REGIOCONTROLLED SYNTHESES OF BENZO[*b*]QUINOLIZINIUM AND HETEROISOQUINOLINIUM CATIONS

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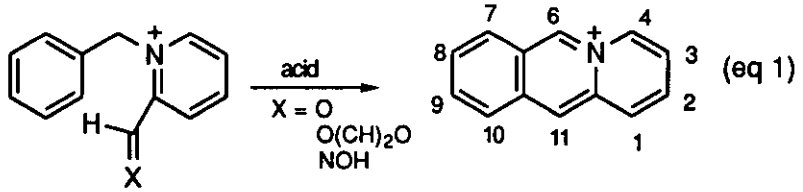
Abstract - A regiocontrolled synthesis of 10-alkoxy and alkyl substituted benzo[*b*]quinolizinium salts is described. Synthesis of a novel 9-alkoxythiazolo[3,2-*b*]isoquinolinium cation is reported. In addition the synthesis of several new *N*-alkylimidazo[1,2-*b*]isoquinolin-4-ium cations is described. Condensation of dianions (**1**) with heteroaromatic aldehydes and ketones provides diols in 35-85% yield. Cyclization of diols (**2**) with $POCl_3$ gives previously unreported 10-substituted benzo[*b*]quinolizinium cations and heteroisoquinolinium cations (**3**) in 35-90% yield.

The utility of the benzo[*b*]quinolizinium cation in inverse-electron demand Diels-Alder (IED-DA) reactions was demonstrated by Fields,[2] Bradsher,[3] and other workers.[4] Extensive investigations by these workers detailed the scope and limitations of the methodology and described the synthesis of several substituted benzo[*b*]quinolizinium,[5] phenyl substituted imidazo[1,2-*b*]isoquinolin-4-ium[6] and aryl-substituted thiazolo[3,2-*b*]isoquinolinium cations (**3**).[7] Preparation of these systems was accomplished through cyclization of benzyl-quaternaries with strong acid (eq 1).

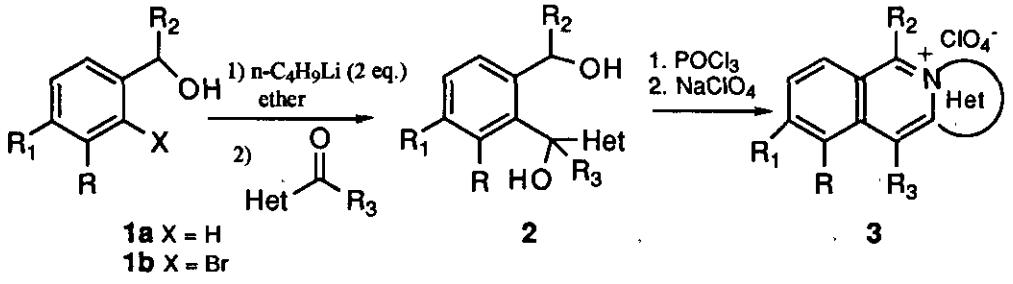


This method provided many mono- and di-substituted benzo[*b*]quinolizinium cations (**3**), but precluded regiospecific synthesis of monosubstituted 10-alkoxy- and 10-alkylbenzo[*b*]quinolizinium cations (**3**). Bradsher and coworkers made several 4 - and 11 - substituted benzo[*b*]quinolizinium cations through halogen - metal

exchange, but this methods suffers from availability of the starting dibromides.[8] We required the previously unreported substituted quinolizinium cations (**3**, R=H). Adaptation of the existing methodology through application of blocking groups was impractical for our purposes.

Consequently a more specific method was required which is more applicable to the preparation of 10-alkoxybenzo[*b*]quinolizinium and 9-alkoxyheteroisoquinolinium derivatives. The method developed is shown in equation 2. Diols (**2**) were readily prepared with regiocontrol in 35-85% isolated yield from the reaction of alkoxy substituted benzyl alcohols[9] (**1a**) by treatment with *n* -BuLi at -40°C to 25°C to form the dianion to which was added the appropriate heterocyclic carbonyl compounds. 10-Alkoxy substituted benzo[*b*]quinolizinium and 9-alkoxythiazolo[3,2-*b*]isoquinolinium cations (**3**) were prepared from **2** by cyclodehydration with $POCl_3$ or with triflic anhydride in 35-95% yield as shown in Table 1.

Other reagents including $SOCl_2$, PCl_5, mesyl chloride and tosyl chloride were less effective. The overall yields (**1** to **3**) range from 15% to 71%. In some cases an overall yield was lowered by competing formation of the tetrahydroisobenzofuran (**4**). Formation of isobenzofuran derivatives (**4**) was more pronounced when secondary benzyl alcohols were utilized.



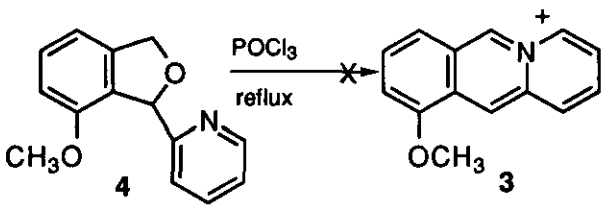
Several novel imidazo[1,2-*b*]isoquinolin-4-ium cations and benzo[*b*]quinolizinium cation were made in a similar fashion as described in equation 2. The substituted 2-lithio-benzyl alkoxide was generated by metal halogen exchange of a substituted bromobenzyl alcohol (**1b**). Subsequent addition to a heterocyclic carbonyl compound led to the diols (**2**) in good yield. Cyclodehydration as described above gave the desired benzo[*b*]quinolizinium and imidazo[1,2-*b*]isoquinolin-4-ium cations (**3**), Table 2. When R becomes more sterically demanding as in R= t-C_4H_9, dianion addition suffers from a competing Cannizzarro type reaction. In this case the problem precipitated by the strong alkoxide can be circumvented through protection of the benzyl alcohol as its *tert*-butyldimethylsilyl ether and subsequent deprotection with *n* -$C_4H_9N^+F^-$.

Table 1. Preparation of 10-Alkoxybenzo[*b*]quinolizinium and Thiazolo[3,2-*b*]isoquinolinium Cations (**3**).

Het	X	R	R_1	R_2	R_3	Yield (%) 3[a]	formula	Anal. Calcd/ Found C	H	N
2-pyridine	H	OCH_3	H	CH_3	H	38	$C_{15}H_{14}NO_5Cl$	55.67	4.36	4.33
								55.71	4.29	4.27
2-pyridine	H	OCH_3	H	H	H	40	$C_{14}H_{12}NO_5Cl$	54.29	3.91	4.52
								54.07	3.80	4.48
2-pyridine	H	OC_3H_7	H	H	H	51	$C_{16}H_{16}NO_5PF_6$	50.14	4.21	3.65
								49.86	4.19	3.61
2-pyridine	H		$-OCH_2O-$	H	H	25	$C_{14}H_{10}NO_6Cl$	51.97	3.11	4.33
								52.34	3.14	4.19
2-pyridine	H	OCH_3	Cl	H	H	71	$C_{14}H_{11}NO_5Cl_2$	48.86	3.22	4.07
								48.86	3.28	4.13
2-thiazole	H	OCH_3	H	H	H	45	$C_{12}H_{10}NO_5SCl$	45.64	3.13	4.44
								45.93	3.45	4.36

a. Overall yield of solids after purification on silica gel or by crystallization.

The tetrahydroisobenzofuran byproduct (**4**) described earlier was obtained as a major side product during cyclodehydration when using dehydrating agents other than $POCl_3$. The tetrahydroisobenzofuran (**4**)[10] was shown not to be an intermediate in this reaction process since after prolonged heating of **4** in refluxing $POCl_3$ or other reagents, **4** was recovered unchanged (eq 3).



(eq 3)

The condensation of dianions with hetero-carbonyls followed by cyclodehydration enables us to synthesize novel heteroisoquinolinium cations. This methodology solves the problem of regioselectivity present during cyclization of benzyl quaternaries such as depicted in equation 1. This methodology yields previously

Table 2. Preparation of substituted Benzo[*b*]quinolizinium and Imidazo[1,2-*b*]isoquinolin-4-ium Cations (3).

Het	X	R	R_1	R_2	R_3	Yield (%) 3[a]	formula	Anal. C	Calcd/ H	Found N
2-pyridine	Br	H	H	CH_3	H	22 (35)[b]	$C_{14}H_{12}NO_4Cl \cdot H_2O$	53.94	4.53	4.49
								53.87	4.49	4.70
2-pyridine	Br	H	OCH_3	H	H	34 (38)[b]	known compound			
2-pyridine	Br	H	H	C_4H_9	H	13	$C_{17}H_{18}NO_4Cl$	60.81	5.40	4.17
								60.70	5.34	4.16
1-(CH_2(4-$OCH_3C_6H_4$))imidazol-2-yl	Br	H	H	H	H	58	$C_{19}H_{17}N_2OPF_6$	52.54	3.95	6.45
								52.59	3.85	6.51
1-(CH_3)imidazol-2-yl	Br	H	H	H	H	60	$C_{12}H_{11}N_2PF_6$	43.92	3.38	8.54
								43.57	3.32	8.58
1-(CH_2α-naphthyl)imidazol-2-yl	Br	H	H	H	H	20	$C_{22}H_{17}N_2PF_6$	58.15	3.74	6.17
								58.00	3.93	6.08
1-(CH_2β-naphthyl)imidazol-2-yl	Br	H	H	H	H	18	$C_{22}H_{17}N_2PF_6$	58.15	3.74	6.17
								57.93	3.52	5.97

[a]Overall yield of solids after purification by silica gel chromatography or by crystallization; [b]Yield of compounds reported by the Bradsher method.

inaccessible 9-alkoxy substituted heteroisoquinolinium and 10-alkoxy substituted benzo[*b*]quinolizinium cations complementing the Bradsher procedure.

EXPERIMENTAL SECTION

Melting points were determined on a Mel-Temp apparatus and are uncorrected. Infrared spectra were recorded on a Nicolet 20SX FTIR. Nmr spectra were acquired in the indicated solvent on a JEOL-FX270, General Electric QE-300 or Bruker-AC200 FTNMR. Mass spectra were recorded on a Nermag R10/10 coupled to a Varian 3400 Gas Chromatograph or on a *JEOL JMS-01SC spectrometer. Elemental analyses were performed* by Galbraith Laboratories, Knoxville, TN. Thin layer chromatography (tlc) was performed on E. Merck 5x20, Kieselgel 60 F-254 plates. Chromatography was done by the flash method as described by Still.[11] Columns were packed with Kieselgel 60, 230-400 mesh. Anhydrous THF was distilled from sodium-benzophenone ketyl. Alkyllithium reagents were titrated with diphenylacetic acid.[12] Other materials and reagents were purified by standard procedures where needed.

Representative experimental procedure: Preparation of **2**. (R = OCH_3, $R_1 = R_2 = R_3 = H$, Het = 2-pyridine) A solution of 3-methoxybenzyl alcohol (**1a**) (63.5 g, 0.46 mol) in anhydrous ether (1500 ml) was cooled to -40°C. *n* -BuLi (100 ml, 10 M) was slowly added over 30 min under an atmosphere of Ar. The cooling bath was then removed and the reaction was allowed to warm to room temperature. After 30 min the solution was cooled to -20°C, and pyridine 2-carboxaldehyde (69.7g, 0.65 mol) was added in one portion. The resulting solution was allowed to warm to room temperature. After 60 min at room temperature, the reaction was quenched by addition of a saturated solution of NH_4Cl. The mixture was extracted with ethyl acetate (3x300 ml). The combined extracts were dried with anhydrous Na_2SO_4 and concentrated to 200 ml. Ether (200 ml) was added and the resulting solid was filtered and recrystallized from acetonitrile:ether (1:1) to yield the diol (**2**), 68.5 g (60.7%) as an amorphous tan solid: Ir (KBr) 3402, 3168, 1586, 1467, 1260, 767 cm^{-1}; ms (CI) *m/z* 246 (M+1) 228, 214, 198, 168, 149; ^1H nmr (300 MHz, $CDCl_3$) δ 8.37 (d, *J* = 4.6 Hz, 1H), 7.71 (dt, *J* = 1.5 Hz, 8 Hz, 1H), 7.61 (d, *J* = 8.0 Hz, 1H), 7.25 (t, *J* =7.9 Hz, 1H), 7.12 (t, *J* = 7.9 Hz, 1H), 7.03 (d, *J* = 7.3 Hz, 1H), 6.84 (d, *J* = 8.1 Hz, 1H), 6.30 (br s, 1H), 5.18 (br s, 2H), 4.95 (d, *J* = 11.9 Hz, 1H), 4.41 (d, *J* = 11.9 Hz, 1H), 3.78 (s, 3H); Anal. Calcd for $C_{14}H_{15}NO_3$: C, 68.56; H, 6.16; N, 5.71. Found; C, 68.44; H,6.13; N, 5.65. Cyclization of **2**: To a stirred, precooled 0°C solution of $POCl_3$[13] (70 ml, 0.75 mol) was

added **2** (50 g, 0.20 mol) as a solid portionwise. After addition was completed the reaction flask was immediately lowered into a preheated oil bath at 110°C which resulted in rapid evolution of gas and an exotherm. After 6 min the solution was cooled to room temperature and toluene (200 ml) was added. Concentration under reduced pressure gave a black residue.[14] To the residue was added water (600 ml) followed by aqueous $NaClO_4$ (48.8 g, 0.4 mol). The resulting solid was filtered. The perchlorate was crystallized from hot methanol to yield 10-methoxybenzo[*b*]isoquinolizinium perchlorate (**3**) as a tan-yellow solid 42 g (66%): mp 188-191°C; Ir (KBr) 1644, 1550, 1280, 1092, 749 cm^{-1}; ms (SIms) *m/z* 210, 195, 167, 154; ^1H nmr (300 MHz, DMSO-d6) δ 10.34 (s, 1H), 9.3 (s, 1H), 9.23 (d, *J* = 6.9 Hz, 1H), 8.67 (d, *J* = 8.8 Hz, 1H), 8.06 (t, *J* = 7.8 Hz, 1H), 7.98-7.87 (m, 3H), 7.47 (d, J = 7.25 Hz, 1H), 4.12 (s, 3H); uv (λ_{max}, 95% EtOH) 211, 255, 376 nm; Anal. Calcd for $C_{14}H_{12}NO_5Cl$: C, 54.29; H, 3.91; N, 4.52. Found: C, 54.07; H, 3.80; N, 4.48.

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10. Prepared in an analogous fashion to the following reference (substituted $SnCl_2{\cdot}2H_2O$ as the Lewis acid of choice) S. Kim, K. N. Chung, and S. J. Yang, *J. Org. Chem.*, 1987, **52**, 3917.
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13. Triflic anhydride could be used interchangeably (3- 4 eq. versus substrate): **Very exothermic!**
14. Chromatography was only used if the tetrahydrofuran side product (**4**) was in abundance. A short plug of SiO_2 was used with 10% CH_3OH/CH_2Cl_2 as elutant. The compound (**4**) travels with the solvent front and the benz[*b*]quinolizinium cation (**3**) has R_f value of 0.1.

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