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Original article

Chemoselective synthesis of novel aminoindolizines using aminopyridines, acetylenic diesters and α-halo ketones

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ABSTRACT

A chemoselective synthesis of novel indolizine derivatives were reported *via* three-component reactions of aminopyridines, acetylenic diesters and α-halo ketones. In these reactions, the zwitterion generated from aminopyridines and acetylenic diesters reacted with α-halo ketones to produce indolizine skeleton in good to high yields under mild reaction conditions.

1. Introduction

Bridgehead nitrogen heterocycles play a prominent role in nature due to their presence as a key scaffold in biologically active pharmaceuticals, agrochemicals, and functional materials [1,2]. Among this class of heterocyclic compounds, indolizine derivatives have attracted considerable attention with respect to their significant biological activities, including antioxidant [3], antimicrobial [4], anti-inflammatory [5], analgesic [6], antiviral [7], antitumor [8], hypoglycemic [9], CNS depressant [10], anti-acetylcholine [11], and 5-HT3 receptor antagonists activities [12]. In addition, some indolizine compounds have been found to possess fluorescence activities [13] and the capacity to form surface films [14], which enables them for designing novel classes of fluorescent dyes [15], chemosensors [16], and biological markers [17]. Owing to the increasing importance of indolizine derivatives, new and efficient methods have been offered for the synthesis of these heterocycles by synthetic organic chemists [18,19].

The reactions of nitrogen heterocycles like pyridine and isoquinoline with activated acetylenes proceeded through a zwitterionic intermediate [20,21], which undergoes further reaction with electron-deficient carbonyl groups such as ninhydrin [22], ethyl pyruvate [23], benzofuran-2,3-diones [24], 1,3-dimethylalloxan [25], to afford spiro[1,3]-oxazines. However, when α-halogen substituted ketones were used as electrophiles in these reactions, different results were reported. Pyridine and 3-substituted pyridines (X = CH_3, Cl, Br) in reaction with mono- and di-α-halo ketones and DMAD led to formation of the corresponding [1,3]-oxazines [26]. In addition, pyridine in reaction with hexachloroacetone [27] under the same reaction conditions and phenacyl bromide [28] in the presence of basic alumina using microwave energy, resulted in indolizine derivatives. These results encouraged us to study the reactions of amino pyridines with α-halo ketones and dialkyl acetylenedicarboxylates in more detail. Herein, we report three-component reactions of pyridines **1–3** and dialkyl acetylenedicarboxylates **4a–c** with different α-halo ketones **5a–c** in dichloromethane at room temperature resulting in chemoselective synthesis of indolizine derivatives **6-8** without formation of any [1,3]-oxazines **9** (Scheme 1).

2. Experimental

Dimethyl acetylenedicarboxylate (DMAD), diethyl acetylenedicarboxylate (DEAD), di-*tert*-butylacetylene-dicarboxylate (DTAD), 3-aminopyridine, 4-aminopyridine, 4-dimethylaminopyridine

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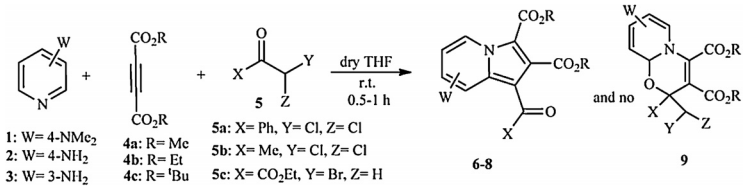


Scheme 1. Synthesis of indolizine derivatives **6-8**.

(DMAP), 2,2-dichloroacetophenone (=2,2-dichloro-1-phenylethanone), 1,1-dichloroacetone (=1,1-dichloropropan-2-one), ethyl bromopyruvate, phenacyl chloride, phenacyl bromide, and chloroacetone were purchased from Fluka and Merck and used without further purification. Melting points were measured on an Electrothermal 9100 apparatus. NMR spectra were recorded with a Bruker DRX-400 AVANCE instrument (400.1 MHz for ^{1}H, 100.6 MHz for ^{13}C) with $CDCl_3$ and DMSO-d_6 as solvents. Chemical shifts are given in parts per million (δ) relative to TMS, and coupling constants (J) are reported in hertz (Hz). IR spectra were recorded on an FT-IR Bruker vector 22 spectrometer. Mass spectra were recorded on a Finnigan-Matt 8430 mass spectrometer operating at an ionization potential of 70 eV. Elemental analyses were carried with a Perkin-Elmer 2400II CHN Elemental Analyzer.

2.1. General procedure for synthesis of compounds *6aa–8cb*

To a magnetically stirred solution of α-halo ketones (1 mmol) and acetylenic diesters (1 mmol) in dry THF (10 mL) at ambient temperature was added dropwise a solution of aminopyridines (1 mmol) in dry THF (2 mL) over 10 min. The reaction mixture was then allowed to stir for 0.5–1 h. After completion of the reaction, as indicated by TLC (*n*-hexane/ethyl acetate, 7:3), the solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel (Merck, 230–240 mesh) using a mixture of *n*-hexane/ethyl acetate (3:2) as eluent to give the desired product.

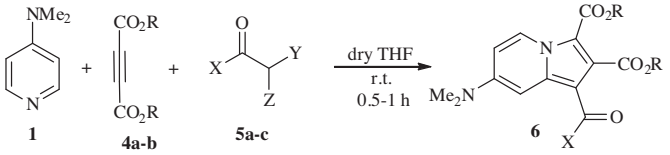
Dimethyl 1-benzoyl-7-(dimethylamino)indolizine-2,3-dicarboxylate (**6aa**): Yellow powder, mp: 212–214 °C; yield (0.35 g, 92%); IR (KBr, cm^{-1}): ν_{max} 3061 (C_{sp^2}–H), 2995 and 2948 (C_{sp^3}–H), 1738 (C=O, ester), 1689 (C=O, ketone), 1647 (C=C), 1230 (C_{sp^2}–O), 1098 (C_{sp^3}–O); ^{1}H NMR (400.1 MHz, $CDCl_3$): δ 3.05 (s, 6H, NMe_2), 3.51 and 3.86 (2s, 6H, 2 × OMe), 6.66 (dd, 1H, $^{3}J_{HH}$ = 7.6 Hz, $^{4}J_{HH}$ = 2.4 Hz, CH), 7.10 (d, 1H, $^{4}J_{HH}$ = 2.4 Hz, CH), 7.42–7.52 (m, 3H, $2CH_{ortho}$ and CH_{para}), 7.64–7.67 (m, 2H, $2CH_{meta}$), 9.31 (d, 1H, $^{3}J_{HH}$ = 7.6 Hz, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 39.8 (NMe_2), 51.7 and 52.3 (2 × OMe), 96.1 and 105.3 (2 × CH), 108.8 and 110.4 ($2C_q$), 128.0 ($2CH_{ortho}$), 128.2 ($2CH_{meta}$), 128.7 (CH), 130.8 (CH_{para}), 131.4 and 141.1 ($2C_q$), 141.8 (C_{ipso}), 149.1 ($CNMe_2$), 160.9 and 166.2 (2C=O, ester), 190.4 (C=O, ketone); MS, *m/z* (%): 380 ($M^{+\bullet}$, 100), 349 (12), 303 (55), 277 (16), 262 (8), 245 (16), 219 (7), 186 (8), 159 (11), 139 (6), 105 (8), 77 (18); Anal. Calcd. for $C_{21}H_{20}N_2O_5$ (380.39): C 66.31, H 5.30, N 7.36%. Found: C 66.51, H 5.32, N 7.38%.

Experimental procedures and spectral data of new compounds are available in Supporting information file.

3. Results and discussion

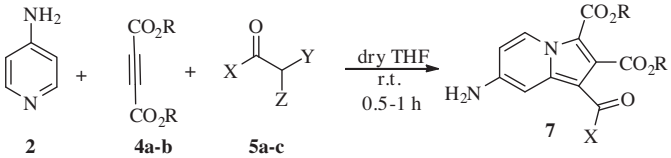
Initially, three component reaction of 4-*N*,*N*-dimethylaminopyridine (DMAP) **1** with DMAD **4a** in the presence of **5a** was carried out at room temperature for 0.5 h affording the corresponding indolizine **6aa** in high yield (Table 1, entry 1). When this reaction was performed with α-bromopyrovate **5c**, the yield of the indolizine product **6ac** significantly decreased (Table 1, entry 3). This could be due to lower electrophilicity of the C_α relative to the carbonyl group in compound **5c**. DMAP **1** reacted smoothly with dialkyl acetylenedicarboxylate **4b** and ketones **5a–c** to form the indolizines **6ba–6bc** (Table 1, entries 4–6). Similarly, 4-aminopyridine **2** and 3-aminopyridine **3** treated with acetylenic esters **4a–c** and ketones **5a–c** under the same reaction conditions and moderate to high yields of expected indolizine products were obtained and results are shown in Tables 2 and 3, respectively. Lower yields of the products in the case of 3-aminopyridine **3**

Table 1
Synthesis of indolizine derivatives **6aa–6bc** using 4-*N*,*N*-dimethyl aminopyridine.



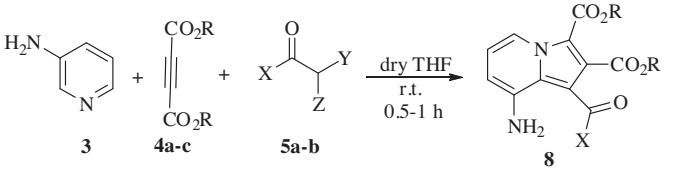
Entry	4a–b	5a–c	Product	Yield (%)
1	**4a**	**5a**	**6aa**	92
2	**4a**	**5b**	**6ab**	85
3	**4a**	**5c**	**6ac**	72
4	**4b**	**5a**	**6ba**	90
5	**4b**	**5b**	**6bb**	81
6	**4b**	**5c**	**6bc**	69

Table 2
Synthesis of indolizine derivatives **7aa–7bc** using 4-aminopyridine.



Entry	4a–b	5a–c	Product	Yield (%)
1	**4a**	**5a**	**7aa**	91
2	**4a**	**5b**	**7ab**	88
3	**4b**	**5a**	**7ba**	87
4	**4b**	**5b**	**7bb**	83
5	**4b**	**5c**	**7bc**	56

Table 3
Synthesis of indolizine derivatives **8aa–8cb** using 3-aminopyridine.



Entry	4a–c	5a–b	Product	Yield (%)
1	**4a**	**5a**	**8aa**	69
2	**4a**	**5b**	**8ab**	58
3	**4b**	**5a**	**8ba**	63
4	**4b**	**5b**	**8bb**	55
5	**4c**	**5a**	**8ca**	54
6	**4c**	**5b**	**8cb**	52