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SYNTHESIS OF BENZO[G]INDOLIZINES. REACTION OF ACID ANHYDRIDES WITH ISOQUINOLINIUM METHYLIDES

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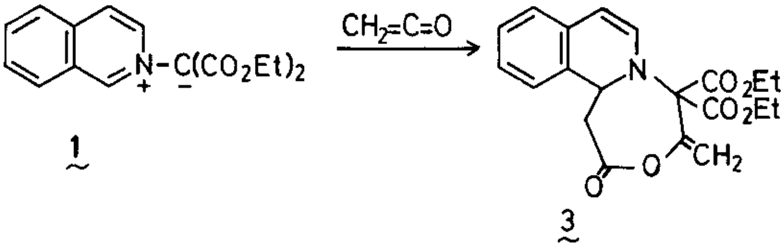
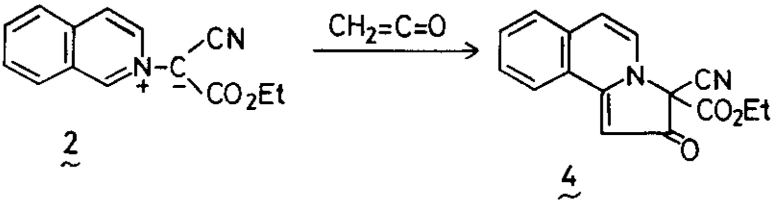
Abstract —— Reaction of isoquinolinium bis(ethoxycarbonyl)-methylide (1) with acid anhydrides, such as acetic anhydride, propionic anhydride, n-butyric anhydride, and phenylacetic anhydride, gives rise to the benzo[g]indolizines, ethyl 2-acyloxy-pyrrolo[2,1-a]isoquinoline-3-carboxylate (where acyl is acetyl (5), propionyl (6), n-butyryl (7), and phenylacetyl (8), respectively). Similar reaction of isoquinolinium cyano(ethoxycarbonyl)methylide (2) affords the same products (5, 6, 7, and 8).

It is well known that N-heterocyclic ylides such as pyridinium and isoquinolinium methylide undergo 1,3-dipolar cycloaddition to give indolizine and benzoindolizine derivatives.[1] In the preceding paper,[2] we have reported the reaction of ketene with isoquinolinium methylides such as isoquinolinium bis(ethoxycarbonyl)methylide (1) and cyano(ethoxycarbonyl)methylide (2) to give variant products. For instance, reaction of ketene with the methylide (1) gave rise to the oxazepine derivative, diethyl 4-methylene-2-oxo-1,2,4,5-tetrahydro-12bH-1,4-oxazepino[5,4-a]isoquinoline-5,5-dicarboxylate (3) in 64% yield. On the other hand, reaction of ketene with the methylide (2) afforded the benzo[g]indolizine derivative, ethyl 3-cyano-2,3-dihydro-2-oxopyrrolo[2,1-a]isoquinoline-3-carboxylate (4).

Ketene can be produced on dehydration of acetic acid, and is very active toward an active hydrogen to give the acetylated compound.[3] The present investigation was undertaken to compare the activities of ketene and acetic anhydride, and we found that reactions of the methylides (1 and 2) with acetic anhydride afforded a sole product, ethyl 2-acetoxypyrrolo[2,1-a]isoquinoline-3-carboxylate (5). Moreover, reactions of the methylides (1 and 2) with acid anhydrides, such as propionic anhydride, n-butyric anhydride, and phenylacetic anhydride, proceeded in like fashion giving the corresponding benzo[g]indolizine derivatives.





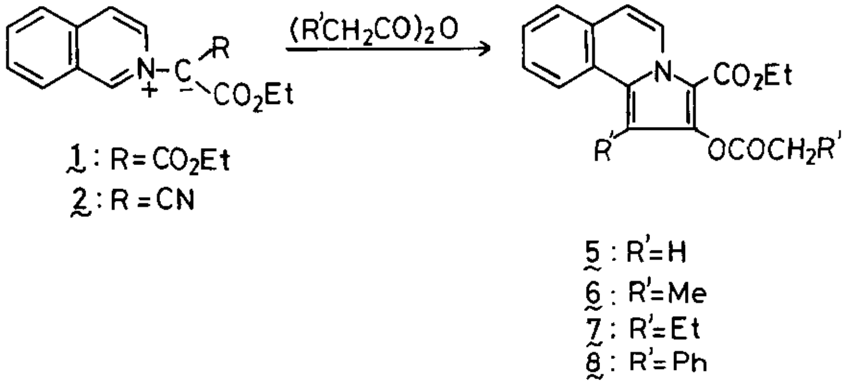
Isoquinolinium bis(ethoxycarbonyl)methylide (1) (1.4 g) was heated under reflux in acetic anhydride (5 ml) for 5 hr. The reaction mixture was condensed under reduced pressure and the resulting residue was added to ice-water (20 ml). The mixture was extracted with chloroform. Purification of the extract by silica gel column chromatography gave the product, ethyl 2-acetoxypyrrolo[2,1-a]isoquinoline-3-carboxylate (5), as needles (from methanol) (0.25 g, 17%), mp 159-160° (Found: C, 68.7; H, 5.15; N, 4.8. $C_{17}H_{15}NO_4$ requires C, 68.65; H, 5.1; N, 4.7%), νmax ($CHCl_3$) 1770, 1690 cm^{-1}, δ ($CDCl_3$) 1.38 (3H, t, J=7 Hz, $OCH_2\underline{CH_3}$), 2.32 (3H, s, $COCH_3$), 4.34 (2H, q, J=7 Hz, $O\underline{CH_2}CH_3$), 6.81 (1H, s, 1-H), 6.97 (1H, d, J=7.5 Hz, 6-H), 7.34-7.77 (3H, m, 7, 8, and 9-H), 7.90-8.08 (1H, m, 10-H), 9.14 (1H, d, J=7.5 Hz, 5-H).

Following the same procedure, the methylide (2) was allowed to react with acetic anhydride to give a low yield (8%) of the indolizine (5).

Similarly, reaction of propionic anhydride with the methylides (1) and (2) gave the same product, ethyl 1-methyl-2-propionyloxypyrrolo[2,1-a]isoquinoline-3-carboxylate (6) in 15 and 12% yield, respectively. Needles (from petroleum ether), mp 110° (Found: C, 70.1; H, 5.85; N, 4.45. $C_{19}H_{19}NO_4$ requires C, 70.15; H, 5.9; N, 4.3), νmax ($CHCl_3$) 1765, 1680 cm^{-1}, δ ($CDCl_3$) 1.34 (3H, t, J=7 Hz, $COCH_2\underline{CH_3}$), 1.37 (3H, t, J=7 Hz, $OCH_2\underline{CH_3}$), 2.42 (3H, s, 1-CH_3), 2.72 (2H, q, J=7 Hz, $CO\underline{CH_2}CH_3$), 4.35

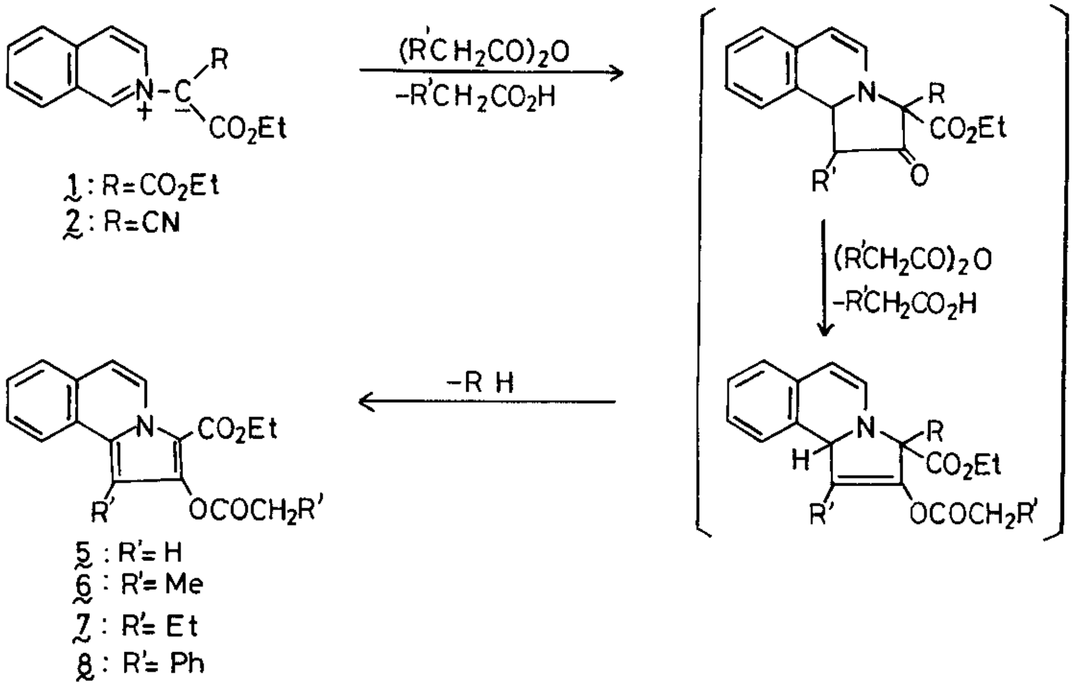
(2H, q, J=7 Hz, O$\underline{\mathrm{CH}}_2CH_3$), 6.93 (1H, d, J=8 Hz, 6-H), 7.38-7.75 (3H, m, 7, 8, and 9-H), 8.10-8.42 (1H, m, 10-H), 9.21 (1H, d, J=8 Hz, 5-H).

Reaction of n-butyric anhydride with the methylides (1) and (2) afforded ethyl 2-butyryloxy-1-ethylpyrrolo[2,1-a]isoquinoline-3-carboxylate (7) in 6 and 5% yields, respectively. Pale yellow needles (from petroleum ether), mp 108° (Found: C, 71.35; H, 6.6; N, 3.8. $C_{21}H_{23}NO_4$ requires C, 71.35; H, 6.55; N, 3.95), ν max (CHCl$_3$) 1765, 1680 cm^{-1}, δ(CDCl$_3$) 1.09 (3H, t, J=7 Hz, CO(CH$_2$)$_2\underline{\mathrm{CH}}_3$), 1.28 (3H, t, J=7.5 Hz, -CH$_2\underline{\mathrm{CH}}_3$), 1.35 (3H, t, J=7 Hz, -OCH$_2\underline{\mathrm{CH}}_3$), 1.64-2.07 (2H, m, -COCH$_2\underline{\mathrm{CH}}_2CH_3$), 2.78 (2H, t, J=7.5 Hz, CO$\underline{\mathrm{CH}}_2CH_2CH_3$), 2.94 (2H, q, J=7.5 Hz, -$\underline{\mathrm{CH}}_2CH_3$), 4.39 (2H, q, J=7 Hz, -O$\underline{\mathrm{CH}}_2CH_3$), 6.95 (1H, d, J=8 Hz, 6-H), 7.39-7.68 (3H, m, 7, 8, and 9-H), 8.07-8.40 (1H, m, 10-H), 9.24 (1H, d, J=8 Hz, 5-H).



Similarly, reaction of phenylacetic anhydride with the methylides (1) and (2) gave the same product, *ethyl 1-phenyl-2-phenylacetoxypyrrolo[2,1-a]isoquinoline-3-carboxylate* (8) in 7 and 12% yields, respectively. Yellow prisms (from petroleum ether), mp 128° (Found: C, 77.75; H, 5.15; N, 3.0. $C_{29}H_{23}NO_4$ requires C, 77.5; H, 5.15; N, 3.1), νmax (CHCl$_3$) 1765, 1685 cm^{-1}, δ (CDCl$_3$), 1.30 (3H, t, J=7 Hz, OCH$_2\underline{\mathrm{CH}}_3$), 3.71 (2H, s, $\underline{\mathrm{CH}}_2$Ph), 4.27 (2H, q, J=7 Hz, O$\underline{\mathrm{CH}}_2CH_3$), 7.03 (1H, d, J=8 Hz, 6-H), 7.10-7.75 (14H, m, arom-H), 9.33 (1H, d, J=8 Hz, 5-H).

Formation of the products (5 - 8) is elucidated as following; reaction of acid anhydride with the methylide would give the benzo[g]indolizine intermediate, which is acylated accompanied by elimination of hydrogen cyanide or ethyl formate to give the products (5, 6, 7, and 8).



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