Yu-An Chang[a]* and Hsiang Chang[b]

[a]Department of Biotechnology, Chung Chou Institute of Technology, Yuanlin Township, Changhua County 51003, Taiwan
[b]Division of Biotechnology, Taiwan Agricultural Research Institute, Council of Agriculture, Wufeng Township, Taichung 41357, Taiwan
*E-mail: cya0520@gmail.com

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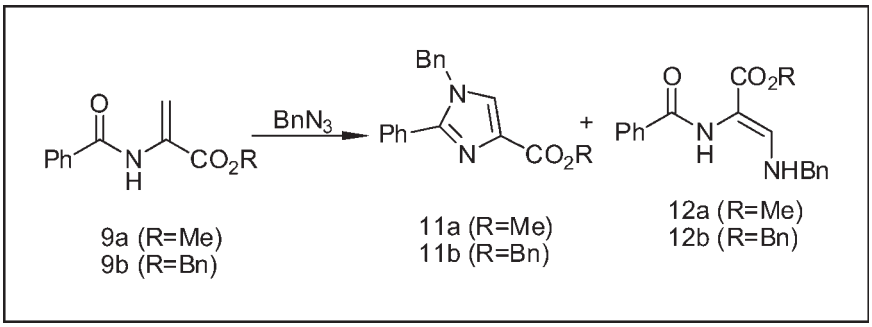

A one-pot synthesis of imidazoles has been established from the addition of azides to 2-amidoacrylates, and this synthetic method demonstrates an efficient synthesis of imidazole-4-carboxylates.

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INTRODUCTION

Over the century, the chemical and biochemical properties of imidazoles in the biological system have been attracting much interest. Even today, research in imidazole chemistry continues unabated. Compounds with imidazole ring systems have many pharmacological properties and play important roles in biochemical processes [1]. Many substituted imidazoles are known as key pharmacophore in modern drugs [2]. Therefore, the preparation of imidazoles has gained considerable attention in recent years [3].

In 1998, Hadjiantou-Maroulis et al. [4] found the pyrolysis of 1-aroylamino-4,5-diphenyl-1,2,3-triazoles (**I**) yields 2,3-diphenyl-2H-azirine (**II**) and 2-aryl-4,5-diphenylimidazoles (**III**) as the major products (Scheme 1).

More recently, great attention has been given to dipolar cycloaddition chemistry using azides, especially azide cycloadditions to alkynes to generate triazoles [5] (Scheme 2). Addition of azides to α,β-unsaturated carbonyl compounds **IV** has been reported in the literature [6–10] (Scheme 3). Particularly interesting were the transformations of 2-amido-3-arylaminoacrylates **V** and **VII** to imidazoles **VI** and **VIII,** respectively [11] (Scheme 4).

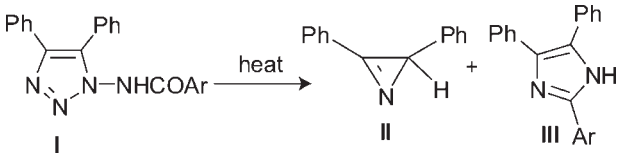
According to Hadjiantou-Maroulis et al. [4], we found a novel synthesis of imidazoles **XI** from 2-aminoacrylates **IX** and azides **X**. To our knowledge, no report has described such a one-pot procedure to synthesize imidazoles **XI** from 2-amidoacrylates **IX** (Scheme 5). In this article, we have systematically investigated each possible reaction of various 2-aminoacrylates and presented the results as follows.

RESULTS AND DISCUSSION

When 2-amidoacrylates **9** were heated with benzyl azide at reflux in toluene, imidazoles **11** were obtained as the main product in the reaction mixture. The effects of temperature, azide equivalents, and reaction time on the yield of imidazoles and byproducts **12** were investigated (Table 1). It is clear that temperature has a pivotal role in the reaction, since only trace amounts of imidazoles were observed under 100°C, and the yield of imidazoles increased with regard to reaction temperature. Likewise, we found that required reaction time could be shortened from 2–4 d to 15 h if reaction temperature increased from reflexing toluene to 190°C in a sealed tube (Table 1, entries 4, 6, and 7). Increased equivalents of benzyl azide appeared to be slightly detrimental to the yield of imidazoles, and more byproducts were yielded (Table 1, entries 6 and 7). Optimal yield of imidazoles was achieved when the reactants were heated in toluene in a sealed tube at 190°C for 15 h (Table 1, entries 4 and 6).

Based on similar imidazole synthesis previously reported [12] and the chemical properties of organic azides, we proposed a mechanism (Scheme 6) that can possibly explain the formation of 2-amido-

Scheme 1



3aminoacrylate byproduct **12** as an intermediate in the synthesis of imidazole **11**. Dipolar cycloaddition of benzyl azide to 2-amidoacrylate **9** should offer the regioisomeric triazolines A and B, even previous studies reported [13] that the formation of triazoline A would be greatly favored over the regioisomeric triazoline B. Thermal decomposition of triazolines A and B would provide compounds C and D, on extrusion of nitrogen, which would yield either aziridine E or imine F. Tautomerization of imine F would provide E-enamine G or the observed Z-enamine **12**, which on intramolecular cyclization would provide imidazole **11** after dehydration of tetrahedral intermediate H.

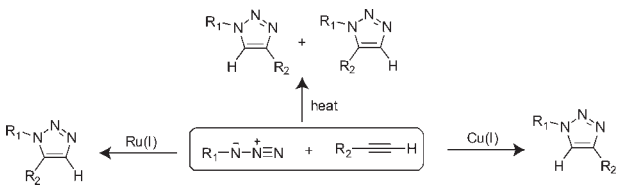
On the basis of proposed mechanism, we suggest that byproduct **12** appeared to be an intermediate contributing to the production of imidazole **11**. We found that enamine **12** was accumulated exclusively only in the sealed reaction conditions where water was confined in reaction system, otherwise imidazole **11** was observed (Table 2) [14].

A one-pot synthesis of imidazoles **11** has been developed from adding azides to 2-amidoacrylates **9**, and this synthetic method represents an efficient synthesis for imidazole-4-carboxylates **11**.

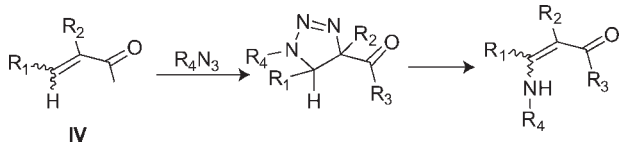
EXPERIMENTAL

All reactions were performed under an atmosphere of dry nitrogen unless noted otherwise. ^{1}H and ^{13}C NMR spectra were recorded on a Varian 300 MHz or 500 MHz spectrometer using $CDCl_3$ as solvent under ambient temperatures unless otherwise noted. Infrared spectra were recorded using an FT-IR spectrometer and are reported in cm^{-1}. Mass spectra were obtained as specified. Low-resolution mass and high-resolution mass spectra were measured with a Hitachi M-52-Instrument or Bruker APEX II mass spectrometer. Melting points were uncorrected and were determined either using recrystallized samples or samples, which crystallized during concentration of the chromatography eluents.

Scheme 2



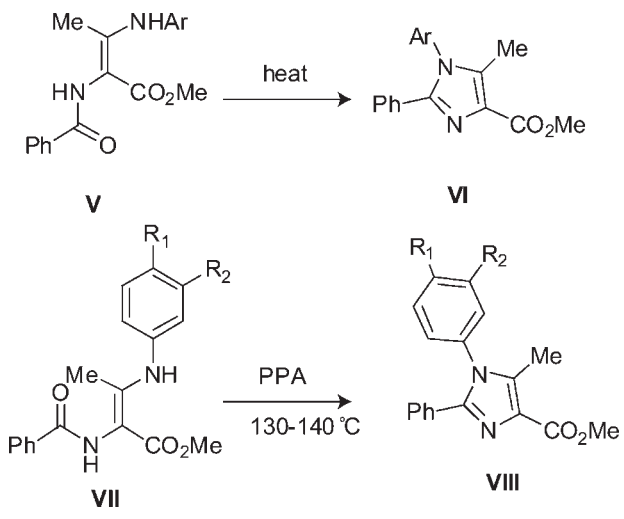
Scheme 3



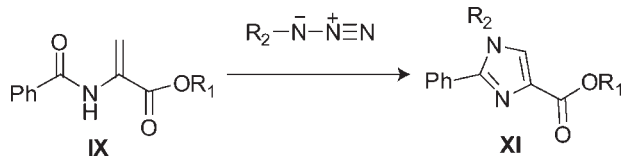
Methyl 2-benzamidoacrylate (9a). The (*S*)-Methyl 2-benzamido-3-hydroxypropanoate compound (1.21 g, 5.40 mmol) was dissolved in 50 mL of dry CH_2Cl_2 in a flame-dried 100-mL round-bottomed flask under Ar. EDC HCl (1.24 g, 6.46 mmol) was added to the solution in one portion followed by CuCl (160.7 mg, 1.62 mmol). The reaction was wrapped in foil and stirred under Ar at room temperature. After 2 h, TLC of the reaction (1:1 hexanes/EtOAc) indicated starting material had been completely consumed, and a new, less polar compound was observed. After 3 h, H_2O (100 mL) was added to the reaction, and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 20 mL), and the combined CH_2Cl_2 layers were washed with H_2O (100 mL), dried over $MgSO_4$, filtered, and concentrated to yield a yellow oil. The oil was purified through a plug (30 g) of silica gel using CH_2Cl_2 and yielded **9a** as a colorless, cloudy liquid (1.06 g, 96% yield). IR: 3300, 3150, 3075, 1740, 1640, 1210, 830, 750 cm^{-1}; ^{1}H NMR (deuteriochloroform): δ 8.49 (br-s, 1H), 7.75 (dd, J = 7.1, 1.9 Hz, 2H), 7.43 (m, 1H), 7.37 (m, 2H), 6.71 (d, J = 1.6 Hz, 1H), 5.90 (d, J = 1.6 Hz, 1H), 3.76 (s, 3H). ^{13}C NMR: δ 165.3, 164.3, 133.9, 131.7, 130.8, 128.4, 126.6, 108.5, 52.7. HRMS (FAB): m/z $[M+H]^+$ calcd for $C_{11}H_{12}NO_3^+$, 206.0817; found, 206.0818.

Benzyl 2-benzamidoacrylate (9b). Compound **9b** was prepared following a similar procedure for **9a**. The (*S*)-Benzyl 2-benzamido-3-hydroxypropanoate compound (1.51 g, 5.03 mmol), EDC HCl (1.17 g, 6.12 mmol), and CuCl (0.15 g, 1.51 mmol) provided an oil. Chromatography through silica gel using CH_2Cl_2 yielded **9b** as a white solid (1.45 g, 99% yield); mp 51–52°C. IR (KBr): 3310, 3140, 3010, 1735, 1630, 1210, 840, 730 cm^{-1}; ^{1}H NMR: δ 8.56 (br-s, 1H), 7.84 (dd, J = 7.0, 1.5 Hz, 2H), 7.55 (m, 1H), 7.47 (m, 2H), 7.41–7.36 (m, 5H),

Scheme 4



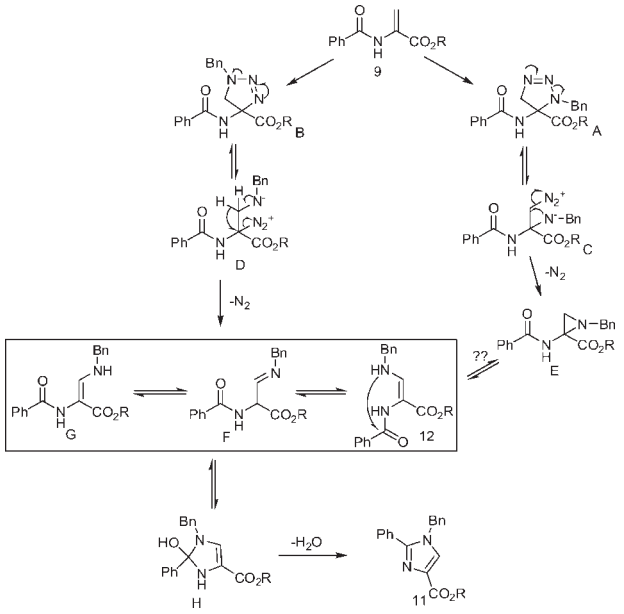
Scheme 5



6.82 (d, J = 2.0 Hz, 1H), 6.06 (d, J = 2.0 Hz, 1H), 5.32 (s, 2H). ^{13}C NMR: δ 165.7, 164.2, 135.0, 134.2, 132.0, 131.0, 128.8, 128.7, 128.6, 128.2, 126.9, 109.1, 67.9. HRMS (FAB): m/z $[M+H]^+$ calcd for $C_{17}H_{16}NO_3^+$, 282.1130; found, 282.1140.

General procedure for the preparation of imidazoles from 2-amidoacrylates and azides. Methyl 1-benzyl-2-phenyl-1H-imidazole-4-carboxylate (11a). Compound **9a** (116.2 mg, 0.57 mmol) and benzyl azide (0.11 mL, 0.87 mmol) were dissolved in 5 mL of toluene in a sealed pyrex tube fitted with a stir bar. The tube was heated in an oil bath maintained at 190°C. After 1 h, the colorless solution turned yellow in color, and gradually, the color became brown. After 15 h, the reaction was cooled to RT and concentrated. The crude brown oil was purified through 25 g of silica gel using a solvent gradient from CH_2Cl_2 to 80% CH_2Cl_2/EtOAc and yielded pure **12a** (26.5 mg, 15.1% yield), pure **11a** as an amber oil (84.1 mg, 50.8% yield), and a mixture of **12a** and **11a** (26.1 mg). Total yield of **11a** isolated as amber oil was 90.1 mg (54%). **11a** was recrystallized from EtOAc/hexanes to produce light yellow crystals. Rf = 0.14 (1:1 hexanes/EtOAc). IR (KBr): 3010, 1735, 1590, 1320, 1210, 840, 730 cm^{-1}; ^{1}H NMR: δ 7.69 (s, 1H), 7.60 (m, 2H), 7.44–7.40 (m, 3H), 7.37–7.32 (m, 3H), 7.09 (m, 2H), 5.23 (s, 2H), 3.90 (s, 3H). ^{13}C NMR: δ 163.0, 148.8, 135.4, 132.5, 129.2, 129.0, 128.8, 128.7, 128.2, 127.9, 126.9, 126.5, 51.3, 50.5. HRMS (FAB): m/z $[M+H]^+$ calcd for $C_{18}H_{17}N_2O_2^+$, 293.1290; found, 293.1293.

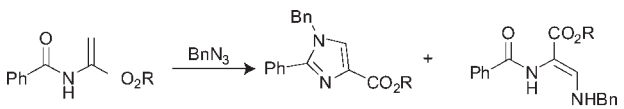
Scheme 6. Proposed formation mechanism of imidazole.



(Z)-Methyl 2-benzamido-3-(benzylamino)acrylate (12a). Compound **12a** was isolated as amber oil. Total yield isolated was 46.6 mg (27%). Compound **12a** was recrystallized from 70% EtOH/H_2O to yield colorless crystals. Rf = 0.26 (1:1 hexanes/EtOAc). IR (KBr): 3270, 3140, 3010, 2400, 1750, 1630, 840, 730 cm^{-1}; ^{1}H NMR: δ 8.00 (br, 1H), 7.84 (m, 2H), 7.51 (m, 1H), 7.44 (m, 2H), 7.37–7.26 (m, 6H), 6.50 (br, 1H), 4.42 (d, J = 6.0 Hz, 2H), 3.73 (s, 3H). ^{13}C NMR: δ 166.5, 164.8, 140.1, 138.5, 134.0, 131.6, 131.3, 128.73, 128.69, 128.6, 128.51, 128.46, 127.2, 127.1, 127.0, 126.9, 52.5, 51.6. HRMS

Table 1

Investigation of reaction conditions for the addition of benzyl azide to 2-amidoacrylates.



9a (R=Me)
9b (R=Bn)

11a (R=Me)
11b (R=Bn)

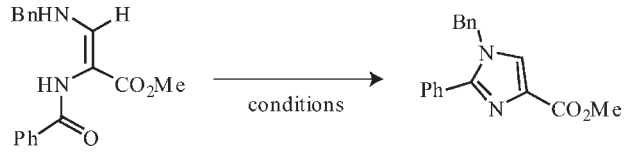
12a (R=Me)
12b (R=Bn)

						Result/yield (%)	
Entry	R	BnN_3 (equiv)	Solvent	Temp (°C)	Time	11a/11b	12a/12b
1	Me	1.5	Toluene	110	2 d	29	7
2	Me	1.5	Toluene	110	4 d	33	4
3	Me	1.3	Xylene	150	26 h	52	13
4	Me	1.5	Toluene	190[a]	15 h	54	27
5	Bn	1.5	Toluene	110	4 d	39	10
6	Bn	1.5	Toluene	190[a]	15 h	63	18
7	Bn	3.0	Toluene	190[a]	15 h	54	25

[a] Reaction was performed in a sealed pyrex tube and heated in an oil bath.

Table 2

Thermal cyclization of methyl 2-benzamido-3-(benzylamino) acrylate (12a).



Entry	Solvent	Temp (°C)	Time	Result/yield (%) 11a
1	Anisole	154[a]	15 h	40
2	Toluene	190[b]	15 h	No reaction
3	Toluene	110	15 h	35

[a] According to Stanovik et al. [11].
[b] Reaction was performed in a sealed pyrex tube and heated in an oil bath.

(FAB): m/z $[M]^+$ calcd for $C_{18}H_{18}N_2O_3^+$, 310.1317; found, 310.1297.

Benzyl 1-benzyl-2-phenyl-1H-imidazole-4-carboxylate (11b). Compound **11b** was prepared following the general procedure for the synthesis of imidazoles from acrylates and azides. Acrylate **9b** (0.14 g, 0.51 mmol) and benzyl azide (0.10 mL, 0.79 mmol) were heated in toluene (5 mL) in a sealed pyrex tube for 15 h in a 190°C oil bath. Chromatography through 25 g of silica gel using a solvent gradient from CH_2Cl_2 to 90% CH_2Cl_2/EtOAc yielded pure **12b**, **11b**, and a mixture of **11b** and **12b** as amber oils. Total yield of **11b** was 120 mg (63%). IR (KBr): 3010, 1735, 1667, 1590, 1310, 1160, 820, 730 cm^{-1}; ^1H NMR: δ 7.65 (s, 1H), 7.56 (m, 2H), 7.44 (m, 2H), 7.42–7.29 (m, 9H), 7.05 (d, $J = 7.0$ Hz, 2H), 5.36 (s, 2H), 5.18 (s, 2H). ^{13}C NMR: δ 162.6, 149.2, 136.1, 135.6, 132.8, 129.4, 129.3, 129.1, 129.0, 128.44, 128.36, 128.3, 128.2, 128.0, 127.2, 126.7, 66.0, 50.7. HRMS (FAB): m/z $[M+H]^+$ calcd for $C_{24}H_{21}N_2O_2^+$, 369.1603; found, 369.1602.

(Z)-Benzyl 2-benzamido-3-(benzylamino)acrylate (12b). Compound **12b** was isolated as amber oil (35 mg, 18%). IR : 3270, 3140, 3010, 2400, 1735, 1630, 1210, 840, 730 cm^{-1}; ^1H NMR: δ 9.04 (br, 1H), 7.84 (d, $J = 7.5$ Hz, 2H), 7.79 (d, $J = 7.5$ Hz, 2H, isomer), 7.51 (m, 1H), 7.45–7.26 (m, 13H), 6.59 (br, 1H), 5.21 (s, 2H), 4.44 (d, $J = 6.0$ Hz, 2H). ^{13}C NMR: δ 164.9, 138.4, 136.5, 134.0, 131.6, 128.8, 128.7, 128.6, 128.53, 128.47, 128.02, 127.98, 127.5, 127.2, 127.1, 126.9, 66.1, 52.6. HRMS (FAB): m/z $[M]^+$ calcd for $C_{24}H_{22}N_2O_3^+$, 386.1630; found, 386.1628.

General procedure for thermal cyclization of methyl 2-benzamido-3-(benzylamino)acrylate (12a). A mixture of **12a** (0.01 mol) and toluene (6 mL) were heated under reflux for 1.5–15 h, volatile components were evaporated *in vacuo*, the residue was triturated with toluene–hexane or with Et_2O, and the precipitate was collected by filtration to give **11a**.

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[14] The thermal cyclization of enamine compound is reversible reaction, so no reaction was observed in the sealed pyrex tube.