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Controlling chemoselectivity—application of DMF di-*t*-butyl acetal in the regioselective synthesis of 3-monosubstituted indolizines

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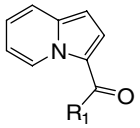
Abstract—Among a number of DMF dialkyl acetals investigated for the regioselective synthesis of 3-acylindolizines, the di-*t*-butyl acetal, via its iminium intermediate readily formed in situ, provides the highest chemoselectivity for the intermolecular cyclization of picolinium salts. DMF di-*t*-butyl acetal was applied to the syntheses of a variety of 3-acylated indolizines including alkyl, aryl, and heteroaryl substituents.

1. Introduction

Synthetic indolizine derivatives have been reported, among many others, as calcium channel blockers,[1] PLA_2 inhibitors,[2] histamine H_3 receptor antagonists,[3] and 5-HT_3 receptor antagonists.[4] Indolizines was also applied as fluorescent molecular probes in the studies of cell functions.[5] 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.[6–10] However, the regioselective syntheses of 3-monosubstituted indolizines, for instance, 3-acylindolizine (**1**), remain a challenging task.[11,12]

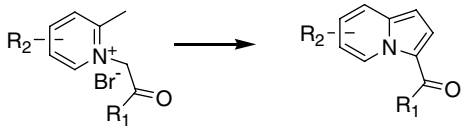


(**1**)

Friedel–Crafts acylation of indolizine was reported to favor the electron rich 3-position but often complicated with low selectivities and low yields.[13,14] Meanwhile, the preparation of indolizine substrates used in the Friedel–Crafts reactions often required lengthy steps and suffered from low yields. Gevorgyan's group recently reported the synthesis of 3-alkylindolizines via copper promoted cyclization of alkynyl pyridines.[15] A recent report from the same research group described the synthesis of 3-arylindolizine via palladium catalyzed regioselective arylation of indolizine.[16] Kaloko and Hayford described the formation of 3-alkoxylmethylindolizines when (*Z*)-2-pyridine silylated vinylacetylenes was treated with alcohols in the presence of CsF.[17] Herein we report the discovery of DMF di-*t*-butyl acetal as a useful reagent for the highly regioselective formation of 3-acylated indolizines via an intermolecular cyclization of picolinium salt (Scheme 1).

2. Results and discussions

The base-promoted intramolecular condensation of picoline quaternary salts (**2**) is a well-established method



Scheme 1. Reagents and conditions: $Me_2NCH(OBu^t)_2$ (10 equiv), DMF, 130–135 °C, 10 min.

Keywords: Indolizine; Regioselective synthesis; DMF di-*t*-butyl acetal; Picolinium salt.
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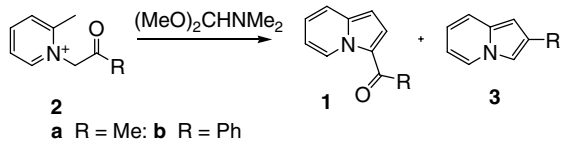
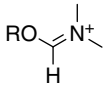


Scheme 2.

for the synthesis of 2-substituted indolizine derivatives (the Chichibabin cyclocondensation).[18] It was described as well that **2a** reacted with DMF dimethyl acetal to afford 3-acetylindolizine (**1a**) as a minor product in a 17% yield, together with the Chichibabin product **3a** in 23% (Scheme 2).[19] Under the same reaction conditions, however, cyclocondensation reaction occurred predominately for picolinium **2b**, and 2-phenylindolizine (**3b**) was reported as the only product in a 97% yield.

We found that when DMF dimethyl acetal was used in large excess (10 equiv) and when the reaction temperature was controlled at about 130–135 °C, the formation of the intermolecular cyclization product **1a** was favored over the 2-methylindolizine (**3a**) in a 3 to 2 ratio and in an isolated yield of 48% after silica gel flash column separation. More interestingly, although the originally described method failed to promote the formation of 3-aroylindolizine (**1**, R = Ar), we found that under our improved reaction conditions (10 equiv DMF dimethyl acetal, 130–135 °C), 3-(4-cyanobenzoyl)indolizine (**1**, R = 4-CNC_6H_4–)[20] was obtained in a 54% yield and was favored over the 2-(4-cyanophenyl)indolizine in about 3 to 2 ratio by ^{1}H NMR analysis.

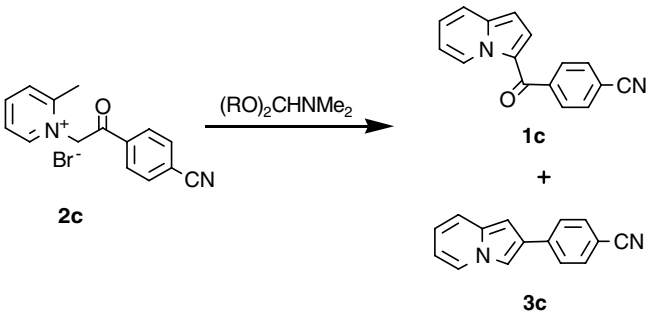
The formation of 3-acylindolizines proceeds presumably via intermolecular cyclization involving methoxy-methylene-dimethyl-ammonium (**I**, R = CH_3) as the active species formed from DMF dimethyl acetal. In the absence of DMF dimethyl acetal, picolinium salts **2** undergo intramolecular condensation to form exclusively product **3**. When large excess of DMF dimethyl acetal is applied, the presence of abundant methoxymethylene-dimethyl-ammonium (**I**) kinetically favors the competing inter-molecular cyclization reaction, leading to the formation of the desired product **1**.



(**I**)

Encouraged by the promising results and in order to improve the chemoselectivity, we investigated other DMF acetals, $(RO)_2CHNMe_2$, to explore their usefulness and advantages. As seen in Table 1, DMF di-*t*-butyl acetal was found to be the superior reagent in the selective formation of 3-aroylindolizine (**2**, R = 4-CNC_6H_4–). When it was used in excess (10–15 equiv), the desired product was formed in a 92:8 ratio and isolated in an 80% yield (entry 8). The reaction proceeded quickly and was usually completed within 10 min of heating at 130–135 °C in DMF. The selectivity decreased when lesser amount of DMF di-*t*-butyl acetal

Table 1. Inter- versus intra-molecular cyclization: the effect of DMF—dialkyl acetals



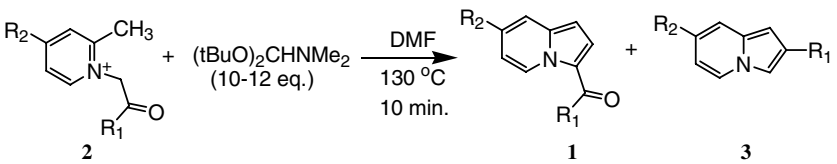
R	**1c**:**3c** ratio (^{1}H NMR)	**1c**% (isolated)
Methyl	60/40	54
Ethyl	50/50	40
Benzyl	40/60	32
n-Propyl	50/50	47
neo-Pentyl	60/40	51
c-Hexyl	50/50	40
i-Propyl	80/20	71
t-Butyl	92/8	80

(i.e., 5 equiv) was applied. The use of sterically less hindered di-*i*-propyl acetal (10–15 equiv) resulted in a reduced selectivity (entry 7). All other acetals studied, including methyl, ethyl, *n*-propyl, cyclohexyl, neopentyl, and benzyl, gave diminished selectivity toward the formation of the desired 3-aroylindolizine, ranging from 40 to 60%. Clearly, the bulky *t*-butyl groups favored the formation of its corresponding iminium (**I**, R = *t*-Bu) intermediate and therefore facilitated the intermolecular cyclization.

With the discovery of DMF di-*t*-butyl acetal as a useful reagent, we studied its application to the synthesis of a variety of 3-acylated indolizines. The results are summarized in Table 2. With 10–12 equiv of DMF di-*t*-butyl acetal, all reactions proceed quickly and completed within 10 min of heating in DMF at 130–135 °C. After an aqueous work-up and removal of organic solvents, the resulting crude reaction mixture was analyzed by ^{1}H NMR to determine the product selectivity. The isolation of the desired 3-acylindolizines was easily achieved by silica gel column purification.

As shown in Table 2, the highest selectivity (95:5) toward 3-acylated indolizines was achieved with picolinium salts (2) where the benzoyl group is substituted with electron withdrawing groups (i.e., 4-nitrophenyl in entry 7). In contrast, electron-rich aromatic systems such as furanyl (entry 13) and methoxyphenyl (entries 4 and 5) resulted in only moderate selectivity (about 4 to 1), which is similar to the unsubstituted phenyl moiety (entry 3). Comparing the results from entries 7 and 11, the dichloro-phenyl group rendered a superior selectivity to monochloro-phenyl substrate. Interestingly, aryls substituted with a cyano group in general afforded an excellent selectivity ($\geqslant$90:10), regardless the substitution nature of the picolinium moiety. A direct comparison of cyano and chloro substitutions (entries 9 and 12 vs entries 6 and 11, respectively) indicated that cyano group

Table 2. Synthesis of 3-acylindolizines from DMF di-*t*-butyl acetal



2 **1** **3**

Entry	R_2	R_1	**1** (%) (isolated yield)	**1**:**3** ratio (^{1}H NMR)
1	H	Methyl	62	65/35
2	H	Ethyl	83	90/10
3	H	Phenyl	58	75/25
4	H	4-Methoxyphenyl	68	80/20
5	H	3-Methoxyphenyl	55	75/25
6	H	4-Chlorophenyl	64	80/20
7	H	4-Nitrophenyl	75	95/5
8	H	3-Cyanophenyl	67	95/5
9	H	4-Cyanophenyl	80	92/8
10	H	3,4-Dichlorophenyl	65	95/5
11	H	5-Chlorothien-2-yl	54	85/15
12	H	5-Cyanothien-2-yl	80	95/5
13	H	2-Furanyl	36	60/40
14	Cl	4-Cyanophenyl	65	90/10
15	Et	4-Cyanophenyl	73	90/10
16	OH	4-Cyanophenyl	30	95/5
17	$MeOCH_2O$	4-Cyanophenyl	75	90/10

gave a better selectivity. In most cases, the reaction proceeded cleanly and the desired product **1** was obtained in a good to excellent yield after flash column (silica gel) separation. One exception was observed with *para*-hydroxy-picolinium salt (entry 16). Although ^{1}H NMR analysis of crude reaction mixture indicated an excellent selectivity (95/5), the desired product was isolated in only a 30% yield due to decomposition during the reaction. When the OH was protected with methoxymethyl group (entry 17), much higher yield (75%) of the desired 3-substituted indolizine was obtained.

In summary, DMF di-*t*-butyl acetal is found to be a highly useful reagent for the synthesis of a variety of 3-acylated indolizines, which in other ways are not readily accessible. The short reaction time and easiness of handling should render this new method applicable to the synthesis of 3-substituted indolizines, which could be further functionalized regioseletively at other positions. In our laboratory, we have successfully applied this method for the synthesis of a variety of indolizine derivatives that ultimately led to the discovery STA-5312, a novel microtubule inhibitor selected for development.[20]

General procedure: A mixture of 1-[2-(4-cyanophenyl)-2-oxo-ethyl]-2-methyl-pyridinium bromide[21] (1 mmol) and DMF di-*t*-butyl acetal (10 mmol) in DMF (7 ml) was heated at 130 °C for 10 min. The reaction was quenched with ice water (20 ml) and extracted with ethyl acetate (15 ml × 3). The extracts were dried (Na_2SO_4) and the solvent was evaporated. Proton NMR measurement of the crude product mixture indicated a ratio of 92:8 of the major and the minor products. The residue was subjected to silica gel column chromatography (30–50% ethyl acetate in hexanes) to give 197 mg (80%) 3-(4-cyanobenzoyl) indolizine as a white crystalline. Mp 156–157 °C (recrystallized from ethyl acetate); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm), 9.98 (d, $J = 6.6$ Hz, 1H), 7.89–7.77 (m, 4H), 7.60 (d, $J = 11$ Hz, 1H), 7.30–7.22 (m, 2H), 7.01 (m, 1H), 6.57 (d, $J = 6.1$ Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm), 181.75, 144.91, 140.17, 132.12, 129.41, 129.23, 126.92, 125.43, 122.09, 118.88, 118.42, 114.60, 114.12, 103.61; ESMS calcd for $C_{16}H_{10}N_2O$: 246.1. Found: 247.1 $(M+H)^+$. Anal. Calcd for $C_{16}H_{10}N_2O$: C, 78.03; H, 4.09; N, 11.38. Found: C, 77.82; H, 3.92; N, 11.11.

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