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Application of DMF–methyl sulfate adduct in the regioselective synthesis of 3-acylated indolizines

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Abstract—A number of 3-acylated indolizines were synthesized in good to excellent yields by a newly established reaction between picolinium salts and the methylsulfate salt of **A** (R = Me), the adduct formed from DMF–Me_2SO_4 as the key reagent. The low cost, short reaction time, mild reaction condition, and easy purification of the products make this an attractive new method for the synthesis of indolizine compounds. A variety of functional groups (nitro, cyano, ester, methoxy, and halogens) were well tolerated under the reaction conditions.
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1. Introduction

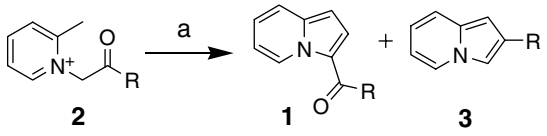
As a well-recognized bioisostere of indole—a fundamentally important molecular template for novel therapeutics, indolizine continues to attract interests from both the pharmaceutical and academic communities. Examples of reported synthetic indolizine derivatives, among many others, are their use as anti-tuberculosis agents,[1] PLA_2 inhibitors,[2] histamine H_3 receptor antagonists,[3] 5-HT_3 receptor antagonists,[4] MPtpA/MPtpB phosphatases inhibitors, which are involved in infectious diseases,[5] and as 15-lipoxygenase inhibitors.[6]

The significance of indolizines in drug discovery, natural products, and biological science has generated increased interests in the invention of novel synthesis of indolizines with well-defined substitution patterns.[7–14] Particularly interesting to us is the regioselective synthesis of 3-mono substituted indolizines as they served as key intermediates to a novel class of indolizine type microtubule inhibitors demonstrating strong in vitro and in vivo antitumor activities, and more significantly, overcoming multiple-drug resistance (MDR) in a number of cancer types.[15,16]

Yet, only a limited number of methods were available in the literature for the syntheses of 3-monosubstituted indolizines. Recently, the synthesis of 3-alkylindolizines via copper-promoted cyclization of alkynyl pyridines was reported by the Gevorgyan's group[17] The same research group described the syntheses of 3-arylindolizines via a palladium-catalyzed regioselective arylation of indolizine[18] Kaloko and Hayford described the formation of 3-alkoxylmethylindolizines when (*Z*)-2-pyridinesilylated vinylacetylenes was treated with alcohols in the presence of CsF.[19]

We recently reported the regioselective syntheses of 3-mono-acylindolizine (**1**), via an intermolecular cyclization of DMF di-*t*-butyl acetal and picolinium salts (Scheme 1).[20]

In general, this reaction provides selectively the desired compound **1** over the Chichibabin cyclocondensation[21] **3** at ratios ranging from 65/35 to 95/5. Chromatographic purification results in isolation of **1** in moderate



Scheme 1. Reagents and conditions: (a) $Me_2NCH(t\text{-}BuO)_2$ (10 equiv), DMF, 130–135 °C, 10 min.

Keywords: Indolizine; Regioselective synthesis; Methyl sulfate; DMF; Picolinium salt.
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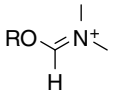
to excellent yields. Although it is applicable to a variety of picolinium substrates, the requirement of large excess (10 mol equiv) of this relatively expensive reagent encouraged us to search for a more affordable alternative reagent that promotes the intermolecular reaction. Herein we report the application of DMF–Me_2SO_4 adduct as a useful reagent for the synthesis of 3-monoacyl indolizines **1** with even higher chemo-selectivity toward the intermolecular condensation.

2. Results and discussions

As suggested previously,[20] the formation of 3-acylindolizines proceeds via intermolecular cyclization involving *t*-butoxy-methylene-dimethyl-ammonium (**A**, R = *t*-Bu) as the active species formed from DMF di-*t*-butyl acetal. We reasoned that the reactivity of an iminium **A** and the easiness of its formation would have profound effect on the fate of the picolinium salts. The bulky *t*-butyl groups favored the formation of its corresponding iminium **A** (R = *t*-Bu), hence facilitated the intermolecular cyclization. When large excess of DMF di-*t*-butyl acetal is applied, the presence of abundant the iminium species (**A**, R = *t*-Bu) kinetically drives the intermolecular cyclization reaction over the competing intramolecular condensation reaction, leading to the selective formation of the desired products **1**.

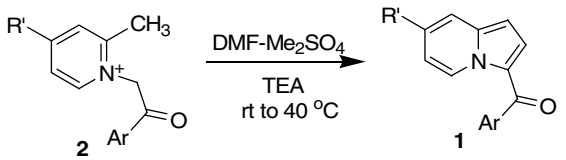


(**A**)

It was reported that when DMF was treated with Me_2SO_4 an adduct was readily formed as the methylsulfate salt of **A** (R = Me), which was applied to the syntheses of enaminones,[22] dioxolanes and dioxanes[23] and in the Beckmann rearrangement of cyclohexanone oxime to its corresponding ε-caprolactam.[24]

We found that the desired indolizine products **1** were formed as the major products when the picolinium salts **2** were treated with the DMF–Me_2SO_4 adduct, the methylsulfate salt of **A** (R = Me), in the presence of Et_3N as a base (Table 1). In all cases, the selectivity ratio between the intermolecular condensation products **1** and the intramolecular condensation products **2** ranges from 95% to >99%, as measured by HPLC analysis. Although chromatographic purification was often used to isolate the purified products **1**, they could be easily obtained by recrystallization of the crude when the reactions were performed at gram scale or higher (based on the picolinim salt). The isolated yield of the desired products **1** ranges from 58% to 91%. The reaction proceeded quickly under mild conditions. Hence, a variety of functional groups (nitro, cyano, ester, methoxy, and halogens) were well tolerated under the reaction conditions. Those functional groups, either on the pyridine moiety (R′) or on the other aryl group, do not have significant impact on both the selectivity and the isolated yield of **1**, further demonstrating the broad scope of the reaction. The method was also applicable to hetero aryl group such as thiophene leading to the formation of the corresponding product in 91% yield (entry 14).

Table 1. Synthesis of 3-acylindolizines

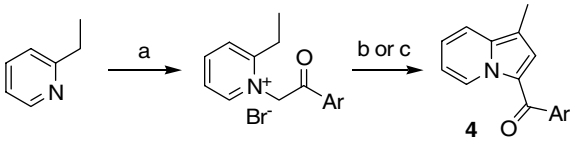


Entry	R′	Ar	Yield[a] (1%)
1	H	Phenyl	63
2	H	3-Cyanophenyl	91
3	H	4-Cyanophenyl	85
4	H	4-Methoxyphenyl	58
5	H	3-Methoxyphenyl	75
6	H	4-Chlorophenyl	73
7	H	4-Nitrophenyl	68
8	H	4-Flourophenyl	67
9	H	4-Methylphenyl	90
10	H	3,4-Dichlorophenyl	75
11	H	4-(2-Propyl)phenyl	83
12	H	4-Methoxycarbonylphenyl	88
13	H	4-Trifluorophenyl	70
14	H	5-Chlorothien-2-yl	91
15	NO_2	4-Cyanophenyl	75
16	Et	4-Cyanophenyl	87
17	MeO	4-Chlorophenyl	73
18	CO_2Me	4-Cyanophenyl	77
19	$MeOCH_2O$	4-Cyanophenyl	70

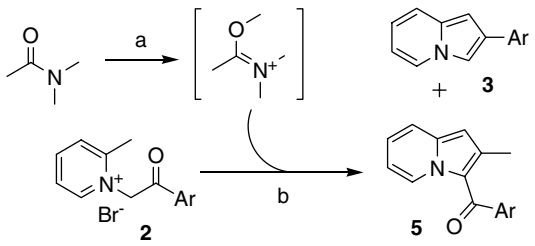
[a] Isolated yield.

Disappointing result was observed when the reaction was applied to the 2-ethylpyridinium salt, which was prepared by the N-alkylation of 2-ethylpyridine with 2-bromo-4′-cyano-acetophenone (Scheme 2, Ar: 4-cyanophenyl). When the pyridinium salt was reacted with DMF-Me_2SO_4 adduct with TEA as a base, the desired product **4** was isolated in only 6% yield. Interestingly, when the previously described DMF di-*t*-butyl acetal was used in large access (12 equiv),[20] a much cleaner reaction was achieved. And the product **4** was obtained in 75% yield after chromatographic purification. This represents a new method for the regioselective synthesis of 1,3-disubstitued indolizine derivative.

We also attempted to further extend the reaction to acetamide leading to the regioselective synthesis of 2,3-disubstitued indolizines (Scheme 3). Thus, *N*,*N*-dimethylacetamide (DMA) was treated with Me_2SO_4 and then reacted with picolinium salt **2** (Ar: 5-chlorothien-2-yl)



Scheme 2. Reagents and conditions: (a) 2-bromo-4′-cyano-acetophenone, MeCN, 60 °C; (b) DMF–Me_2SO_4, TEA; (c) $DMF(OBu^t)_2$ (12 equiv), 130 °C, 10 min.



Scheme 3. Reagents and conditions: (a) Me_2SO_4, 130 °C, 2 h; (b) **2**, TEA, rt, overnight.

under similar conditions. In this case, the ratio between the desired product **5** and the intramolecular condensation 2-arylindolizene (**3**) is about 1:1, likely due to the increased steric hindrance caused by the methyl group in the DMA–Me_2SO_4 iminium adduct. After chromatographic purifications, the isolated yield of **5** is low yield (16%), indicating the reaction conditions need further optimization in order to achieve optimal results.

In summary, a variety of 3-acylated indolizines were synthesized in good to excellent yields using the methylsulfate salt of **A** (R = Me), the adduct formed from DMF and Me_2SO_4 as the key reagent. The low cost of DMF/Me_2SO_4, the short reaction time, the mild reaction conditions, and the easy purification of the products make this an attractive new method for the synthesis of indolizine compounds. The methodology is amendable to large scale synthesis and was successfully applied to the kilogram manufacturing of STA-5312, a novel microtubule inhibitor selected for development.[26]

3. General procedure

3-(5-Chlorothiophenecarbonyl)-indolizine (Table 1, entry 11): A mixture of equal mole equivalent of DMF and Me_2SO_4 (2 mL) was stirred at 60–80 °C for 3 h. After cooled to room temperature, the DMF–Me_2SO_4 adduct was added to a solution of 1-[2-(5-chlorothiophen)-2-oxo-ethyl]-2-methyl-pyridinium bromide[25] (0.168 g, 0.5 mmol) in DMF (1 mL) at room temperature. After the reaction mixture was stirred for 15 min, Et_3N (3.5 mL) was then added. The reaction mixture was stirred for 1 h while keeping the temperature at ~40 °C. The reaction was quenched with ice water (20 mL) and extracted with ethyl acetate (10 mL × 3). The extracts were dried (Na_2SO_4) and condensed (HPLC/ LC–MS analysis of the crude product indicated >99% selectivity of the desired product over the side reaction product). Further purified by column chromatography (silica gel and 20% ethyl acetate in hexanes) gave 120 mg (91%) of 3-(5-chlorothiophene-2-carbonyl)-indolizine as a crystalline solid. Mp: 71.5–72 °C; ^{1}H NMR ($CDCl_3$) δ (ppm), 9.79 (d, $J = 7.2$ Hz, 1H), 7.61 (d, $J = 4.5$ Hz, 1H), 7.55–7.50 (m, 2H), 7.15(t, $J = 7.5$ Hz, 1H), 6.95 (d, $J = 3.9$ Hz, 1H), 6.88 (t, $J = 7.2$ Hz, 1H), 6.53 (d, $J = 4.8$ Hz, 1H); ^{13}C NMR ($CDCl_3$) δ (ppm), 174.9, 144.0, 140.0, 136.2, 130.5, 128.7, 127.0, 124.8, 124.6, 121.8, 118.8, 114.0, 103.2; ESMS Calcd for $C_{13}H_8ClNOS$: 261.00. Found: 262.0 $(M+H)^+$ Anal. Calcd for $C_{13}H_8ClNOS$: C, 59.66; H, 3.08; N, 5.35. Found: C, 59.47; H, 2.90; N, 5.16.

3-(4-Cyanobenzoyl)-indolizine (Table 1, entry 3): To a stirred suspension of 1-[2-(4-cyanophenyl)-2-oxo-ethyl]-2-methyl-pyridinium bromide (5 g, 12 mmol) in DMF (50 mL) was added 40 mL DMF–Me_2SO_4 After the addition, the reaction mixture was stirred at rt for 15 min. To it was then added Et_3N (50 mL) while the inner temperature was kept between 25 and 40 °C. After stirring at room temperature for 2 h, the reaction mixture was added to ice water (200 mL) with stirring, which led to the formation of slurry. The precipitates were collected, washed with water, dried under vacuum, and recrystallized from EtOAc to give 3.3 g (85%) of 3-(4-cyanobenzoyl)-indolizine as a white solid. Analytical data are identical to previously reported.[20]

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