 1H).

4-Chloro-1*H*-indole (**3j**):[23] Yellow oil, 67.9 mg, 90% yield. ^{1}H NMR (400 MHz, Chloroform-*d*) *δ*: 8.26 (s, 1H), 7.32 (d, *J*=7.6 Hz, 1H), 7.26 (t, *J*=2.9 Hz, 1H), 7.19～7.10 (m, 2H), 6.71 (t, *J*=2.7 Hz, 1H).

5-Cloro-1*H*-indole (**3k**): Brown solid, 64.2 mg, 85% yield. m.p. 68～69 ℃ (lit.[23] 72～73 ℃); ^{1}H NMR (400 MHz, Chloroform-*d*) *δ*: 8.18 (s, 1H), 7.65 (d, *J*=2.0 Hz, 1H), 7.33 (d, *J*=8.6 Hz, 1H), 7.25 (t, *J*=2.9 Hz, 1H), 7.18 (dd, *J*=8.6, 2.0 Hz, 1H), 6.54 (dd, *J*=3.2, 2.0 Hz, 1H).

5-Bromo-1*H*-indole (**3l**): Brown solid, 95.5 mg, 98% yield. m.p. 76～77 ℃ (lit.[22] 85～87 ℃); ^{1}H NMR (400 MHz, Chloroform-*d*) *δ*: 8.20 (s, 1H), 7.80 (d, *J*=1.5 Hz, 1H), 7.30 (d, *J*=1.7 Hz, 2H), 7.24 (t, *J*=2.8 Hz, 1H), 6.66～6.37 (m, 1H).

6-Bromo-1*H*-indole (**3m**): Light pink solid, 95.1 mg, 97% yield. m.p. 90～91 ℃ (lit.[24] 93～94 ℃); ^{1}H NMR (400 MHz, Chloroform-*d*) *δ*: 8.17 (s, 1H), 7.58 (t, *J*=1.2 Hz, 1H), 7.53 (d, *J*=8.4 Hz, 1H), 7.25 (dd, *J*=8.4, 1.7 Hz, 1H), 7.22 (t, *J*=2.8 Hz, 1H), 6.61～6.53 (m, 1H).

Melatonin (**3n**): White solid, 105.6 mg, 91% yield. m.p. 113～115 ℃ (lit.[25] 118～120 ℃); ^{1}H NMR (400 MHz, Chloroform-*d*) *δ*: 8.12 (s, 1H), 7.28 (d, *J*=1.4 Hz, 1H), 7.05 (dd, *J*=8.1, 2.4 Hz, 2H), 6.90 (dd, *J*=8.8, 2.4 Hz, 1H), 5.61 (s, 1H), 3.89 (s, 3H), 3.62 (q, *J*=6.5 Hz, 2H), 2.97 (t, *J*=6.7 Hz, 2H), 1.96 (s, 3H); ^{13}C NMR (100 MHz, Chloroform-*d*) *δ*: 170.2, 154.1, 131.6, 127.7, 122.9, 112.6, 112.4, 112.1, 100.4, 56.0, 39.8, 25.3, 23.4.

Carprofen (**3o**): White solid, 118.8 mg, 87% yield. m.p. 180～181 ℃ (lit.[26] 188～190 ℃); ^{1}H NMR (400 MHz, DMSO-d_6) *δ*: 11.37 (s, 1H), 8.18 (d, *J*=2.1 Hz, 1H), 8.09 (d, *J*=8.1 Hz, 1H), 7.49 (d, *J*=8.5 Hz, 1H), 7.41 (d, *J*=1.4 Hz, 1H), 7.37 (dd, *J*=8.6, 2.1 Hz, 1H), 7.11 (dd, *J*=8.2, 1.5 Hz, 1H), 3.83 (q, *J*=7.1 Hz, 1H), 1.44 (d, *J*=7.1 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) *δ*: 176.0, 141.0, 140.3, 138.8, 125.6, 124.1, 123.3, 121.1, 120.9, 120.1, 119.2, 112.8, 110.3, 45.6, 19.4.

2-(5-Methoxy-2-methyl-1*H*-indol-3-yl)acetic acid (**3p**): White solid, 86.6 mg, 79% yield. mp 162～163 ℃; ^{1}H NMR (400 MHz, DMSO-d_6) *δ*: 10.65 (s, 1H), 7.13 (d, *J*=8.6 Hz, 1H), 6.89 (d, *J*=2.4 Hz, 1H), 6.63 (dd, *J*=8.7, 2.4 Hz, 1H), 3.73 (s, 3H), 2.30 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) *δ*: 173.7, 153.5, 134.2, 130.6, 129.2, 111.4, 110.0, 104.3, 100.5, 55.8, 30.4, 11.9; HRMS (ESI) calcd for $C_{12}H_{14}NO_3$ [M+H$^+$] 220.0968, found 220.0965.

N-(Pyridin-2-ylmethyl)acetamide (3q):[27] Yellow oil, 66 mg, 88% yield. ^{1}H NMR (400 MHz, Chloroform-*d*) *δ*: 8.55～8.53 (m, 1H), 7.71～7.65 (m, 1H), 7.50～6.97 (m, 2H), 6.94 (s, 1H), 4.56 (d, *J*=6.6 Hz, 2H), 2.08 (s, 3H).

Indolin-2-one (**3r**): White solid, 54.6 mg, 82% yield. m.p. 119～120 ℃ (lit.[28] 124～125 ℃); ^{1}H NMR (400 MHz, Chloroform-*d*) *δ*: 8.57 (s, 1H), 7.24 (t, *J*=7.7 Hz, 2H), 7.11～7.00 (m, 1H), 6.91 (d, *J*=7.8 Hz, 1H), 3.57 (s, 2H).

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Indoline-2,3-dione (**3s**): Orange crystal, 66.9 mg, 91% yield. m.p. 195～196 ℃ (lit.[29] 198～120 ℃); ^{1}H NMR (400 MHz, Chloroform-*d*) *δ*: 8.05 (s, 1H), 7.65 (d, *J*=7.5 Hz, 1H), 7.60 (td, *J*=7.7, 1.3 Hz, 1H), 7.16 (t, *J*=7.6 Hz, 1H), 6.94 (d, *J*=7.9 Hz, 1H).

Benzamide (**3t**):[30] White solid, 58.1 mg, 96% yield. m.p. 123～124 ℃ (lit.[30] 127～128 ℃); ^{1}H NMR (400 MHz, Chloroform-*d*) *δ*: 7.92～7.75 (m, 2H), 7.62～7.52 (m, 1H), 7.47 (dd, *J*=8.2, 6.8 Hz, 2H), 6.18 (s, 2H).

4.4 General experimental procedure for Scheme 3

To a sealed tube (100 mL) were added acylated melatonin (10 mmol), NH_3•H_2O (20 mL) and MeOH (30 mL). Then, the tube was sealed and placed in an oil bathe (40 ℃), and reacted at the same temperature for 10 h. After the reaction, the mixture was extracted with EtOAc (50 mL×3), and then the combined organic layer was washed with brine. The resulting organic layer was dried with Na_2SO_4 and the solvent was removed by distillation. The residue was purified by column chromatography on silica gel (petroleum ether/EtOAc, *V*∶*V*=1∶1) to afford the desired melatonin (**3n**) as a white solid (2.04 g, 88%).

Supporting Information HRMS and NMR spectra of compounds **1n**, **1o**, **3a**～**3t**. The Supporting Information is available free of charge via the Internet at http://sioc-journal.cn.

References

[1] (a) Wang, H.; Shi, J.; Tan, J.; Xu, W.; Zhang, S.; Xu, K. *Org. Lett.* **2019**, *21*, 9430.
(b) Wang, X.; Xu, X.; Wang, Z.; Fang, P.; Mei, T. *Chin. J. Org. Chem.* **2020**, *40*, 3738 (in Chinese).
(王向阳, 徐学涛, 王振华, 方萍, 梅天胜, 有机化学, **2020**, *40*, 3738.)
(c) Yang, Q.; Yan, X.-T.; Feng, C.-T.; Chen, D.-X.; Yan, Z.-Z.; Xu, K. *Org. Chem. Front.* **2021**, *8*, 6384.
(d) Ge, Y.-X.; Yan, Q.-Q.; Tian, Y.-F.; Wang, H.-J.; Zhang, C.-F.; Li, Z.-J. *Chin. J. Org. Chem.* **2021**, *41*, 3106 (in Chinese).
(葛雅欣, 闫芹芹, 田云飞, 王海军, 张春芳, 李泽江, 有机化学, **2021**, *41*, 3106.)
(e) Yi, R.-N.; He, W.-M. *Chin. J. Org. Chem.* **2021**, *41*, 1267 (in Chinese).
(易荣楠, 何卫民, 有机化学, **2021**, *41*, 1267.)

[2] Baran, P. S.; Corey, E. J. *J. Am. Chem. Soc.* **2002**, *124*, 7904.

[3] (a) Wen, J.; Wang, F.; Zhang, X. M. *Chem. Soc. Rev.* **2021**, *50*, 3211.
(b) Jiang, X.-L.; Zhu, S.-L. *Chin. J. Org. Chem.* **2021**, *41*, 3745 (in Chinese).
(江晓莉, 朱少林, 有机化学, **2021**, *41*, 3745.)

[4] (a) Zhang, M.; Zhang, Y.; Jie, X.; Zhao, H.; Li, G.; Su, W. P. *Org. Chem. Front.* **2014**, *1*, 843.
(b) Luo, H.; Pei, N.; Zhang, J. *Chin. J. Org. Chem.* **2021**, *41*, 2990 (in Chinese).
(罗欢欢, 裴娜, 张敬, 有机化学, **2021**, *41*, 2990.)
(c) Feng, Y.-L.; Shi, B. *Chin. J. Org. Chem.* **2021**, *41*, 3753 (in Chinese).
(冯亚岚, 史炳锋, 有机化学, **2021**, *41*, 3753.)
(d) Sun, S.-Z.; Wang, X.; Cheng, T.-J.; Xu, H.; Dai, H.-X. *Chin. J. Org. Chem*. **2020**, *40*, 3371 (in Chinese)
(孙尚政, 王星, 程泰锦, 徐辉, 戴辉雄, 有机化学, **2020**, *40*, 3371.)
(e) Liu, Y.-Y.; Zhang, Y.; Wan, J.-P. *J. Org. Chem.* **2017**, *82*, 8950.
(f) Du, Y.; Liu, Y.-Y.; Wan, J.-P. *J. Org. Chem.* **2018**, *83*, 3403.

[5] (a) Wuts, P. G. M.; Greene, T. W. *Protective Groups in Organic Synthesis*, 4th ed., Wiley-Interscience, Hoboken, **2006**, pp. 773～789.
(b) Yoo, M.; Jung, K.-W. *ChemistrySelect* **2018**, *3*, 1527.

[6] Spaggiari, A.; Blaszczak, L. C.; Prati, F. *Org. Lett.* **2004**, *6*, 3885.

[7] Koenig, S. G.; Vandenbossche, C. P.; Zhao, H.; Mousaw, P.; Singh, S. P.; Bakale, R. P. *Org. Lett.* **2009**, *11*, 433.

[8] Sultane, P. R.; Mete, T. B.; Bhat, R. G. *Org. Biomol. Chem.* **2014**, *12*, 261.

[9] Wang, A.-E.; Chang, Z.; Liu, Y.-P.; Huang, P.-Q. *Chin. Chem. Lett.* **2015**, *26*, 1055.

[10] Kita, Y.; Nishii, Y.; Onoue, A.; Mashima, K. *Adv. Synth. Catal.* **2013**, *355*, 3391.

[11] Shimizu, Y.; Morimoto, H.; Zhang, M.; Ohshima, T. *Angew. Chem., Int. Ed.* **2012**, *51*, 8564.

[12] (a) Lian, F.; Xu, K. *Chin. J. Org. Chem.* **2020**, *40*, 3490 (in Chinese).
(廉菲, 徐坤, 有机化学, **2020**, *40*, 3490.)
(b) Meng, Z.-Y.; Feng, C.-T.; Xu, K. *Chin. J. Org. Chem.* **2021**, *41*, 2535 (in Chinese).
(蒙泽银, 冯承涛, 徐坤, 有机化学, **2021**, *41*, 2535.)
(c) Lian, F.; Xu, K.; Zeng, C. *Chem. Rec.* **2021**, *21*, 2290.
(d) Li, J.; Zhang, S.; Xu, K. *Chin. Chem. Lett.* **2021**, *32*, 2729.
(e) Zhang, S.; Li, L.; Li, J.; Shi, J.; Xu, K.; Gao, W.; Zong, L.; Li, G.; Findlater, M. *Angew. Chem., Int. Ed.* **2021**, *60*, 7275.
(f) Jiang, Y.; Xu, K.; Zeng, C. *CCS Chem.* **2021**, *3*, 1911.

[13] Tordjman, S.; Chokron, S.; Delorme, R.; Charrier, A.; Bellissant, E.; Jaafari, N.; Fougerou, C. *Curr. Neuropharmacol.* **2017**, *15*, 434.

[14] Wang, Y.-H.; Tian, J.-S.; Tan, P.-W.; Cao, Q.; Zhang, X.-X.; Cao, Z.-Y.; Zhou, F.; Wang, X.; Zhou, J. *Angew Chem., Int. Ed.* **2020**, *59*, 1634.

[15] Kerr, W. J.; Lindsay, D. M.; Owens, P. K.; Reid, M.; Tuttle, T.; Campos, S. *ACS Catal.* **2017**, *7*, 7182.

[16] Roth, G. J.; Heckel, A.; Colbatzky, F.; Handschuh, S.; Kley, J.; Lintz, T. L.; Lotz, R.; Grunt, U. T.; Walter, R.; Hilberg, F. *J. Med. Chem.* **2009**, *52*, 4466.

[17] Castelo-Branco, F. S.; Lima, E. C.; Domingos, J. L. O.; Pintob, A. C.; Lourenço, M. C. S.; Gomes, K. M.; Costa-Lima, M. M.; Araujo-Lima, C. F.; Aiub, C. A. F.; Felzenszwalb, I.; Costa, T. E. M. M.; Penido, C.; Henriques, M. G.; Boechat, N. *Eur. J. Med. Chem.* **2018**, *146*, 529.

[18] He, K.-H.; Tan, F.-F.; Zhou, C.-Z.; Zhou, G.-J.; Yang, X.-L.; Li, Y. *Angew. Chem., Int. Ed.* **2017**, *56*, 3080.

[19] Wang, Q.-F.; Chai, H.; Yu, Z.-K. *Organometallics* **2018**, *37*, 584.

[20] Wu, J.-J.; Talwar, D.; Johnston, S.; Yan, M.; Xiao, J.-L. *Angew. Chem., Int. Ed.* **2013**, *52*, 6983.

[21] Huang, Y.-Q.; Song, H.-J.; Liu, Y.-X.; Wang, Q.-M. *Chem.-Eur. J.* **2018**, *24*, 2065.

[22] Zhang, J.-Y.; Chen, S.-Y.; Chen, F.-F.; Xu, W.-S.; Deng, G.-J.; Gong, H. *Adv. Synth. Catal.* **2017**, *359*, 2358.

[23] Ning, X.-S.; Liang, X.; Hu, K.-F.; Yao, C.-Z.; Qu, J.-P.; Kang, Y.-B. *Adv. Synth. Catal.* **2018**, *360*, 1590.

[24] Barykina, O. V.; Snider, B. B. *Org. Lett.* **2010**, *12*, 2664.

[25] Song, W. Z.; Dong, K.; Li, M. *Org. Lett.* **2020**, *22*, 371.

[26] Wang, M.; Fan, Q.-L.; Jiang, X.-F. *Org. Lett.* **2018**, *20*, 216.

[27] Omer, H. M.; Liu, P.; Brummond, K. M. *J. Org. Chem.* **2020**, *85*, 7959.

[28] Lin, W.; Hu, M.-H.; Feng, X.; Fu, L.; Cao, C.-P.; Huang, Z.-B.; Shi, D.-Q. *Tetrahedron Lett.* **2014**, *55*, 2238.

[29] Laursen, S. R.; Jensen, M. T.; Lindhardt, A. T.; Jacobsen, M. F.; Skrydstrup, T. *Eur. J. Org. Chem.* **2016**, *2016*, 1881.

[30] Zhang, F.; Li, L.; Zhang, J. *Sci. Rep.* **2019**, *9*, 2787.

(Zhao, C.)

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