HETEROCYCLES, Vol. 95, No. 1, 2017, pp. 251-267. © 2017 The Japan Institute of Heterocyclic Chemistry
Received, 1st July, 2016, Accepted, 9th August, 2016, Published online, 19th October, 2016
DOI: 10.3987/COM-16-S(S)13

ONE-POT SYNTHESIS OF FUSED 2-PYRIDONES FROM HETEROARYLACRYLIC ACID VIA CURTIUS REARRANGEMENT AND MICROWAVE-ASSISTED THERMAL ELECTROCYCLIZATION

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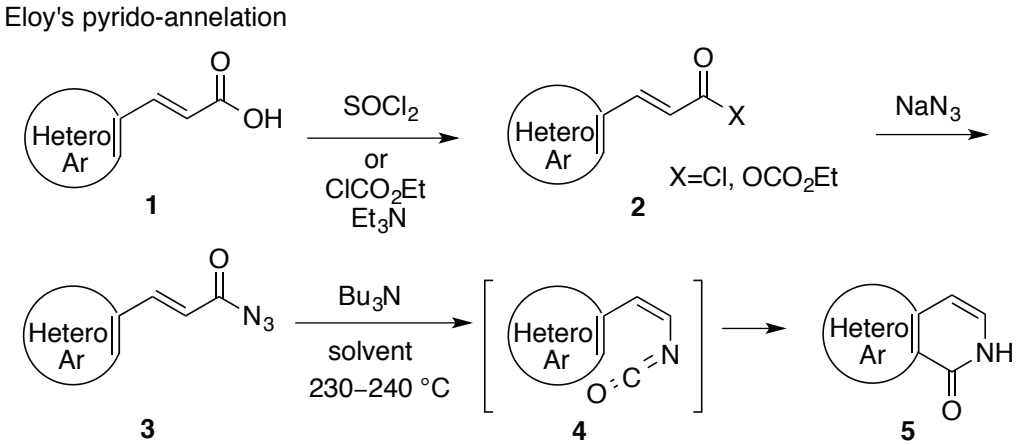
We dedicate this paper to Professor Dr. Masakatsu Shibasaki on the celebration of his 70th birthday.

Abstract – We investigated the one-pot synthesis of several fused 2-pyridone ring systems based on a Curtius rearrangement, followed by a microwave-assisted thermal electrocyclization of a 2-aza-6π-electron system including isocyanate. We synthesized seven heterocyclic compounds containing a fused 2-pyridone ring. In these results, the one-pot synthesis of fused 2-pyridone ring system **5** from (*E*)-acrylic acids **1** under microwave irradiation conditions was more effective than the conventional reaction conditions in terms of the yield and the reaction time.

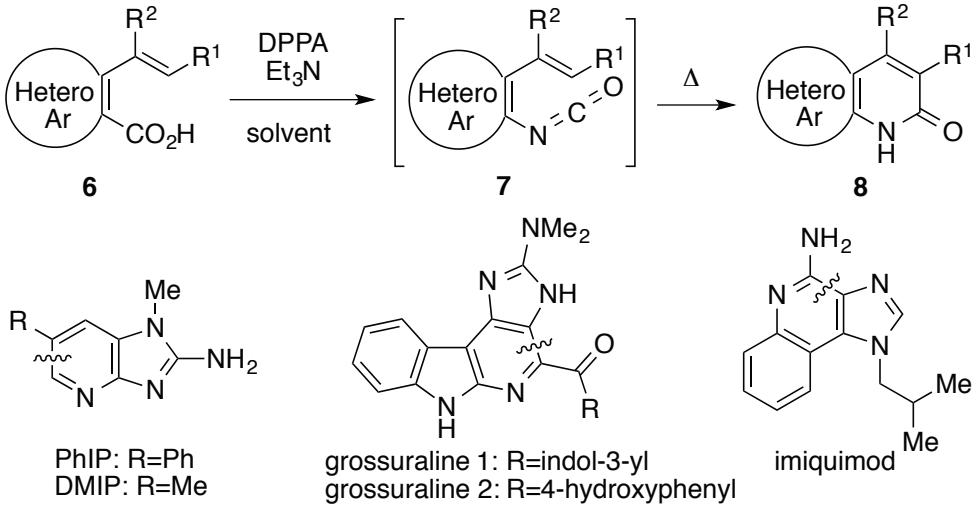
INTRODUCTION

Fused pyridines are emerging as useful pharmacophores in the synthetic studies of biologically active compounds.[1–3] We are interested in the synthesis of biologically active fused heterocyclic compounds, including natural products, based on a thermal electrocyclization of either hexatriene or azahexatriene systems incorporating a principal aromatic or heteroaromatic moiety.



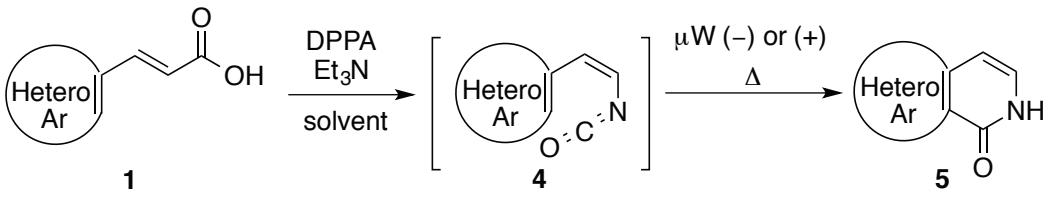
Scheme 1

In 1970, Eloy and co-workers reported the synthesis of fused pyridones **5** from acyl azide **3** via a Curtius rearrangement, followed by thermal electrocyclization (Scheme 1).[4] Thereafter, several researchers have reported the synthesis of biologically active compounds containing a fused heterocyclic ring, using modified Eloy's pyrido-annelation.[1,3] Conventionally, the isocyanates **4** were generated by thermal decomposition of the acyl azides **3**, which were obtained from acyl chloride **2** or acid anhydride **2** with sodium azide, via Curtius rearrangement.[4] Conversely, we focus on the direct conversion of isocyanates obtained by heating the carboxylic acids in the presence of diphenylphosphoryl azide (DPPA) via Curtius rearrangement, which was developed by Shioiri and co-workers.[5] Therefore, we investigated the synthesis of fused 2-pyridone ring systems **8** based on a thermal electrocyclization of an 2-aza-6π-electron system **7** including an isocyanate. The isocyanate **7** was generated from **6** using Shioiri's reaction (Scheme 2). So far, we have achieved the synthesis of PhIP and DMIP having an imidazo[4,5-*b*]pyridine,[6] grossularines having an α-carboline,[7] and imiquimod having an imidazo[4,5-*c*]quinolone[8] using a thermal electrocyclization of a 2-aza-6π-electron system involving an isocyanate.



Scheme 2

Recently, it has been established that microwave (μW) irradiation facilitates unique chemical processes with special attributes such as enhanced reaction rates, higher yields, greater selectivity, and ease of manipulation. We have recently reported the construction of several fused 2-pyridone ring systems, such as furo[3,2-*h*]isoquinoline,[9] phenanthridine,[10] benzo[*c*]phenanthridine,[11] azaanthraquinone,[12] β-carboline,[13] and pyrano[2,3,4-*ij*]isoquinoline alkaloids,[14] using a microwave-assisted thermal electrocyclization of a 1-aza-6π-electron system. In addition, we have reported the total synthesis of isocryptolepine by a one-pot synthesis of an indolo[3,2-*c*]quinolone ring system based on a Curtius rearrangement followed by microwave-assisted thermal electrocyclization of 2-aza-6π-electron system.[15]



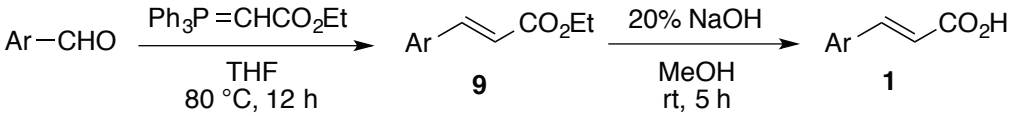
Scheme 3

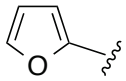
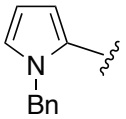
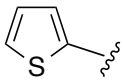
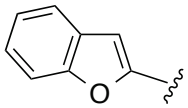
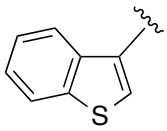
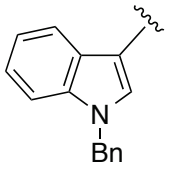
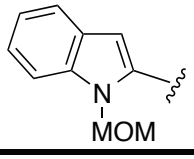
In the present work, we describe the one-pot synthesis of various fused pyridine ring systems **5** based on a Curtius rearrangement followed by a microwave-assisted thermal electrocyclization of a 2-aza-6π-electron system **4** including isocyanate, and the results are compared with those performed using a conventional method (Scheme 3).

RESULTS AND DISCUSSION

We planned to synthesize fused heteroaromatic compounds using the proposed method. The key isocyanate intermediate was prepared from a 3-heteroarylacrylic acid by Curtius rearrangement, using Shioiri's condition. We selected six heterocyclic compounds such as furan, pyrrole, thiophene, benzofuran, benzothiophene, and indole as the aromatic heterocycles. Wittig reaction of the known heteroarylcarbaldehyde with (ethoxycarbonylmethylidene)triphenylphosphorane afforded the (*E*)-heteroarylacrylate **9a**–**g**.[16] Subsequent hydrolysis of the (*E*)-heteroarylacrylate **9a**–**g** with 20% aqueous NaOH in MeOH gave the (*E*)-acrylic acid **1a**–**g** (Table 1).

Table 1. Synthesis of (*E*)-acrylate 9 and (*E*)-acrylic acid 1



Ar—CHO		Yield (%) of **9**		Yield (%) of **1**	
	**9a** [1)]	80	**1a** [1),3)]	62
	**9b** [2)]	99	**1b** [3)]	93
	**9c** [1)]	95	**1c** [1),3)]	99
	**9d** [1)]	75	**1d** [1),3)]	89
	**9e**	99	**1e** [3)]	70
	**9f**	99	**1f** [3)]	96
	**9g**	78	**1g**	79

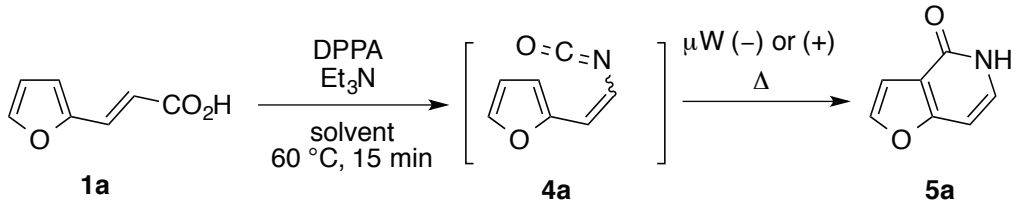
1) ref.16a, 2) ref.16b, 3) ref. 4a

Synthesis of furo[3,2-*c*]pyridin-4-one

The furo[3,2-*c*]pyridine derivatives are emerging as useful pharmacophores in several therapeutic areas such as antipsychotic molecules,[1a] protease kinase inhibitors,[1b] and antibacterial compounds.[1c] Eloy and co-workers reported the synthesis of furo[3,2-*c*]pyridin-4-one (**5a**) from (*E*)-3-(2-furyl)acrylic acid (**1a**) in three steps (Scheme 1).[4] Treatment of **1a** with $SOCl_2$ give the acyl chloride **2**, which was reacted with NaN_3 to obtain the acyl azide **3**. Subsequently, treatment of the acyl azide **3** with Bu_3N in diphenyl ether at 230–240 °C was provided the desired furopyridone **5a** in 45% yield (Table 2, entry 11). This result proceeded by Curtius rearrangement to generate the isocyanate **4a**, followed by an electrocyclization of

4a. In addition, Rao and co-workers also synthesized the furopyridone **5a** from acryl azide **3** shown in Scheme 1 in 80% yield using modified Eloy's condition (entry 12).[1c]

Table 2. Synthesis of furo[3,2-*c*]pyridin-4-one (5a)



1a **4a** **5a**

Entry	Solvents	μW	Temp. (°C)	Time (h)	Yield (%) of **5a**
1	1,2-dichlorobenzene	–	180	20	80
2	1,2-dichlorobenzene	+	180	1	51
3	1,2-dichlorobenzene	+	180	2	99
4	1,2-dichlorobenzene	+	150	1	49
5	bromobenzene	–	150	1	64
6	bromobenzene	–	150	20	72
7	bromobenzene	+	150	1	98
8	bromobenzene	+	100	1	35
9	toluene	–	100	5	19
10	toluene	+	100	4	10
11	diphenyl ether	–	230-240	1	45 [1)]
12	diphenyl ether	–	230	1	80 [2)]

1) Treatment of 3-(2-furyl)acryloyl azide with tributylamine in diphenyl ether at 230–240 °C affored pyridone **5a**.
2) To a solution of tributylamine in diphenyl ether heated at 230 °C was added a solution of 3-(2-furyl)acryloyl azide in dichloromethane over a period of 30 min. The reaction mixture was continued to stir at the same temperature for another 30 min.

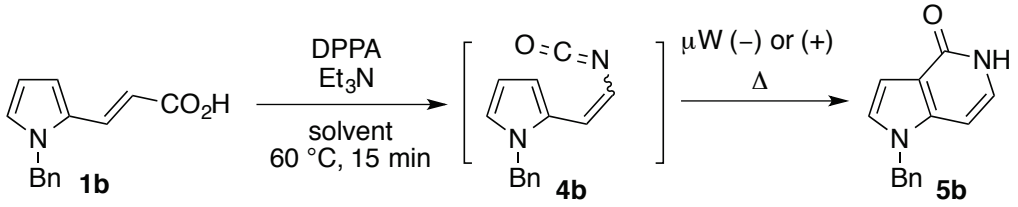
We investigated the one-pot synthesis of furopyridone **5a** from (*E*)-3-(2-furyl)acrylic acid (**1a**), and the conditions for this reaction were optimized (reaction time, temperature, solvent, and microwave parameters). First, treatment of **1a** with DPPA and Et_3N in 1,2-dichlorobenzene at 60 °C for 15 min generated the isocyanate **4a** in situ (monitored the disappearance of acrylic acid by TLC), which was then heated at 180 °C for 20 h. As a result, the furopyridone **5a** was obtained in 80% yield (entry 1). Subsequently, when the reaction was performed in 1,2-dichlorobenzene at 180 °C, under microwave irradiation, **5a** was obtained in 99% yield and the reaction time was reduced from 20 h to 2 h compared to conventional condition (entry 3). When this reaction was performed in the same solvent at 150 °C, under microwave irradiation, yield of **5a** was decreased from 99% to 49% (entry 4). Second, the use of bromobenzene instead of 1,2-dichlorobenzene as solvent was investigated under various cyclization

conditions (entries 5–8). Heating at 150 °C under microwave irradiation afforded **5a** in 98% yield (entry 7). Conversely, the cyclization in toluene did not proceed efficiently under each condition of microwave heating and conventional heating (entries 9 and 10). Furthermore, the cyclization of this substrate was also affected by the solvent (entries 4 vs. 7 and 8 vs. 10).

Synthesis of pyrrolo[3,2-*c*]pyridin-4-one

The pyrrolo[3,2-*c*]pyridine derivatives have been investigated as pharmacophores with potential antipsychotic activity together with thieno[3,2-*c*]pyridines and furo[3,2-*c*]pyridines.[1a] Eloy and co-workers reported the synthesis of pyrrolo[3,2-*c*]pyridone **5b** from 3-(pyrrol-2-yl)acryloyl azide (Table 3, entry 8).[4]

Table 3. Synthesis of pyrrolo[3,2-*c*]pyridin-4-one (5b)



Entry	Solvents	μW	Temp. (°C)	Time (h)	Yield (%) of **5b**
1	1,2-dichlorobenzene	–	180	20	45
2	1,2-dichlorobenzene	+	180	1	24
3	1,2-dichlorobenzene	+	180	3	14
4	bromobenzene	+	150	1	27
5	bromobenzene	+	100	2	24
6	toluene	–	100	2	14
7	toluene	+	100	2	21
8	diphenyl ether	–	230-240		48[1)]

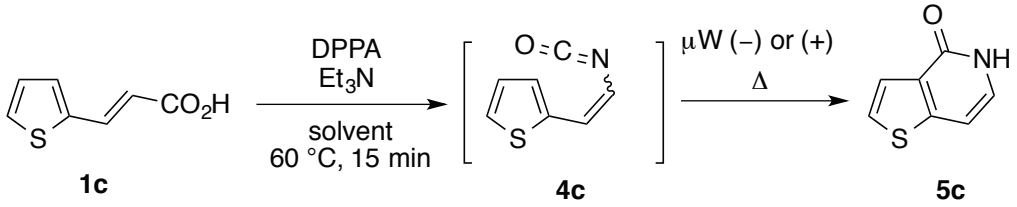
1) Treatment of 3-(pyrrol-2-yl)acryloyl azide with tributylamine in diphenyl ether at 230–240 °C afforded pyridone **5b**.

As shown in Table 3, we investigated the one-pot synthesis of pyrrolopyridone **5b** from 3-(pyrrol-2-yl)acrylic acid **1b**. First, the one-pot reaction of **1b** was performed in 1,2-dichlorobenzene under conventional conditions at 180 °C to produce the desired pyrrolopyridone **5b** in 45% yield (entry 1). Second, the conditions for this reaction were optimized (reaction time, temperature, solvent, and microwave parameters). We did not observe an improved yield from these experiments compared with the conventional conditions (entry 1). Moreover, it was inferred that the microwave irradiation conditions are not more effective than the conventional conditions for this substrate (entries 2–7). As the cause, many of unknown compounds were obtained along with the pyrrolopyridone **5b**.

Synthesis of thieno[3,2-*c*]pyridin-4-one

As aforementioned, to identify compounds with potential antipsychotic activity using 4-substituted thienopyridines, thieno[3,2-*c*]pyridin-4-one was synthesized as a precursor. New and co-workers reported the synthesis of thieno[3,2-*c*]pyridin-4-one **5c** from 3-(2-thienyl)acryloyl azide using Eloy's condition (Table 4, entry 11).[1a] As shown in Table 4, we investigated the one-pot synthesis of thienopyridone **5c** from (*E*)-3-(thiophen-2-yl)acrylic acid **1c**. First, the one-pot reaction of **1c** was performed under conventional conditions to produce the desired thienopyridone **5c** (entries 1, 2, 5, and 6). Second, the conditions for this reaction were optimized (reaction time, temperature, solvent, and microwave parameters). The results from these experiments show that the microwave irradiation conditions are more effective than the conventional conditions (entries 2 and 5) for increasing the yield and decreasing the reaction time (entries 4 and 7). Therefore, the microwave-irradiation-based heating at 180 °C for 2 h in 1,2-dichlorobenzene was the best condition to complete the reaction (entry 4).

Table 4. Synthesis of thieno[3,2-*c*]pyridin-4-one (5c)



1c **4c** **5c**

Entry	Solvents	μW	Temp. (°C)	Time (h)	Yield (%) of **5c**
1	1,2-dichlorobenzene	–	180	1	6
2	1,2-dichlorobenzene	–	180	20	31
3	1,2-dichlorobenzene	+	180	1	37
4	1,2-dichlorobenzene	+	180	2	74
5	bromobenzene	–	150	1	45
6	bromobenzene	–	150	20	19
7	bromobenzene	+	150	1	52
8	bromobenzene	+	100	2	25
9	toluene	–	100	3	21
10	toluene	+	100	2	10
11	diphenyl ether	–	230-240		22 [1)]

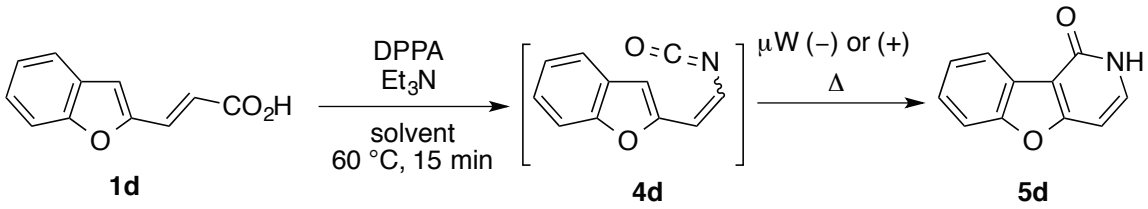
1) Treatment of 3-(thiophen-2-yl)acryloyl azide with tributylamine in diphenyl ether at 230–240 °C affored pyridone **5c**.

Synthesis of benzofuro[3,2-*c*]pyridin-1-one

The benzofuropyridines are one of the important heterocyclic compounds, which show significant biological and pharmaceutical properties.[2] Eloy and co-workers reported the synthesis of

benzofuro[3,2-*c*]pyridin-1-one **5d** from 3-(2-benzofuryl)acryloyl azide in 62% yield (Table 5, entry 10).[4] As shown in Table 5, we investigated the one-pot synthesis of benzofuropyridone **5d** from (*E*)-3-(benzofuran-2-yl)acrylic acid **1d**. First, the one-pot reaction of **1d** was performed in 1,2-dichlorobenzene under conventional conditions at 180 °C to produce the desired benzofuropyridone **5d** in 62% yield (entry 1). Second, the conditions for this reaction were optimized (reaction time, temperature, solvent, and microwave parameters). The results indicate that the microwave irradiation conditions are more effective than the conventional conditions (entries 1 and 5) for increasing the yield and decreasing the reaction time (entries 3 and 6). Furthermore, the cyclization reaction of this substrate was also affected by the solvent (entries 4 vs. 6). From the above results it is seen that heating at 180 °C for 2 h in 1,2-dichlorobenzene under microwave irradiation was the best method to complete the reaction (entry 3).

Table 5. Synthesis of benzofuro[3,2-*c*]pyridin-1-one (5d)



1d **4d** **5d**

Entry	Solvents	μW	Temp. (°C)	Time (h)	Yield (%) of **5d**
1	1,2-dichlorobenzene	–	180	20	62
2	1,2-dichlorobenzene	+	180	1	53
3	1,2-dichlorobenzene	+	180	2	99
4	1,2-dichlorobenzene	+	150	1	14
5	bromobenzene	–	150	1	26
6	bromobenzene	+	150	1	54
7	bromobenzene	+	100	2	41
8	toluene	–	100	2	30
9	toluene	+	100	1	22
10	diphenyl ether	–	230-240		62[1)]

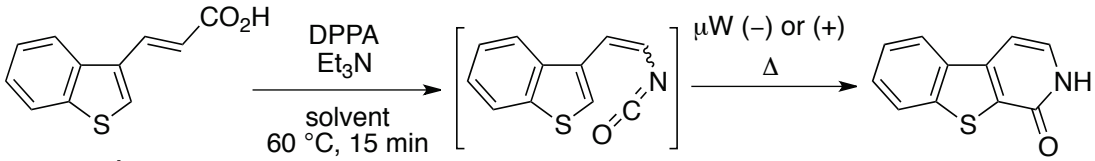
1) Treatment of 3-(benzofuran-2-yl)acryloyl azide with tributylamine in diphenyl ether at 230–240 °C affored pyridone **5d**.

Synthesis of benzo[*b*]thieno[2,3-*c*]pyridin-1-one

Eloy and co-workers synthesized benzothieno[2,3-*c*]pyridin-1-one **5e** from 3-(benzothiophen-3-yl)acryloyl azide in diphenyl ether at 220 °C (Table 6, entry 10).[4] Camaioni and co-wokers synthesized the pyridone **5e** using modified Eloy's condition leading to the discovery of new tankyrase inhibitors.[3] As shown in Table 6, we investigated the one-pot synthesis of benzothienopyridone

5e from (*E*)-3-(benzothiophen-3-yl)acrylic acid (**1e**), and the conditions for this reaction were optimized (reaction time, temperature, solvent, and microwave parameters). The cyclization of this substrate by heating at temperatures higher than 150 °C afforded the desired product **5e** in excellent yield (entries 1–5). The most efficient reaction condition was the cyclization of **4e** in bromobenzene at 150 °C for 1 h under microwave irradiation (entry 6).

Table 6. Synthesis of benzothieno[2,3-*c*]pyridin-1-one (5e)



1e **4e** **5e**

Entry	Solvents	μW	Temp. (°C)	Time (h)	Yield (%) of **5e**
1	1,2-dichlorobenzene	–	180	1	77
2	1,2-dichlorobenzene	–	180	20	99
3	1,2-dichlorobenzene	+	180	1	99
4	bromobenzene	–	150	1	87
5	bromobenzene	–	150	20	99
6	bromobenzene	+	150	1	99
7	bromobenzene	+	100	1	35
8	toluene	–	100	2	29
9	toluene	+	100	2	29
10	diphenyl ether	–	230-240	1	74 [1)]

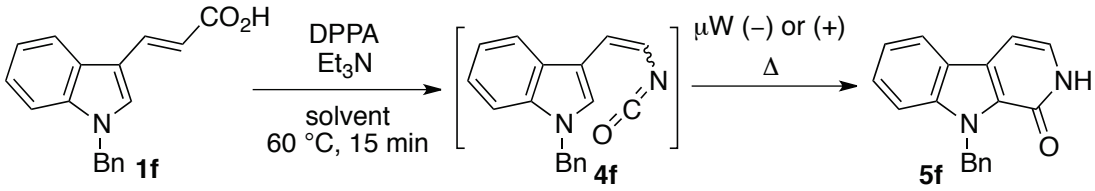
1) Treatment of 3-(benzothiophen-2-yl)acryloyl azide with tributylamine in diphenyl ether at 230–240 °C affored pyridone **5e**.

Synthesis of pyrido[3,4-*b*]indol-1-one

Pyrido[3,4-*b*]indole (β-carboline) is present in several natural products, and its compounds have been synthesized using methods such as Bischler–Napieralski reaction[17] and Pictet–Spengler reaction[18] as a key step. We previously reported the construction method of the pyrido[4,3-*b*]indole framework using thermal electrocyclization based on 1-aza-6π-electron systems.[19,20] As shown in Table 7, we investigated the synthesis of pyrido[4,3-*b*]indol-1-one **5f** from (*E*)-3-(indol-3-yl)acrylic acid **1f**. First, when the reaction was performed in 1,2-dichlorobenzene at 180 °C for 1 h under conventional heating, **5f** was obtained in 73% yield (entry 1). To improve the yield, the reaction time was prolonged, but the yield decreased (entry 2). Second, the conditions for this reaction were optimized (reaction time, temperature, solvent, and microwave parameters). The results from these optimization experiments show that the microwave

irradiation conditions (entries 3 and 4) were not more effective than the conventional condition (entry 1) in terms of the yield.

Table 7. Synthesis of pyrido[3,4-*b*]indol-1-one (5f)



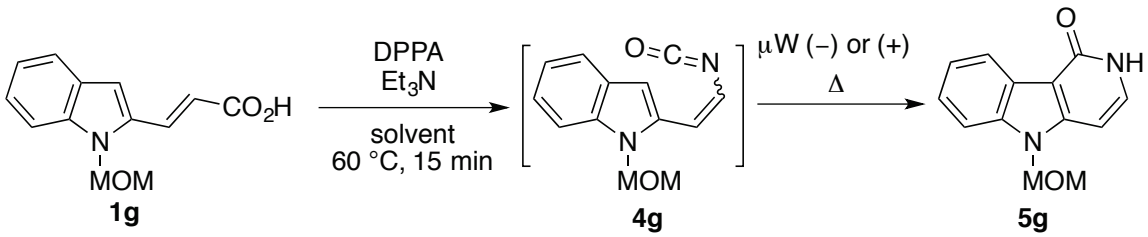
Entry	Solvents	μW	Temp. (°C)	Time (h)	Yield (%) of **5f**
1	1,2-dichlorobenzene	–	180	1	73
2	1,2-dichlorobenzene	–	180	20	10
3	1,2-dichlorobenzene	+	180	0.5	18
4	1,2-dichlorobenzene	+	180	1	63
5	bromobenzene	–	150	1	63
6	bromobenzene	+	150	0.5	24
7	bromobenzene	+	150	1	69
8	bromobenzene	+	100	2	18
9	toluene	–	100	10	10
10	toluene	+	100	7	4
11	diphenyl ether	–	230-240		40 [1)]

1) Treatment of 3-(indol-3-yl)acryloyl azide with tributylamine in diphenyl ether at 230–240 °C affored pyridone **5f**.

Synthesis of pyrido[4,3-b]indol-1-one

Pyrido[4,3-*b*]indole (γ-carboline) framework was synthesized using several strategies.[21] However, the construction of pyrido[4,3-*b*]indole framework at the C1–C1a bond position has not been reported to date. As shown in Table 8, we investigated the one-pot synthesis of pyridone **5g** using the proposed cyclization reactoin, and the conditions for this reaction were optimized (reaction time, temperature, solvent, and microwave parameters) (entries 1–5). From these experiments, it is observed that the microwave irradiation conditions (entries 2, 4, and 7) were more effective than the conventional conditions (entries 1, 3, and 6) in terms of the pyridone **5g** yield from the 3-(indol-2-yl)acrylic acid **1g**. From these results, it is observed that the most efficient reaction condition was the cyclization of **4g** in bromobenzene at 150 °C for 1 h under microwave irradiation (entry 4).

Table 8. Synthesis of pyrido[4,3-*b*]indol-1-one (5g)



Entry	Solvents	μW	Temp. (°C)	Time (h)	Yield (%) of **5g**
1	1,2-dichlorobenzene	–	180	20	38
2	1,2-dichlorobenzene	+	180	1	68
3	bromobenzene	–	150	1	52
4	bromobenzene	+	150	1	84
5	bromobenzene	+	100	2	42
6	toluene	–	100	2	16
7	toluene	+	100	2	32

CONCLUSION

We focused on the synthetic method for isocyanates developed by Shioiri and co-workers and investigated the one-pot synthesis of various fused 2-pyridone ring systems based on a Curtius rearrangement, followed by a microwave-assisted thermal electrocyclization of a 2-aza-6π-electron system including isocyanate. We synthesized seven heterocyclic compounds containing a fused 2-pyridone moiety, which have interesting pharmaceutical potential. Except for 3-(pyrrol-2-yl)acrylic acid **1b**, one-pot synthesis of fused 2-pyridone ring system **5** from (*E*)-acrylic acids **1** under microwave irradiation conditions proved to be more effective than the conventional conditions in terms of the yield and the reaction time. We could establish an efficient one-pot synthesis method for various types of aromatic heterocyclic fused 2-pyridone. Currently, we are investigating the total synthesis of natural products and a research study of biologically active compounds based on these heterocyclic fused 2-pyridone ring.

EXPERIMENTAL

General Methods: All non-aqueous reactions were carried out under an atmosphere of nitrogen in dried glassware unless otherwise noted. Solvents were dried and distilled according to standard protocols. Analytical thin-layer chromatography was performed with Silica gel $60PF_{254}$ (Merck). Silica gel column chromatography was performed with Silica gel 60 (70–230 mesh, Kanto Co. Lit.). All melting points were determined on Yanagimoto micro melting point apparatus and are uncorrected. Proton nuclear magnetic resonance (^{1}H-NMR) spectra were recorded on a JEOL AL-300 at 300 MHz. Chemical shifts

are reported relative to Me_4Si (δ 0.00). NMR spectra were measured with $CDCl_3$ unless otherwise noted. Multiplicity is indicated by one or more of the following: s (singlet); d (doublet); t (triplet); q (quartet); m (multiplet); br (broad). Carbon nuclear magnetic resonance (^{13}C-NMR) spectra were recorded on a JEOL AL-300 at 75 MHz. Chemical shifts are reported relative to $CDCl_3$ (δ 77.0) and DMSO-d_6 (δ 39.7). Infrared spectra were recorded with ATR method using a Shimadzu FTIR-8000 spectrophotometer and Technologies DuraScop. Low and high-resolution mass spectra were recorded on JEOL JMS-700 spectrometers by direct inlet system.

General procedure for (*E*)-heteroarylacrylate 9 by Wittig reaction: A solution of arylcarbaldehyde (10.4 mmol) and (ethoxycarbonylmethylene)triphenylphosphorane (14.6 mmol) in THF (20 mL) was heated at 80 °C for 12 h. After cooling to an ambient temperature, the reaction mixture was quenched with water, and then was extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, and evaporated *in vacuo*. The residue was purified by column chromatography (silica gel, 30 g) using EtOAc-hexane (3:97, v/v) as an eluent to give the (*E*)-acrylate **9**.

Ethyl (*E*)-3-(2-furyl)acrylate 9a

IR (ATR) ν: 1702 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.32 (3H, t, *J* = 7.2 Hz), 4.25 (2H, q, *J* = 7.2 Hz), 6.31 (1H, d, *J* = 15.6 Hz), 6.46 (1H, dd, *J* = 1.5, 3.5 Hz), 6.61 (1H, d, *J* = 3.5 Hz), 7.43 (1H, d, *J* = 15.6 Hz), 7.48 (1H, d, *J* = 1.5 Hz). ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 14.2, 60.4, 112.2, 114.6, 115.9, 131.0, 144.6, 150.9, 167.1. MS (EI) *m*/*z*: 166 (M^+); HRMS (EI) Calcd for $C_9H_{10}O_3$: 166.0630. Found: 166.0634.

Ethyl (*E*)-3-(*N*-benzylpyrrol-2-yl)acrylate 9b

IR (ATR) ν: 1697 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.28 (3H, t, *J* = 7.2 Hz), 4.18 (2H, q, *J* = 7.2 Hz), 5.21 (2H, s), 6.13 (1H, d, *J* = 15.6 Hz), 6.25 (1H, dd, *J* = 1.7, 3.8 Hz), 6.73 (1H, dd, *J* = 1.7, 3.8 Hz), 6.83 (1H, dd, *J* = 1.7, 3.8 Hz), 7.05 (2H, d, *J* = 6.4 Hz), 7.27–7.35 (3H, m), 7.57 (1H, d, *J* = 15.6 Hz). ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 14.3, 50.6, 60.1, 109.9, 111.8, 113.3, 126.3, 126.4, 127.7, 128.8, 129.1, 132.1, 137.3, 167.6. MS (EI) *m*/*z*: 255 (M^+); HRMS (EI) Calcd for $C_{16}H_{17}NO_2$: 255.1259. Found: 255.1247.

Ethyl (*E*)-3-(2-thienyl)acrylate 9c

IR (ATR) ν: 1702 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.33 (3H, t, *J* = 7.0 Hz), 4.25 (2H, q, *J* = 7.0 Hz), 6.24 (1H, d, *J* = 15.8 Hz), 7.05 (1H, dd, *J* = 3.7 Hz), 7.25 (1H, d, *J* = 3.7 Hz), 7.37 (1H, d, *J* = 3.7 Hz), 7.89 (1H, d, *J* = 15.8 Hz). ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 14.3, 60.4, 117.0, 128.0, 128.3, 130.8, 137.0, 140.0, 166.8. MS (EI) *m*/*z*: 182 (M^+); HRMS (EI) Calcd for $C_9H_{10}O_2S$: 182.0402. Found: 182.0418.

Ethyl (*E*)-3-(benzofuran-2-yl)acrylate 9d

IR (ATR) ν: 1714 cm^{-1}. mp 69–71 °C (EtOAc). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.35 (3H, t, *J* = 7.2 Hz), 4.28 (2H, q, *J* = 7.2 Hz), 6.58 (1H, d, *J* = 15.7 Hz), 6.94 (1H, s), 7.24 (1H, t, *J* = 7.7 Hz), 7.36 (1H, t, *J* =

7.7 Hz), 7.48 (1H, d, *J* = 7.7 Hz), 7.55 (1H, d, *J* = 15.7 Hz), 7.58 (1H, d, *J* = 7.7 Hz). ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 14.3, 60.6, 111.0, 111.4, 119.0, 121.7, 123.3, 126.4, 128.3, 131.2, 152.4, 155.5, 166.7. MS (EI) *m/z*: 216 (M^+); HRMS (EI) Calcd for $C_{13}H_{12}O_3$: 216.0786. Found: 216.0794.

Ethyl (*E*)-3-(benzo[*b*]thien-3-yl)acrylate 9e

IR (ATR) ν: 1702 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.36 (3H, t, *J* = 7.3 Hz), 4.30 (2H, q, *J* = 7.3 Hz), 6.55 (1H, d, *J* = 16.1 Hz), 7.39–7.50 (2H, m), 7.76 (1H, s), 7.89 (1H, d, *J* = 5.9 Hz), 7.97 (1H, d, *J* = 16.1 Hz), 8.04 (1H, d, *J* = 5.9 Hz); ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 14.3, 60.6, 118.7, 122.0, 123.0, 124.9, 125.0, 128.0, 131.6, 136.3, 137.1, 140.5, 167.1. MS (EI) *m/z*: 232 (M^+); HRMS (EI) Calcd for $C_{13}H_{12}O_2S$: 232.0558. Found: 232.0568.

Ethyl (*E*)-3-(*N*-benzylindol-3-yl)acrylate 9f

IR (ATR) ν: 1697 cm^{-1}. mp 79–81 °C (EtOAc). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.34 (3H, t, *J* = 7.2 Hz), 4.26 (2H, q, *J* = 7.2 Hz), 5.32 (2H, s), 6.43 (1H, d, *J* = 16.0 Hz), 7.14–7.16 (2H, m), 7.24–7.35 (6H, m), 7.41 (1H, s), 7.90 (1H, d, *J* = 16.0 Hz), 7.94 (1H, d, *J* = 3.3 Hz). ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 14.4, 50.4, 60.0, 110.4, 112.1, 113.0, 120.7, 121.4, 123.1, 126.3, 126.9, 128.0, 128.9, 132.4, 136.1, 137.6, 137.9, 168.2. MS (EI) *m/z*: 305 (M^+); HRMS (EI) Calcd for $C_{20}H_{19}NO_2$: 305.1416. Found: 305.1432.

Ethyl (*E*)-3-(*N*-methoxymethylindol-2-yl)acrylate 9g

IR (ATR) ν: 1702 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.35 (3H, t, *J* = 7.2 Hz), 3.28 (3H, s), 4.28 (2H, q, *J* = 7.2 Hz), 5.56 (2H, s), 6.54 (1H, d, *J* = 15.8 Hz), 6.99 (1H, s), 7.15 (1H, t, *J* = 7.7 Hz), 7.29 (1H, t, *J* = 7.7 Hz), 7.46 (1H, d, *J* = 7.7 Hz), 7.62 (1H, d, *J* = 7.7 Hz), 7.83 (1H, d, *J* =15.8 Hz). ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 14.4, 50.3, 56.0, 73.9, 106.9, 109.9, 113.2, 117.7, 121.3, 121.7, 124.6, 127.7, 134.7, 139.5, 168.3. MS (EI) *m/z*: 259 (M^+); HRMS (EI) Calcd for $C_{15}H_{17}NO_3$: 259.1208. Found: 259.1212.

General procedure for (*E*)-heteroarylacrylic acid 1: To a solution of (*E*)-acrylate **9** (8.9 mmol) in MeOH (10 mL) was added 20% aqueous NaOH solution (5 mL), and then was stirred at rt for 5 h. The reaction mixture was diluted with water, and then was acidified with 10% HCl aqueous solution to precipitate the carboxylic acid. The precipitate was filtrated off to give the crude acrylic acid **1**.

(*E*)-3-(2-Furyl)acrylic acid 1a

R (ATR) ν: 1681, 3073 cm^{-1}. mp 139–140 °C (MeOH). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 6.33 (1H, d, *J* = 15.7 Hz), 6.49 (1H, dd, *J* = 1.8, 3.6 Hz), 6.67 (1H, d, *J* = 3.6 Hz), 7.51 (1H, d, *J* = 15.7 Hz), 7.52 (1H, d, *J* = 1.8 Hz); ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 112.4, 114.8, 115.8, 133.0, 145.3, 150.6, 172.4. MS (EI) *m/z*: 138 (M^+); HRMS (EI) Calcd for $C_7H_6O_3$: 138.0317. Found: 138.0324.

(*E*)-3-(*N*-Benzylpyrrol-2-yl)acrylic acid 1b

IR (ATR) ν: 1666 cm^{-1}. mp 182–183 °C (EtOAc-hexane). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 5.22 (2H, s), 6.11 (1H, d, *J* = 15.5 Hz), 6.27 (1H, t, *J* = 3.9 Hz), 6.79 (1H, d, *J* = 3.9 Hz), 6.88 (1H, t, *J* = 3.9 Hz), 7.04

(2H, d, *J* = 7.1 Hz), 7.29–7.33 (3H, m), 7.61 (1H, d, *J* = 15.5 Hz); ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 50.7, 110.2, 111.9, 113.0, 126.4, 127.1, 127.9, 128.8, 128.9, 134.1, 137.1, 172.3. MS (EI) *m/z*: 227 (M^+); HRMS (EI) Calcd for $C_{14}H_{13}NO_2$: 227.0946. Found: 227.0958.

(*E*)-3-(2-Thienyl)acrylic acid 1c

IR (ATR) ν: 1670 cm^{-1}. mp 142–143 °C (EtOAc-hexane). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 6.24 (1H, d, *J* = 15.6 Hz), 7.07 (1H, dd, *J* = 3.6, 5.1 Hz), 7.30 (1H, d, *J* = 3.6 Hz), 7.42 (1H, d, *J* = 5.1 Hz), 7.90 (1H, d, *J* = 15.6 Hz); ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 115.9, 128.2, 129.3, 131.6, 139.2, 139.4, 172.1. MS (EI) *m/z*: 154 (M^+); HRMS (EI) Calcd for $C_7H_6O_2S$: 154.0089. Found: 154.0073.

(*E*)-3-(Benzofuran-2-yl)acrylic acid 1d

IR (ATR) ν: 1666 cm^{-1}. mp 187–188 °C (EtOAc-hexane). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 6.60 (1H, d, *J* = 15.6 Hz), 7.00 (1H, s), 7.26 (1H, t, *J* = 7.4 Hz), 7.39 (1H, t, *J* = 5.8 Hz), 7.51 (1H, d, *J* = 7.7 Hz), 7.61 (1H, d, *J* = 7.7 Hz), 7.63 (1H, d, *J* = 15.6 Hz); ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 100.5, 111.4, 117.5, 121.8, 123.4, 126.7, 128.2, 133.2, 151.9, 169.8, 176.3. MS (EI) *m/z*: 188 (M^+); HRMS (EI) Calcd for $C_{11}H_8O_3$: 188.0473. Found: 188.0488

(*E*)-3-(Benzo[*b*]thien-3-yl)acrylic acid 1e

R (ATR) ν: 1660 cm^{-1}. mp 219–221 °C (EtOAc-hexane). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 6.56 (1H, d, *J* = 15.9 Hz), 7.43–7.50 (2H, m), 7.84 (1H, s), 7.90 (1H, d, *J* = 7.2 Hz), 8.04 (1H, d, *J* = 7.2 Hz), 8.06 (1H, d, *J* = 15.9 Hz); ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 100.6, 111.5, 112.0, 117.5, 121.9, 123.4, 126.8, 128.3, 133.3, 152.0, 155.8. MS (EI) *m/z*: 204 (M^+); HRMS (EI) Calcd for $C_{11}H_8O_2S$: 204.0245. Found: 204.0233.

(*E*)-3-(*N*-Benzylindol-3-yl)acrylic acid 1f

IR (ATR) ν: 1698 cm^{-1}. mp 101–102 °C (EtOAc-hexane). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 5.33 (2H, s), 6.44 (1H, d, *J* = 15.9 Hz), 7.05–7.26 (2H, m), 7.27–7.34 (7H, m), 7.44 (1H, s), 7.94 (1H, d, *J* = 5.5 Hz), 7.99 (1H, d, *J* = 15.9 Hz); ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 49.2, 93.5, 110.9, 112.4, 120.0, 120.6, 122.2, 125.9, 127.1, 127.5, 128.6, 132.1, 133.3, 136.9, 137.6, 170.3. MS (EI) *m/z*: 277 (M^+); HRMS (EI) Calcd for $C_{18}H_{15}NO_2$: 277.1103. Found: 277.1121.

(*E*)-3-(*N*-Methoxymethylindol-2-yl)acrylic acid 1g

IR (ATR) ν: 1673 cm^{-1}. mp 157–158 °C (EtOAc-hexane). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 3.30 (3H, s), 5.58 (2H, s), 6.55 (1H, d, *J* = 15.8 Hz), 7.07 (1H, s), 7.17 (1H, t, *J* = 7.2 Hz), 7.32 (1H, t, *J* = 7.2 Hz), 7.47 (1H, d, *J* = 7.8 Hz), 7.64 (1H, d, *J* = 7.8 Hz), 7.93 (1H, d, *J* = 15.8 Hz); ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 56.0, 73.9, 106.9, 109.9, 116.3, 117.7, 121.3, 121.7, 124.6, 127.7, 134.7, 139.5, 171.7. MS (EI) *m/z*: 231 (M^+); HRMS (EI) Calcd for $C_{13}H_{13}NO_3$: 231.0895. Found: 231.0887.

General procedure for aromatic heterocycles fused pyridine 5: A solution of acrylic acid **1** (0.30 mmol), DPPA (0.90 mmol), and Et_3N (0.90 mmol) in 1,2-dichlorobenzene (3 mL) were stirred at 60 °C

for 15 min to generate in sute the isocyanate (monitored the disappearance of acrylic acid by TLC), and then was heated under microwave irradiation at 180 °C for 1 h. After cooling to an ambient temperature, the reaction mixture was concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, 10 g) using EtOAc-hexane (1:9 v/v) as an eluent to give the pyridone **5**.

Furo[3,2-*c*]pyridin-4-one 5a

IR (ATR) ν: 1652 cm^{-1}. mp 223–224 °C (EtOAc-hexane). ^{1}H-NMR (300 MHz, DMSO-d_6) δ: 6.66 (1H, d, J = 7.3 Hz), 7.01 (1H, d, J = 2.1 Hz), 7.31 (1H, d, J = 7.3 Hz), 7.55 (1H, d, J = 2.1 Hz), 12.14 (1H, br s). ^{13}C-NMR (75 MHz, DMSO-d_6) δ: 94.7, 106.8, 119.9, 122.1, 128.9, 131.5, 144.0. MS (EI) m/z: 135 (M^+); HRMS (EI) Calcd for $C_7H_5NO_2$: 135.1220. Found: 135.1238.

***N*-Benzylpyrrolo[3,2-*c*]pyridin-4-one 5b**

IR (ATR) ν: 1625 cm^{-1}. mp 196–198 °C (EtOAc). ^{1}H-NMR (300 MHz, DMSO-d_6) δ: 5.24 (2H, s), 6.35 (1H, d, J = 7.3 Hz), 6.88 (1H, d, J = 3.2 Hz), 6.93 (1H, d, J = 3.2 Hz), 7.08–7.10 (3H, m), 7.26–7.36 (3H, m), 11.39 (1H, br s). ^{13}C-NMR (75 MHz, DMSO-d_6) δ: 49.4, 93.6, 103.8, 115.6, 125.6, 127.0, 127.5, 128.6, 128.7, 137.9, 138.9, 159.5. MS (EI) m/z: 224 (M^+); HRMS (EI) Calcd for $C_{14}H_{12}N_2O$: 224.2630. Found: 224.2636.

Thieno[3,2-*c*]pyridin-4-one 5c

IR (ATR) ν: 1637 cm^{-1}. mp 161–163 °C (EtOAc). ^{1}H-NMR (300 MHz, DMSO-d_6) δ: 6.79 (1H, d, J = 7.0 Hz), 7.23 (1H, d, J = 7.0 Hz), 7.31 (1H, d, J = 5.3 Hz), 7.65 (1H, d, J = 5.3 Hz), 12.34 (1H, br s). ^{13}C-NMR (75 MHz, DMSO-d_6) δ: 101.0, 119.9, 121.8, 124.1, 125.1, 128.8, 130.5. MS (EI) m/z: 151 (M^+); HRMS (EI) Calcd for C_7H_5NOS: 151.1830. Found: 151.1842.

Benzofuro[3,2-*c*]pyridin-1-one 5d

IR (ATR) ν: 1637 cm^{-1}. mp 240–242 °C ($CHCl_3$). ^{1}H-NMR (300 MHz, DMSO-d_6) δ: 6.79 (1H, d, J = 7.2 Hz), 7.39–7.48 (2H, m), 7.58 (1H, d, J = 7.2 Hz), 7.72 (1H, d, J = 7.2 Hz), 8.01–8.03 (1H, m), 11.86 (1H, br s). ^{13}C-NMR (75 MHz, DMSO-d_6) δ: 94.5, 110.0, 111.4, 120.8, 123.6, 124.3, 125.8, 135.3, 154.1, 159.5, 162.5. MS (EI) m/z: 185 (M^+); HRMS (EI) Calcd for $C_{11}H_7NO_2$: 185.1820. Found: 185.1828.

Benzo[*b*]thieno[2,3-*c*]pyridin-1-one 5e

IR (ATR) ν: 1643 cm^{-1}. mp 246–248 °C ($CHCl_3$). ^{1}H-NMR (300 MHz, DMSO-d_6) δ: 7.20 (1H, d, J = 7.3 Hz), 7.46–7.63 (3H, m), 8.12 (1H, d, J = 7.3 Hz), 8.33 (1H, d, J = 7.3 Hz), 11.87 (1H, br s). ^{13}C-NMR (75 MHz, DMSO-d_6) δ: 100.2, 100.3, 123.7, 124.0, 125.2, 128.4, 131.5, 135.1, 141.0, 142.2, 158.9. MS (EI) m/z: 201 (M^+); HRMS (EI) Calcd for $C_{11}H_7NOS$: 201.2430. Found: 201.2430.

***N*-Benzylpyrido[3,4-*b*]indol-1-one 5f**

IR (ATR) ν: 1637 cm^{-1}. mp 251–252 °C ($CHCl_3$-hexane). ^{1}H-NMR (300 MHz, DMSO-d_6) δ: 6.03 (2H, s), 7.06 (1H, d, J = 7.7 Hz), 7.11–7.22 (6H, m), 7.42 (1H, t, J = 7.7 Hz), 7.58 (1H, d, J = 7.7 Hz), 8.06 (1H, d, J = 7.7 Hz), 8.23 (1H, s), 11.47 (1H, br s). ^{13}C-NMR (75 MHz, DMSO-d_6) δ: 47.1, 100.3, 111.5, 120.5,

121.8, 121.9, 125.7, 125.7, 126.5, 127.2, 127.3, 127.5, 128.8, 130.1, 138.9, 139.9, 156.5, 175.7. MS (EI) *m/z*: 274 (M^+); HRMS (EI) Calcd for $C_{18}H_{14}N_2O$: 274.3230. Found: 274.3234.

***N*-Methoxymethylpyrido[4,3-*b*]indol-1-one 5g**

IR (ATR) ν: 1644 cm^{-1}. mp 154–156 °C (EtOAc-hexane). ^{1}H-NMR (300 MHz, DMSO-d_6) δ: 3.30 (3H, s), 5.61 (2H, s), 6.66 (1H, d, *J* = 7.3 Hz), 7.36–7.62 (4H, m), 8.44 (1H, d, *J* = 7.3 Hz), 12.30 (1H, br s). ^{13}C-NMR (75 MHz, DMSO-d_6) δ: 55.6, 73.6, 93.0, 110.3, 119.9, 120.6, 121.5, 124.0, 128.9, 132.7, 138.1, 146.0, 159.7. MS (EI) *m/z*: 228 (M^+); HRMS (EI) Calcd for $C_{13}H_{12}N_2O_2$: 228.2510. Found: 228.2522.

ACKNOWLEDGMENTS

This work was supported in part by a Grant-in-Aid for Scientific Research (C) of the Japan Society for the Promotion of Science (grant number 15K07880 for T.C.).

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