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Novel Synthesis of Functionalized Indolizine Derivatives from Huisgen's Zwitterions and 1-Methylimidazole/Dichloroketene Adduct

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Dedicated to Professor Kazem Saidi, on the occasion of his 65th birthday

Abstract: The reactive zwitterionic intermediates, generated from addition of pyridine derivatives to dialkyl acetylenedicarboxylates, react with 1-methylimidazole/dichloroketene adduct to afford functionalized dialkyl 1-(2,2-dichloroacetyl)indolizine-2,3-dicarboxylates in moderate yields.

Key words: indolizine, acetylenic ester, dichloroacetyl chloride, 1-methylimidazole, N-heterocycle

Bridgehead nitrogen heterocycles are important natural products. Among those, indolizines have received much attention due to their interesting molecular structures featured with ten π-delocalized electrons. Indolizine, being isomeric to indole, constitutes the core structure of many naturally occurring alkaloids.[1,2] Indolizine derivatives are important as potential central nervous system depressants,[3] calcium entry blockers,[4] antimycobacterial agents,[5] and novel dyes.[6] They are also key intermediates for the synthesis of cycloazines.[7] The significance of indolizines in drug discovery and biological science attracts continuous interests to the invention of novel synthesis of indolizines with defined substitution patterns.[8,9]

As part of our current studies on the development of new routes to heterocyclic systems,[10–12] we report a simple synthesis of functionalized indolizine derivatives from one-pot reaction of 1-methylimidazole (**1**), dichloroacetyl chloride (**2**), pyridine derivatives **3** and dialkyl acetylenedicarboxylates **4**.[13]

We carried out the reaction between **2**, pyridine (**3a**), and dimethyl acetylenedicarboxylate (DMAD; **4a**) in the presence of stoichiometric amounts of an organic base under various conditions, and the results are shown in Table 1. Using 1-methylimidazole as the base, indolizine derivative **5a** could be obtained in 12–56% yields in different solvents (entries 1–3). As shown in Table 1, THF was the solvent of choice (entry 3). Using other organic bases such as pyridine, Et_3N, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), or *i*-Pr_2EtN, was unsuccessful (Table 1, entries 4–7). Thus, it appears that the presence of **1** is necessary for the formation of the indolizine derivative **5a**.

Table 1 Formation of Compound **5a** from Dichloroacetyl Chloride (**2**), Pyridine (**3a**), and Dimethyl Acetylenedicarboxylate (**4a**) under Different Conditions[a]

Entry	Base	Solvent	Temp	Time[b]	Yield (%)[c]
1	1-methylimidazole	benzene	–10 °C to r.t.	12 h	12
2	1-methylimidazole	CH_2Cl_2	–10 °C to r.t.	12 h	20
3	1-methylimidazole	THF	–10 °C to r.t.	12 h	56
4	pyridine	THF	–10 °C to r.t.	12 h	–
5	Et_3N	THF	–10 °C to r.t.	12 h	–
6	DBU	THF	–10 °C to r.t.	12 h	–
7	*i*-Pr_2EtN	THF	–10 °C to r.t.	12 h	–

[a] General conditions: **2** (1 mmol), **3a** (1 mmol), **4a** (1 mmol), base (1 mol), and solvent (5 mL).
[b] Reaction time for consuming all of the starting materials.
[c] Yields of isolated products.

The reaction between dichloroacetyl chloride (**2**), pyridines **3**, and acetylenic esters **4** in the presence of 1-methylimidazole, proceeded smoothly in anhydrous THF and furnished indolizine derivatives **5** in 54–65% yields (Scheme 1).[13]

The structures of compounds **5a**–**f**, were deduced from their ^{1}H NMR, ^{13}C NMR, and IR spectral data. For example, the ^{1}H NMR spectrum of **5a**, exhibited three singlets for the methoxy (δ = 3.93 and 4.02 ppm) and methine (δ = 6.73 ppm) protons, along with characteristic multipletes for the pyridine moiety. The ^{1}H-decoupled ^{13}C NMR spectrum of **5a** showed 14 distinct resonances in agreement with the proposed structure.

Unambiguous evidence for the structure and stereochemistry of **5b** was obtained from a single crystal X-ray analysis. An ORTEP[14] diagram of **5b** is shown in Figure 1. There are two molecules of **5b** in the unit cell. The structure deduced from the crystallographic experiment, by analogy can be applied to the other products on account of their NMR-spectroscopic similarities. For details of the structure determination and refinement, see the experimental section.

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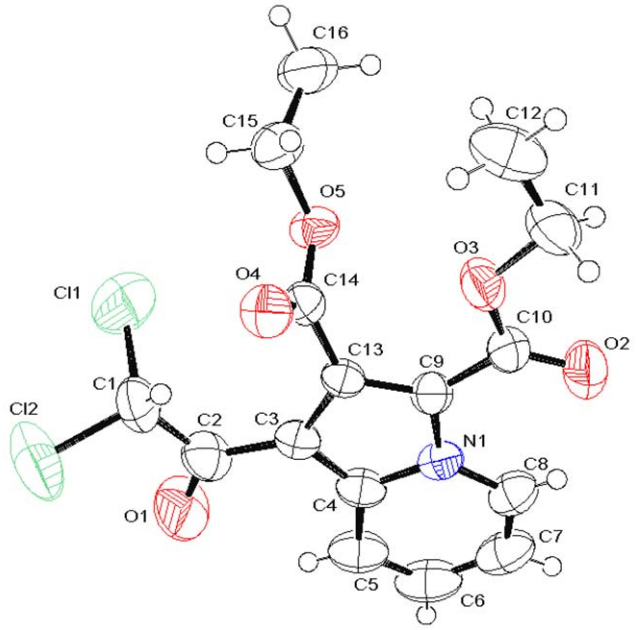


Figure 1 X-Ray crystal structure of **5b**. ORTEP-III plot;[14] arbitrary atom numbering

To extend our knowledge of this transformation, we performed the reaction between isoquinoline and quinoline with **2** and **3a** in the presence of 1-methylimidazole. These reactions led to dimethyl 1-(2,2-dichloroacetyl)pyrrolo[2,1-*a*]isoquinoline-2,3-dicarboxylate (**7**) and dimethyl 3-(2,2-dichloroacetyl)pyrrolo[1,2-*a*]quinoline-1,2-dicarboxylate (**8**) in moderate yields (Figure 2). Compounds **7** and **8** were again fully characterized with their IR, ^{1}H NMR and ^{13}C NMR spectra.[13]

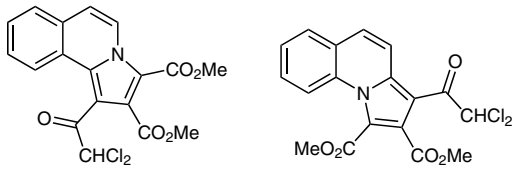
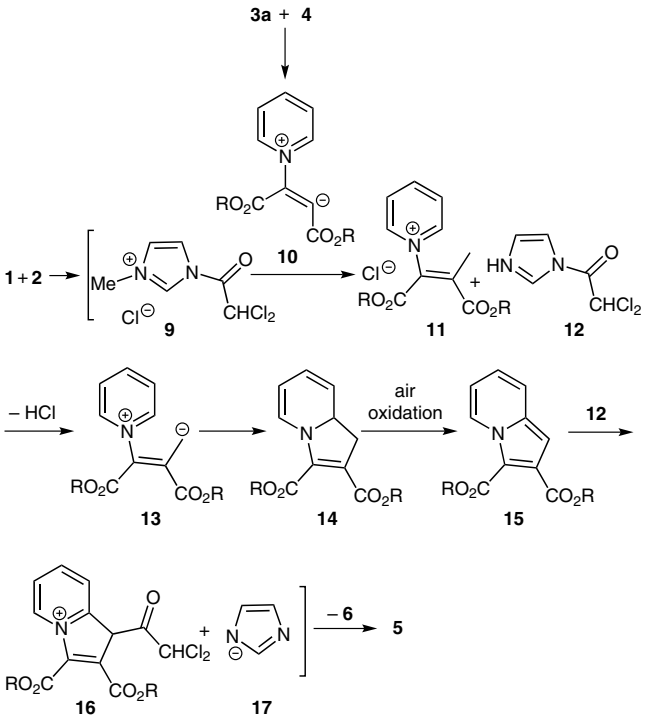


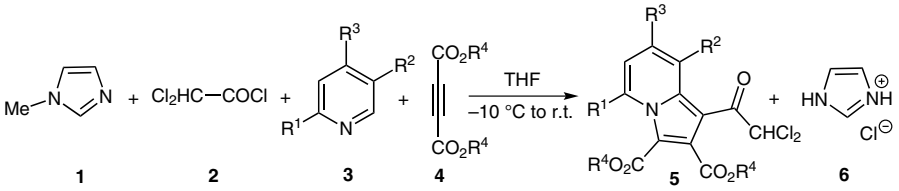
Figure 2

A mechanistic rationalization for the formation of compound **5a**, which may be extended to other indolizine derivatives reported in this work, is given in Scheme 2. Presumably, the initial event is the formation of imidazolium salt **9** in a similar fashion to Batey's 1-methylimidazolium salts,[15] which is attacked by the Huisgen's zwitterionic intermediate **10**, formed from pyridine and DMAD, to afford positively charged ion intermediate **11**. This intermediate undergoes intramolecular cyclization reaction to produce dihydroindolizine derivative **14**, which undergoes aromatization to afford the indolizine **15**. Intermediate **15** is acetylated by **12**, and subsequently is converted into **5** by elimination of **6** (Scheme 2).



Scheme 2

In conclusion, we have described a novel four-component synthesis of functionalized dialkyl 1-(2,2-dichloroace-



3–5	R^1	R^2	R^3	R^4	Yield (%) of 5
a	H	H	H	Me	56
b	H	H	H	Et	62
c	Me	H	H	Me	54
d	H	Me	H	Me	57
e	H	H	Me	Me	65
f	H	H	Et	Me	56

Scheme 1

tyl)indolizine-2,3-dicarboxylates from reaction between the reactive zwitterionic intermediates, generated from addition of pyridine derivatives to dialkyl acetylenedicarboxylates, and 1-methylimidazole/dichloroketene adduct to afford functionalized dialkyl 1-(2,2-dichloroacetyl)indolizine-2,3-dicarboxylates in moderate yields.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(12) Yavari, I.; Seyfi, S.; Nematpour, M.; Hossaini, Z. *Helv. Chim. Acta* **2010**, *93*, 1413.
(13) **General Procedure for Preparation of Compounds 4, 7 and 8**: To a stirred mixture of 1-methylimidazole (0.08 g, 1 mmol) and dichloroacetyl chloride (0.15 g, 1 mmol) in THF (2 mL) was added a solution of the N-heterocycle (1 mmol) in THF (2 mL). Then, a solution of dialkyl acetylenedicarboxylate (1 mmol) in THF (2 mL) was added dropwise. The reaction mixture was stirred for 12 h. The solvent was removed under reduced pressure and the residue was purified by silica gel (Merck 230–240 mesh) column chromatography using a hexane–EtOAc (5:1) mixture as eluent.
Selected Spectroscopic Data
Compound **5a**: pale yellow crystals; yield: 0.36 g (56%); mp 114–116 °C. IR (KBr): 1715, 1700 (C=O), 1493 (C=C), 1254, 1210 (CO), 754 (CCl) cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 3.93 (s, 3 H, MeO), 4.02 (s, 3 H, MeO), 6.73 (s, 1 H, CH), 7.16 (t, ^3J = 6.9 Hz, 1 H, CH), 7.53 (t, ^3J = 8.7 Hz, 1 H, CH), 8.57 (d, ^3J = 9.1 Hz, 1 H, CH), 9.53 (d, ^3J = 7.1 Hz, 1 H, CH). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 52.3 (MeO), 53.3 (MeO), 68.7 (CH), 106.3 (C), 113.9 (C), 116.8 (CH), 120.9 (CH), 128.3 (CH), 129.0 (C), 129.3 (CH), 139.3 (C), 160.2 (C=O), 166.7 (C=O), 180.1 (C=O). EI–MS: *m/z* (%) = 343 (10) [M^+], 312 (5), 280 (10), 260 (100), 230 (14), 202 (7), 172 (5), 143 (20), 130 (7), 115 (14), 89 (8), 78 (9). Anal. Calcd for $C_{14}H_{11}Cl_2NO_5$ (343): C, 48.86; H, 3.22; N, 4.07. Found: C, 48.6; H, 3.3; N, 4.2.
Compound **5b**: pale yellow crystals; yield: 0.44 g (62%); mp 102–104 °C. IR (KBr): 1721, 1700 (C=O), 1495, 1430 (C=C), 1221, 1151 (CO), 756 (CCl) cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 1.40 (t, ^3J = 7.2 Hz, 3 H, Me), 1.44 (t, ^3J = 7.2 Hz, 3 H, Me), 4.42 (q, ^3J = 7.2 Hz, 2 H, CH_2), 4.51 (q, ^3J = 7.2 Hz, 2 H, CH_2), 6.73 (s, 1 H, CH), 7.17 (t, ^3J = 6.0 Hz, 1 H, CH), 7.55 (t, ^3J = 7.9 Hz, 1 H, CH), 8.61 (d, ^3J = 9.1 Hz, 1 H, CH), 9.60 (d, ^3J = 7.1 Hz, 1 H, CH). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 13.9 (Me), 14.2 (Me), 61.4 (CH_2), 62.7 (CH_2), 68.4 (CH), 106.3 (C), 114.0 (C), 116.7 (CH), 120.9 (CH), 128.4 (CH), 128.6 (C), 129.2 (CH), 139.3 (C), 159.9 (C=O), 166.2 (C=O), 180.2 (C=O). EI–MS: *m/z* (%) = 371 (14) [M^+], 326 (10), 288 (24), 271 (30), 225 (15), 214 (18), 170 (12), 143 (9), 91 (100), 78 (10), 55 (27). Anal. Calcd for $C_{16}H_{15}Cl_2NO_5$ (371): C, 51.63; H, 4.06; N, 3.76. Found: C, 51.9; H, 4.2; N, 3.9.
X-ray Crystal Structure Determination of **5b**: Structure determination and refinement data: formula, $C_{16}H_{15}Cl_2NO_5$; M_r 372.19; triclinic, space group P-1, a = 8.778(2), b = 10.099(1), c = 10.193(1) Å, α = 85.86(1)°, β = 72.21(1)°, γ = 82.35(1)°; Z = 2, V = 852.3(2) $Å^3$, D_{calc} = 1.450 Mg/m^3; MoK_α radiation (0.71073 Å); T = 293(2) K. 3586 reflections collected on a Bruker P4 diffractometer, 2964 unique (R_{int} = 0.0229). All heavy atoms have been located by difference Fourier maps and refined anisotropically. All hydrogen atoms except those of the methylene groups and the aromatic ring, have been placed on calculated positions and refined by using the riding model. The remaining hydrogens have been located by difference Fourier maps. Final indices for 1692 reflections with $I > 2\sigma(I)$: R_1 = 0.0615, wR_2 = 0.1561, GOF = 1.054. The crystallographic data of **5b** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 874939. Copies of the data can be obtained, free of charge, via the internet (http://www.ccdc.cam.ac.uk/data_request/cif), e-mail (data_request@ccdc.cam.ac.uk), or fax: [+44(1223)336033].
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