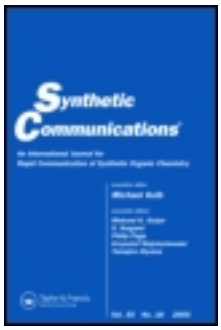

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An Efficient One-Pot Synthesis of 3-Amino-7-azaindoles under Microwave Irradiation

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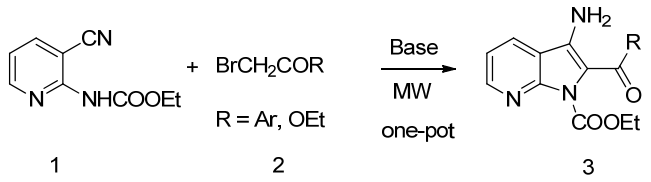
Abstract

An efficient one-pot synthesis of 3-amino-7-azaindoles was developed, starting from ethyl (3-cyanopyridin-2-yl)carbamate and α-bromoketones by microwave-assisted

Thorpe–Ziegler cyclization in the presence of a base. This method features excellent yields, short reaction time (10 min), and high functional group compatibility.

[Supplementary materials are available for this article. Go to the publisher's online edition of *Synthetic Communications*® for the following free supplemental resource(s): Full experimental and spectral details.]



1 2 3

KEYWORDS: 3-amino-7-azaindoles, Thorpe–Ziegler cyclization, microwave irradiation, one-pot synthesis

INTRODUCTION

Azaindole derivatives are important heterocyclic compounds in medicinal chemistry owing to their broad range of biological activities.[1] In particular, 3-amino-7-azaindoles, a typical class of azaindole derivatives, have shown a wide variety of pharmacological properties, and some of them have served as potential drugs, such as adenosine receptor agonists and antagonists[2a] and tumor necrosis factor release inhibitors.[2b] Moreover, these compounds are of considerable interest because of their use as suitable scaffolds for many drugs, namely N-(7-azaindole-3-yl) amide derivatives[3] and pyridopyrrolopyrimidines.[4]

Generally, 3-amino-7-azaindoles can be prepared by several methods, including the conversion of 2-(4-chloro-5H-1,2,3-dithiazolylidene-amino) benzonitriles[5] and the reduction of 3-nitro [3,6a] or 3-nitroso [6b] group of 7-azaindoles. However, the application

of these methods is limited because of the poor availability of starting materials and toxic reagents. To overcome these inherent problems, recently an efficient Thorpe–Ziegler cyclization [2, 4, 7, 8] has been developed for the preparation of 3-amino-7-azaindoles. This method used 2-chloronicotinonitrile analogs as starting materials which can be easily substituted with 2-aminoacetamide [4a], ethyl 2-aminoacetate [7a, 7b], ethyl 2-(methylamino) acetate [7d], and N, N-dimethyl-2-(methylamino)acetamide [2a] to provide substituted intermediates that can undergo subsequent intramolecular cyclization to yield 3-amino-1H-7-azaindoles in the presence of bases. However, this sequence has limited applications because of its narrow scope. Furthermore, these methods generally require a prolonged reaction time, multi synthetic steps and provide only low to moderate overall yields.

It is known that, microwave irradiation, because of its significant enhancement in reaction rates and yields, has emerged as a powerful technique for promoting a variety of chemical reactions. [8] As part of an ongoing program in our laboratory to synthesize a variety of 3-amino-7-azaindoles under mild conditions, we herein report an efficient synthesis of 3-amino-7-azaindoles by microwave-assisted Thorpe–Ziegler cyclization of α-haloketones and ethyl (3-cyanopyridin-2-yl)carbamate (Scheme 1).

RESULTS AND DISCUSSION

Thorpe–Ziegler cyclization generally proceeds smoothly in the presence of bases in aprotic solvents to give the corresponding intramolecular condensation products in poor to moderate yields. Therefore, we first investigated the effect of modifying the base, solvent, temperature, and reaction time under microwave irradiation. The reaction of 1a

with phenacyl bromide (2a) in DMF was chosen as a model to optimize the reaction conditions. The results are summarized in Table 1.

As shown in Table 1, compound 3a could be prepared in moderate yield only in the presence of cesium carbonate (entries 1–5), and DMF was found to be the best reaction medium (entries 4 and 6–8). Note, however, that potassium carbonate was the best base under the conventional method (data not shown). Under the conditions using cesium carbonate and DMF, the yields increased consistently with an increase in temperature from 80 to 100 °C. Further increase to 110 °C, however, led to a decrease in the yield (entries 11 and 12). This might be due to the instability of 3-amino-1H-7-azaindoles at high temperature. On the other hand, the yields increased with time, from 15% (1 min) to a maximum of 89% (10 min) (entries 10 and 13–14). Extending the reaction time to longer than 10 min did not change the yield significantly. Taken together, we concluded that, under microwave irradiation, the optimal conditions were 100 °C, 10 min, and cesium carbonate in DMF. We subsequently used these conditions for the microwave-assisted synthesis of a library of 2-aroylthoxy-3-amino-7-azaindoles. The results, together with those obtained under the conventional method for comparison, are shown in Table 2.

The results in Table 2 indicate that moderate to good isolated yields (57%–82%) could be achieved under the conventional method after a long reaction time (3 h), and the results were highly dependent on the starting materials that were used. Prolonging the reaction time or adding excess 2-bromo-1-aroylethanones 2a–l did not significantly improve the yield. In contrast, under microwave irradiation, the reactions were completed in 10 min and 2-aroylthoxy-3-amino-7-azaindoles were isolated in good to excellent yields (79%–91%). Thus, microwave irradiation increased the yield by 7%–22%. Note that

substituents on the aromatic ring, such as F, Cl, Br, CH_3, CH_3O, CF_3, and NO_2, have practically no obvious effect on the yield under both conventional and microwave conditions. Most interestingly, ethyl (3-cyanopyridin-2-yl)carbamate and 2-bromo-1-(naphthalen-1-yl)ethanone worked equally well to give the desired azaindole derivatives in satisfactory yields (compound 3m, Table 2). However, on the replacement of 2-bromo-1-aroylethanones with ethyl 2-bromoacetate, the yield was relatively low, especially under the conventional method (compound 3n, Table 2). Moreover, no product was detected under both microwave irradiation and conventional heating conditions in the case of 1-bromopropan-2-one (compound 3o, data not shown in Table 2).

In conclusion, we have developed a highly efficient one-step synthesis of 3-amino-7-azaindoles directly by the Thorpe–Ziegler cyclization of ethyl (3-cyanopyridin-2-yl) carbamate with α-bromoketones or ethyl 2-bromoacetate in DMF under microwave irradiation. This reaction features excellent yields, short reaction time (10 min), and easy manipulation.

EXPERIMENTAL

All materials were obtained from commercial sources and were used as received unless stated otherwise. The silica gel (200-300 mesh) for flash column chromatography was from Qingdao Marine Chemical (China), and the distillation range of petroleum was 60-90 °C. ESI-MS spectra were measured on a water UPLC/Quattro Premier XE mass spectrometer. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ or d_6-DMSO using Varian Mercury 400 spectrometers and TMS as an internal reference. Elementary analyses were performed on a Vario EL III elemental analysis instrument. Melting points were measured using a Buchi B-545 melting point apparatus. Microwave-irradiated

reactions were carried out with a USA CEM Discover Focused Microwave Synthesizer (Serial Number DU8290).

General Procedures For Conventional Preparation Of 3a-N ethyl 3-amino-2-benzoyl-1H-pyrrolo[2,3-b]pyridine-1-carboxylate 3a as an example: phenacyl bromide (1.09g, 5.5 mmol) and potassium carbonate (1.52 g, 11 mmol) were added to a solution of 3-cyanopyridin-2-ylcarbamate (955 mg, 5.0 mmol) in dry N, N-dimethylformamide (5.0 mL). After stirring for 3 h at 100 ℃, the reaction mixture was poured into water (80 mL) and extracted with dichloromethane. The combined organic layer was washed extensively with water and brine, and then dried over anhydrous sodium sulfate. The solvent was evaporated, and the residue was purified by chromatography on a silica-gel column (petroleum ether - ethyl acetate, 8/1 by volume) to give compound **3a** (1.16g, 76%).

General Procedures For Microwave-Assisted Preparation Of 3a-N ethyl 3-amino-2-benzoyl-1H-pyrrolo[2,3-b]pyridine-1-carboxylate 3a as an example: In a microwave tube, phenacyl bromide (219 mg, 1.1 mmol) and cesium carbonate (652 mg, 2.0 mmol) were added to a solution of ethyl 3-cyanopyridin-2-ylcarbamate (191 mg, 1.0 mmol) in dry N, N-dimethylformamide (1.0 mL). Then, the sealed microwave tube was placed in CEM Corporation instrumentation and irradiated at 100 ℃ for 10 min. Then, the reaction mixture was poured into water (15 mL) and extracted with dichloromethane. The combined organic layer was washed extensively with water and brine, and then dried over anhydrous sodium sulfate. The solvent was evaporated, and the

residue was purified by chromatography on a silica-gel column (petroleum ether - ethyl acetate, 8/1 by volume) to give compounds **3a** (275mg, 89%). light yellow solid, m.p. 108~109 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.86 (t, *J* = 7.2 Hz, 3H, CH_3), 3.72 (dd, *J* = 7.2 Hz, *J* = 14.4 Hz, 2H, CH_2), 5.81 (s, br, 2H, NH_2), 7.26 (t, *J* = 3.8 Hz, 1H), 7.40~7.47 (m, 3H, H-13), 7.76 (t, *J* = 4.2 Hz, 2H), 7.98 (dd, *J* = 1.6 Hz, *J* = 8.0 Hz, 1H), 8.68 (dd, *J* = 1.6 Hz, *J* = 4.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.4, 63.3, 115.2, 115.3, 118.6, 127.3, 128.5, 129.0, 131.4, 140.3, 149.3 150.1, 150.3, 187.2; ESI MS *m*/*z*: 332.8 $[M+Na]^+$, 310.7 $[M+1]^+$. Anal. calcd. for $C_{17}H_{15}N_3O_3$: C, 66.01; H, 4.89; N, 13.58. Found: C, 65.87; H, 4.78; N, 13.35.

All compounds are new compounds, and were fully characterized by MS, NMR (1H and 13C) and elemental analysis. (See Supporting Information).

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Supporting Information: Full experimental detail, MS, ^{1}H and ^{13}C NMR spectra, elemental analysis. This material can be found via the “Supplementary Content” section of this article’s webpage.’

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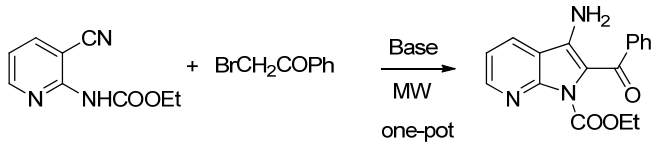
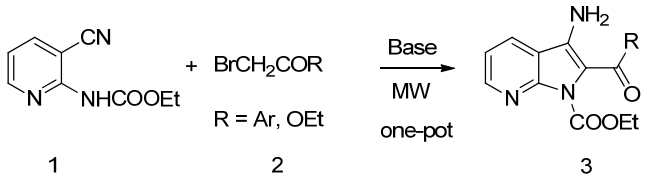
TABLE 1 Optimization of microwave-assisted cyclocondensation of ethyl (3-cyanopyridin-2-yl)carbamate with phenacyl bromide



1 2a 3a

Entry	Solvent	Base	T/ °C	t/min	IsolatedYield/ %
1	DMF	Na_2CO_3	80	10	trace
2	DMF	K_2CO_3	80	10	trace
3	DMF	K_3PO_4	80	10	trace
4	DMF	Cs_2CO_3	80	10	31
5	DMF	KOH	80	10	10
6	THF	Cs_2CO_3	80	10	trace
7	DME	Cs_2CO_3	80	10	trace
8	1,4-dioxan	Cs_2CO_3	80	10	trace
9	DMF	Cs_2CO_3	90	10	76
10	DMF	Cs_2CO_3	100	10	89
11	DMF	Cs_2CO_3	110	10	83
12	DMF	Cs_2CO_3	120	10	51
13	DMF	Cs_2CO_3	100	1	15
14	DMF	Cs_2CO_3	100	5	76
15	DMF	Cs_2CO_3	100	15	85
16	DMF	Cs_2CO_3	100	20	77

TABLE 2 One-Step Synthesis of 3-aminoazaindoles



Entry	R	Microwave irradiation[a]		Conventional heating [b]	
		t/min	Isolated Yield/% [c]	t/min	Isolated Yield/% [c]
3a	Ph	10	89	180	76
3b	4-BrPh	10	82	180	75
3c	4-MePh	10	87	180	70
3d	4-MeOPh	10	85	180	68
3e	4-FPh	10	90	180	79
3f	4-ClPh	10	91	180	82
3g	3,4-F_2Ph	10	86	180	75
3h	4-CF_3Ph	10	83	180	71
3i	4-NO_2Ph	10	84	180	73
3j	2-MePh	10	82	180	69
3k	3-BrPh	10	86	180	76
3l	2-MeOPh	10	81	180	65
3m		10	89	180	72
3n	EtO	10	79	180	57

[a] The temperature for these reactions is 100 °C.

[b] The reaction was carried out at 100 °C.

[c] Isolated yield.

SCHEME 1 Microwave-assisted Thorpe–Ziegler cyclization