Mendeleev Communications

Mendeleev Commun., 2025, **35**, 99–101

One-pot synthesis of functionalized dihydroindolizinones from pyrrolylpropynoates and diethyl aminomalonate

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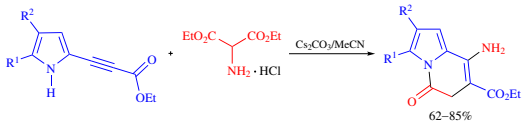
DOI: 10.71267/mencom.7547

3-(Pyrrol-2-yl)propynoates react with diethyl aminomalonate hydrochloride (excess Cs_2CO_3, reflux in MeCN, 6 h) to chemoselectively afford 8-amino-4-oxo-5,6-dihydroindolizine-7-carboxylates in good yields (62–85%).



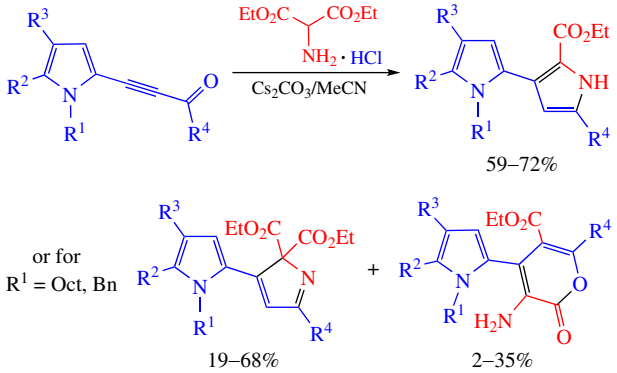
Keywords: pyrrolylpropynoates, diethyl aminomalonate, dihydroindolizinones, nucleophilic addition, base, tetrahydroindolecarboxylate.

Conjugated acetylenic esters and ketones are known to be important highly reactive building blocks in organic chemistry.[1,2] In the last decades, much attention was drawn to pyrrolylacetylenic ketones and esters,[3,4] which became available *via* the room temperature cross-coupling between pyrroles and the corresponding bromoacetylenic derivatives in the solid Al_2O_3 or K_2CO_3 medium.[5,6] This integration of pyrrole ring with acetylene carbonyl system opened simple short approaches to design novel pyrrole-tailored heterocyclic systems.[3–7]

Recently, when studying the reaction of pyrrolylacetylenic ketones with diethyl aminomalonate (popular versatile reagents[8–14]) we showed that depending on the substituents in the pyrrole ring, either 1*H*,1*H*′-2,3′-bipyrroles or 1*H*,2*H*′-2,3′-bipyrroles or pyrrolyl-containing aminopyrones can be synthesized (Scheme 1).[15]

Being amused by this synthetic divergence, we have continued the research in this line and observed herein that NH-unsubstituted 3-(pyrrol-2-yl)propynoates **1a–c**, when reacted with diethyl aminomalonate hydrochloride **2**, gave dihydroindolizinones **3a–c** (Scheme 2).

It is known that indolizines, due to their diverse pharmacological activity, are among the most significant and preferred heterocyclic compounds. They exhibit anticancer,[16–18] antidiabetic,[19] antiinflammatory,[20] antimicrobial,[19] anti-HIV,[19] antitubercular,[19] antiproliferative,[21] antiviral,[22] antioxidant,[23] antihypertensive,[24] antischizophrenia,[25] antiacetylcholine, antihistamine and central nervous system (CNS) depressant[26,27] activities. Among indolizines are inhibitors of monoamine oxidase,[28] aromatase,[29–31] phosphodiesterase,[32] phosphatase,[33] and ACE.[34]

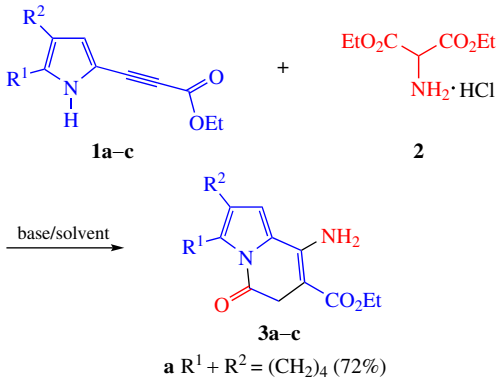


R^1 = H, Me, $CH{=}CH_2$, Oct, Bn; R^2 = H, Ph;
R^3 = H; $R^2 + R^3 = (CH_2)_4$; R^4 = Ph, furyl, thienyl

Scheme 1

We commenced our study with the reaction between ethyl 3-(4,5,6,7-tetrahydro-1*H*-indol-2-yl)propynoate **1a** and diethyl aminomalonate hydrochloride **2** under variable conditions (see Scheme 2). The experiments have shown that in the presence of strong organic bases such as DBU (Table 1, entry 1) or DABCO (entry 2) in MeCN (reflux, 24 h) the conversion of the reactants was close to zero. Also, K_2CO_3 was ineffective in MeCN (reflux, 24 h, entry 3), THF (65 °C, 24 h, entry 4) and DMSO (100 °C, 24 h, entry 5): only the starting reagents were detected (^{1}H NMR) in the reaction mixture. In the presence of KOH in THF (65 °C, 24 h, molar ratio of reagents and base, 1 : 1 : 1, entry 6) and DMSO (100 °C, 6 h, equimolar ratio of reagents and base, entry 8), the starting reagents were also completely recovered from reaction mixtures.

However, with a two-fold molar excess KOH (DMSO, 100 °C, 6 h, see Table 1, entry 7), the reaction proceeded with



a $R^1 + R^2 = (CH_2)_4$ (72%)
b $R^1 = Pr^n$, R^2 = Et (78%)
c $R^1 = Bu^n$, $R^2 = Pr^n$ (85%)

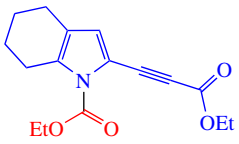
Scheme 2 *Reagents and optimized conditions*: i, Cs_2CO_3, MeCN, 80 °C, 6 h. For optimization with **1a**, see Table 1. Yields given stand for the optimized conditions.

Table 1 Influence of the reaction conditions on the yield of indolizinone **3a**.[a]

Entry	Base	Solvent	Ratio **1a**:**2**:Base	*T*/°C	*t*/h	Yield of **3a** (%)[b]
1	DBU	MeCN	1:1:2	80	24	0[c]
2	DABCO	MeCN	1:1:2	80	24	0[c]
3	K_2CO_3	MeCN	1:1:2	80	24	0[c]
4	K_2CO_3	THF	1:1:2	65	24	0[c]
5	K_2CO_3	DMSO	1:1:2	100	24	0[c]
6	KOH	DMSO	1:1:1	100	6	0[c]
7	KOH	DMSO	1:1:2	100	6	18[d]
8	KOH	DMSO	1:2:2	100	6	traces
9	KOH	THF	1:1:2	65	24	0[c]
10	KOH	MeCN	1:1:1	80	24	traces
11	KOH	MeCN	1:1:2	80	24	40[e]
12	KOH	MeCN	1:2:2	80	24	26[e]
13	Cs_2CO_3	DMSO	1:1:1	100	24	16[e]
14	Cs_2CO_3	DMSO	1:1:2	100	24	34[e]
15	Cs_2CO_3	DMSO	1:2:2	100	24	12[e]
16	Cs_2CO_3	MeCN	1:1:1	80	6	traces
17	**Cs_2CO_3**	**MeCN**	**1:1:2**	**80**	**6**	**72**[e]
18	Cs_2CO_3	MeCN	1:2:2	80	6	37[e]

[a] Reactions were carried out with 1 mmol of acylethynylpyrrole in 50 ml of solvent. [b] The reaction completion time was determined by the disappearance of the signals of the starting reagents in the ^{1}H NMR spectra of the reaction mixtures. [c] Only a mixture of starting reagents was found in the reaction medium. [d] Product **4** was also isolated in 12% yield. [e] The conversion of **1a** is 100%.

complete conversion of the reactants to give two products: indolizinone **3a** and *N*-ethoxycarbonyl derivative of the starting pyrrolylpropynoate **1a**, ethyl 2-(3-ethoxy-3-oxoprop-1-yn-1-yl)-4,5,6,7-tetrahydro-1*H*-indole-1-carboxylate **4** in 18 and 12% yields, respectively. The reaction was accompanied by a strong tarring. The formation of only indolizine **3a** (26% yield) took place, when the reaction was carried out in the system KOH/MeCN at 65 °C for 24 h (entry 12). The system Cs_2CO_3/MeCN turned out to be the best providing the selective formation of indolizinone **3a** in 72% yield (entry 17). This yield was achieved, when the reaction was performed by boiling the reagents (molar ratio **1a/2**/base = 1:1:2) for 6 h. Under these conditions, from pyrrolylpropynoates **1b**,**c** indolizines **3b** and **3c** were also obtained in high yield (see Scheme 2).† With methyl pyrrolylpropynoate **1′a**, the same indolizine **3a** bearing ethoxycarbonyl group was formed in 62% yield implying MeO/EtO exchange in this case.



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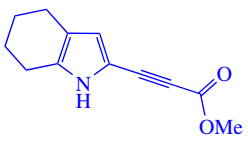
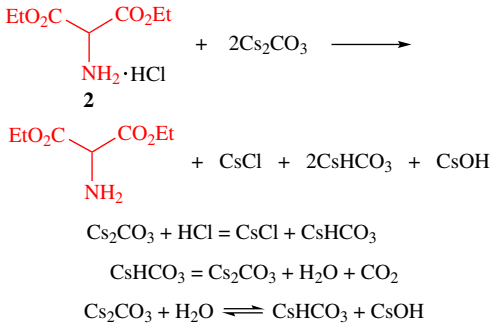


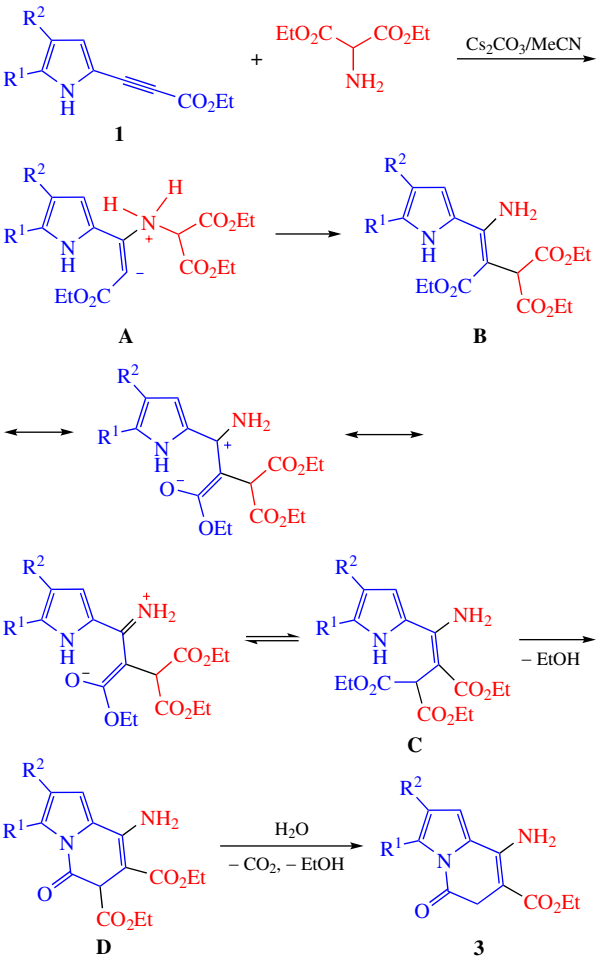
1′a

Considering the mechanistic aspects of the reaction in question, we should take into account the preceding dehydrochlorination of aminomalonate hydrochloride **2** with Cs_2CO_3 to form, apart from aminomalonate, CsCl, $CsHCO_3$, CsOH, H_2O and CO_2 (Scheme 3).



Scheme 3

Eventually, the reaction mixture consists of two liquid (concentrated brine and organic) and several solid (unconsumed Cs_2CO_3, CsCl, $CsHCO_3$, and CsOH) phases and, therefore, here we deal with a kind of phase transfer catalytic process, which should impart essential patterns to this peculiar substituent-governed divergent synthesis that considerably complicates understanding the detailed reaction mechanism (Scheme 4). The assembly of dihydroindolizinone **3** assumingly starts with the nucleophilic addition of the amino group across to the triple bond of compound **1** to give the dipolar intermediate **A**, wherein



Scheme 4

† *Synthesis of indolizinones* **3a**–**c** *(typical procedure)*. A suspension of diethyl aminomalonate hydrochloride **2** (211 mg, 1 mmol) and Cs_2CO_3 (650 mg, 2 mmol) in acetonitrile (50 ml) was stirred at 20–25 °C for 30 min. Then a solution of pyrrolylpropynoate **1a**–**c** (1 mmol) in acetonitrile (50 ml) was added dropwise to the reaction mixture within 10 min. The mixture was stirred at 80 °C for 6 h (^{1}H NMR monitoring until the signals of the starting propynoate **1a**–**c** completely disappeared). After the reaction completion, the mixture was diluted with water (150 ml) and extracted with diethyl ether (4 × 30 ml), the extracts were washed with water (3 × 20 ml) and dried over $CaCl_2$. The residue, after removing the solvent, was fractionated by column chromatography (SiO_2, *n*-hexane/diethyl ether, 1:1) to afford indolizinones **3a**–**c**.

the 1,3-transfer of the malonate moiety to the carbanionic centers occurs affording intermediate **B**. The *trans*-(*E*)-configuration of the next intermediate **C** can be reached *via* the rotation around the $C^{\alpha}=C^{\beta}$ bond which is distributed over the carbonyl group to accept a partially single bond character in the corresponding resonance structures. Then intermediate **C** undergoes the ring closure with the participation of the pyrrole NH-group. One of the ester groups of the latter interacts with N-centered anion in a nucleophilic substitution manner (to release ethoxy anion) thereby closing six-membered pyridinone ring to form intermediate **D**. After decarboxylation of the ester group neighboring to C=O-bond in the intermediate **D**, the final product, indolizinone **3**, is formed (see Scheme 4).

In summary, the reaction providing earlier inaccessible partially hydrated derivatives of amino- and ester-functionalized indolizinones from pyrrolylpropynoate and aminomalonate hydrochloride has been found. Apart from the obvious practical value of this reaction leading to a novel family of pharmaceutically prospective molecules, the results obtained unveil theoretically intriguing issues dealing with the reactivity of both pyrrolylpropynoate and aminomalonate.

This work was supported within the state assignment of IrICh SB RAS (theme no. 122041100031-5). The spectral data were obtained with the equipment of the Baikal Analytical Center for collective use SB RAS.

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.71267/mencom.7547.

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Received: 21st June 2024; Com. 24/7547