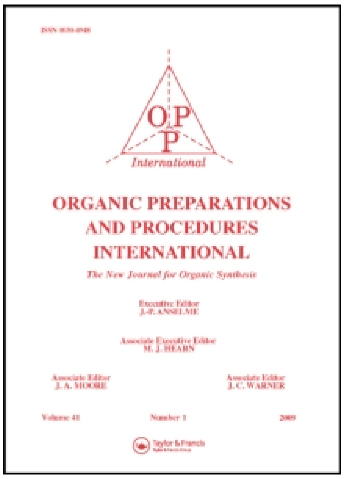

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A NOVEL ACCESS TO SOME 1,4-DICHLOROISOQUINOLINES FROM PHENACYL AZIDES

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A NOVEL ACCESS TO SOME 1,4-DICHLOROISOQUINOLINES FROM PHENACYL AZIDES

Submitted by R. E. Chen, X. H. Zhou, W. H. Zhong and W. K. Su*
(11/01/07)

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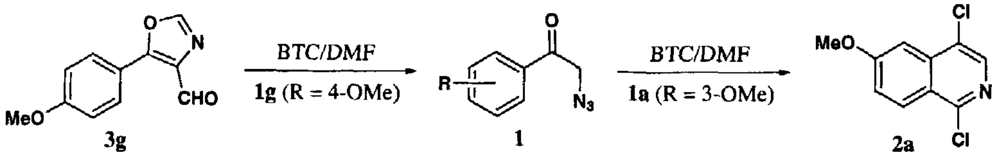
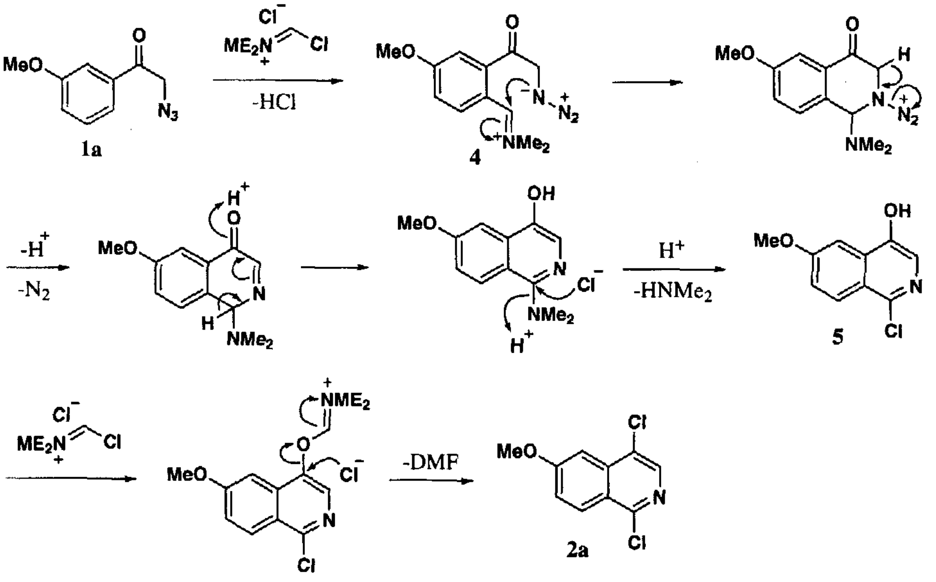
The Vilsmeier-Haack reaction initially used for the formylation of activated aromatic substrates[1] and carbonyl compounds[2] has now evolved into a powerful synthetic tool for the construction of many heterocyclic compounds[3] such as quinolines, indoles, quinazolines, pyridines, etc. In continuation of our previous work on exploring the use of *bis*(trichloromethyl) carbonate (BTC) in organic synthesis,[4] we focused our research on the use of Vilsmeier salts derived from BTC and N,N-dimethylformamide (DMF).[5] Herein we describe a mild and efficient one-step synthesis of substituted 1,4-dichloroisoquinolines and 5-aryloxazole-4-carboxaldehydes from various phenacyl azides under Vilsmeier conditions.

Inspired by the preparation of 5-aryloxazole-4-carboxaldehydes from the reaction of phenacyl azides with $POCl_3$/DMF,[6] we selected 3-methoxyphenacyl azide (**1a**, *Scheme 1*) as the substrate for our initial investigation. To our surprise, treatment of **1a** with the Vilsmeier reagent derived from 1.0 equiv. of BTC and 3.0 equiv. of DMF in 1,2-dichloroethane at 80°C for 4 hours afforded 1,4-dichloro-6-methoxyisoquinoline (**2a**) in 54% yield. It was fully identified by ^1H, ^{13}C NMR, MS and elemental analysis. Attempts to accomplish the cyclization at lower temperatures, using excess of Vilsmeier reagent or by prolonging the reaction time were not rewarded with favorable results (*Table 1*). However, when 4-methoxyphenacyl azide (**1g**) was tested under similar conditions, the normal Vilsmeier cyclization product 5-(4-methoxyphenyl)oxazole-4-carboxaldehyde (**3g**) was obtained in 62% yield (*Scheme 1*).



Scheme 1

Comparison of the result of **1a** with that of **1g** led us to speculate that the difference between them is the conjugative effect of the methoxy group in the former substrate, which increases the nucleophilicity at the *p*-carbon in **1a** and *o*-carbon in **1c** and **1e** towards the Vilsmeier salts, leading to the formylation. Thus a possible mechanism for the formation of the 1,4-dichloroisoquinolines is shown below (*Scheme 2*).

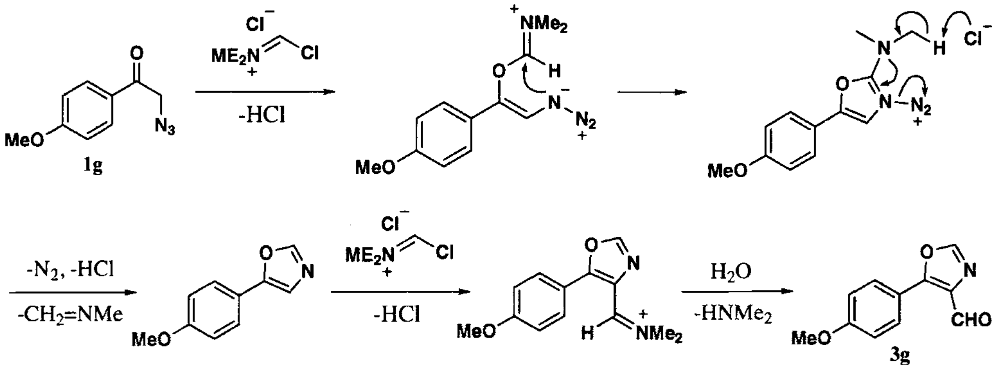


Scheme 2

Table 1. Effect of Reagent, Solvent and Temperature on Cyclization of **1a**

Entry	BTC (equiv.)	Solvent	Temperature (°C)	Reaction time (h)	Yield (%)
1	1.0	$(CH_2Cl)_2$	80	4	54
2	1.0	DMF	80	4	55
3	0.67	$(CH_2Cl)_2$	80	4	40
4	1.33	$(CH_2Cl)_2$	80	4	55
5	1.0	$(CH_2Cl)_2$	60	4	20
6	1.0	$(CH_2Cl)_2$	25	12	0
7	1.0	$(CH_2Cl)_2$	80	8	50

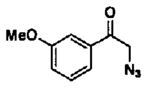
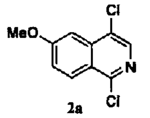
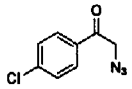
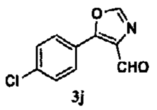
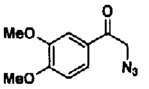
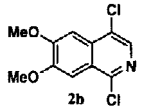
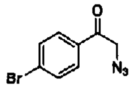
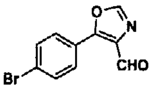
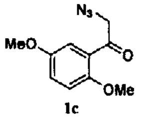
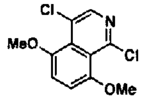
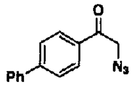
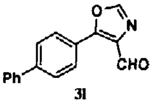
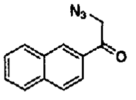
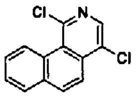
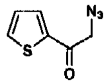
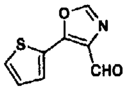
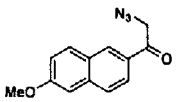
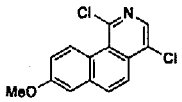
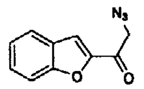
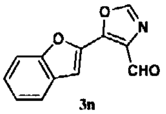
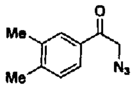
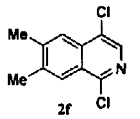
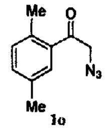
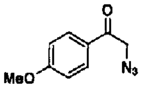
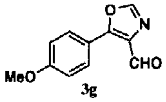
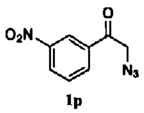
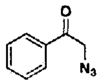
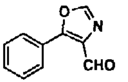
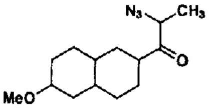
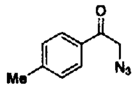
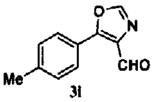
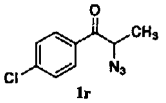
The formation of the oxazole-4-carboxaldehydes can be rationalized in terms of the mechanism proposed by Majo and Perumal (*Scheme 3*)[6a]. The lower yields obtained for **1h~l** are likely due to the formation of unknown complex by-products. As for **1m** and **1n**, only trace products were detected under similar conditions.



Scheme 3

Evidently the presence of a *m*-methoxy group on the aromatic ring is required for the formation of 1,4-dichloroisoquinolines in moderate to high yield (**Entries 1~3, 5**). In comparison, the *m*-methyl group in **1f** renders the compound less active and provide the corresponding 1,4-dichloroisoquinoline **2f** in only 15% yield (**Entry 6**). It was surprising that 2,5-dimethylphenacyl azide (**1o**) gave very complex results and no cyclization product could be isolated, which cannot be explained at present. Substrates **1g~l** provided the normal cyclization products 5-aryloxazole-4-carboxaldehydes **3g~l** in moderate yields. However, if there is a strong electron-withdrawing group (NO_2) on the aromatic ring (as in **1p**), no product could be obtained. Attempted cyclization of 2-azido-1-arylethanones **1q** or **1r** resulted only in the recovery of the starting materials. Although the replacement of $POCl_3$ by BTC provides somewhat lower yields probably due to the lower reactivity[7] of the corresponding iminium salt, reactions using the BTC/DMF system as Vilsmeier reagent avoid the formation of phosphorus salts and thus will be advantageous in industrial applications.

Table 2. Vilsmeier Cyclization of Phenacyl Azides using BTC/DMF System

Entry	Substrate	Product[a]	Yield (%)	Entry	Substrate	Product[a]	Yield (%)
1	 1a	 2a	54	10	 1j	 3j	30 (36[b])
2	 1b	 2b	75	11	 1k	 3k	38 (42[b])
3	 1c	 2c	42	12	 1l	 3l	40 (45[b])
4	 1d	 2d	8	13	 1m	 3m	trace
5	 1e	 2e	87	14	 1n	 3n	trace
6	 1f	 2f	15	15	 1o	None	----
7	 1g	 3g	62	16	 1p	None	----
8	 1h	 3h	38	17	 1q	None	----
9	 1i	 3i	33 (36[b])	18	 1r	None	----

a) All the unknown products were characterized by ^{1}H NMR, ^{13}C NMR, MS and elemental analysis. b) Yields reported in reference using POCl$_3$/DMF.[6a]

Table 3. The Analysis Data of the Cyclization Products

Cmpd.[a]	mp (°C)	^{1}H NMR (δ)	^{13}C NMR (δ)	MS (m / z)	Elemental Analysis (Found)		
					C	H	N
2a	113-115	4.01 (s, 3H, OCH_3), 7.28 (d, 1H, J=2.0 Hz, Ar *H*), 7.39 (s, 1H, Ar *H*), 7.87 (d, 1H, J=8.8 Hz, Ar *H*), 8.82 (s, 1H, Ar *H*)	55.8, 101.6, 121.4, 124.0, 124.4, 129.6, 137.6, 144.3, 149.0, 162.7.	227(M^+, 45), 229 (M^++2, 30), 231 (M^++4, 5), 135 (100)	52.66 (52.53)	3.09 (3.17)	6.14 (6.23)
2b	186-187	4.04 (s, 3H, OCH_3), 4.09 (s, 3H, OCH_3), 7.17 (s, 1H, Ar *H*), 7.37 (s, 1H, Ar *H*), 8.72 (s, 1H, Ar *H*)	56.2, 56.4, 102.2, 105.2, 124.0, 124.4, 132.5, 142.3, 147.1, 151.0, 154.9	257 (M^+, 75), 259 (M^++2, 50), 261 (M^++4, 8), 149 (100)	51.19 (51.27)	3.51 (3.45)	5.43 (5.51)
2c	137-139	3.91 (s, 3H, OCH_3), 3.98 (s, 3H, OCH_3), 6.82 (d, 1H, J=8.8 Hz, Ar *H*), 7.06 (d, 1H, J=8.8 Hz, Ar *H*), 9.26 (s, 1H, Ar *H*)	55.9, 57.2, 105.9, 113.6, 121.9, 123.2, 128.3, 145.3, 146.8, 148.7, 150.4	257 (M^+, 83), 259 (M^++2, 54), 261 (M^++4, 9), 149 (100)	51.19 (51.28)	3.51 (3.44)	5.43 (5.50)
2d	171-172	7.72 (dd, 1H, $J_{1,2}$ = 7.2, 7.2 Hz, Ar *H*), 7.78 (dd, 1H, $J_{1,2}$ = 7.2, 7.2 Hz, Ar *H*), 7.95 (d, 1H, J = 7.6 Hz, Ar *H*), 8.07 (dd, 2H, J_1 = 9.2 Hz, J_2 = 8.4 Hz, Ar *H*), 8.70 (d, 1H, J = 7.6 Hz, Ar *H*), 9.68 (s, 1H, Ar *H*)	121.1, 122.3, 125.1, 126.5, 128.4, 128.6, 128.8, 129.1, 131.7, 133.8, 135.7, 144.2, 145.5	247 (M^+, 100), 249 (M^++2, 66), 251 (M^++4, 11), 177 (22)	62.93 (63.05)	2.84 (2.77)	5.65 (5.69)
2e	173-175	3.99 (s, 3H, OCH_3), 7.30 (d, 1H, J = 2.4 Hz, Ar *H*), 7.40 (dd, 1H, J = 9.2 Hz, 2.4 Hz, Ar *H*), 7.98 (d, 1H, J = 9.2 Hz, Ar *H*), 8.10 (d, 1H, J = 9.2 Hz, Ar *H*), 8.61 (d, 1H, J = 9.2 Hz, Ar *H*), 9.60 (s, 1H, Ar *H*)	55.6, 109.1, 119.5, 121.8, 122.9, 123.9, 125.4, 125.5, 133.3, 133.5, 134.6, 143.8, 144.4, 159.6	277 (M^+, 39), 279 (M^++ 2, 26), 281 (M^++4, 4), 262 (100), 264 (57)	60.46 (60.31)	3.26 (3.22)	5.04 (5.21)
2f	102-103	2.48 (s, 3 H, CH_3), 2.53 (s, 3 H, CH_3), 7.72 (s, 1 H, Ar *H*), 7.94 (s, 1 H, Ar *H*), 8.84 (s, 1 H, Ar *H*)	20.1, 20.9, 123.2, 125.9, 127.1, 127.4, 129.9, 134.4, 138.5, 143.4, 148.9.	225 (M^+, 48), 227 (M^++2, 32), 229 (M^++4, 5), 91 (100)	58.43 (58.33)	4.01 (4.08)	6.19 (6.31)

Table 3. Continued...

Cmpd.[a]	mp (°C)	^{1}H NMR (δ)	^{13}C NMR (δ)	MS (m / z)	Elemental Analysis (Found)		
					C	H	N
3g	120-121	3.87 (s, 3H, OCH_3), 6.99 (d, 2H, *J* = 8.4 Hz, Ar *H*), 8.04 (d, 2H, *J* = 8.8 Hz, Ar *H*), 8.28 (s, 1H, Ar *H*), 9.99 (s, 1H, C*H*O)	55.4, 114.3, 118.7(2¥CH), 128.7(2¥CH), 141.8, 144.2, 162.2, 163.1, 184.0	203 (M$^+$, 100), 204 (M$^+$+1, 27), 175 (18)	65.02 (65.14)	4.46 (4.54)	6.89 (6.81)
3h	55-56	7.49-7.54 (m, 3H, Ar *H*), 8.11 (d, 2H, Ar *H*), 8.33 (s, 1H, Ar *H*), 10.02 (s, 1H, C*H*O)	123.5, 126.9(2¥CH), 129.5(2¥CH), 130.0, 142.0, 144.2, 163.1, 184.0,	173 (M$^+$, 100), 174 (M$^+$+1, 25)	69.36 (69.45)	4.07 (3.98)	8.09 (8.15)
3i	90-91[b]	2.43 (s, 3H, CH_3), 7.31 (d, 2H, *J*= 7.6 Hz, Ar *H*), 8.00(d, 2H, *J* = 7.6 Hz, Ar *H*), 8.30 (s, 1H, Ar *H*), 10.01 (s, 1H, C*H*O)	----	----	----	----	----
3j	128-129[c]	7.50 (d, 2H, *J* = 8.4 Hz, Ar *H*), 8.06 (d, 2H, *J* = 8.4 Hz, Ar *H*), 8.35 (s, 1H, Ar *H*), 10.02 (s, 1H, C*H*O)	----	----	----	----	----
3k	136-137[d]	7.21 (d, 2H, *J* = 8.0 Hz, Ar *H*), 7.54 (d, 2H, *J* = 8.0 Hz, Ar *H*), 8.22 (s, 1H, Ar *H*), 9.64 (s, 1H, C*H*O)	----	----	----	----	----
3l	161-163[e]	7.13-7.03 (m, 5H, Ar *H*), 7.39 (d, 2H, *J* = 8.0 Hz, Ar *H*), 7.83 (d, 2H, *J* = 8.0 Hz, Ar *H*), 8.25 (s, 1H, Ar *H*), 9.65 (s, 1H, C*H*O)	----	----	----	----	----

a) All the compounds are yellow except for **3g** which is white. b) *Lit.*[6a] 90°C. c) *Lit.*[6a] 130°C. d) *Lit.*[6a] 135°C. e) *Lit.*[6a] 160°C.

EXPERIMENTAL SECTION

Melting points were obtained on a capillary melting point apparatus and are uncorrected. Infrared spectra were recorded on a Thermo Nicolet Avatar 370 spectrophotometer. ^{1}H NMR spectra were measured on a Varian Mercur plus-400 spectrometer (400 MHz) in $CDCl_3$ using TMS as internal standard. ^{13}C NMR spectra were determined in $CDCl_3$ on Varian Mercur plus-100 spectrometer (100 MHz) with TMS as internal standard. Chemical shifts (δ) are expressed in ppm and coupling constants *J* are given in Hz. Mass spectra were obtained on a Trace DSQ mass spectrometer. Elemental analysis was performed on a VarioEL-3 instrument. The starting material phenacyl azides **1** were prepared according to the literature method.[8] Organic solvents were obtained from commercial sources.

General Procedure.- A solution of the phenacyl azide (5 mmol) in $ClCH_2CH_2Cl$ (20 mL) was added dropwise to an ice-cold magnetically stirred mixture of the Vilsmeier reagent prepared from DMF (15 mmol) and BTC (5 mmol) in $ClCH_2CH_2Cl$ (40 mL). The reaction mixture was gradually allowed to attain room temperature and heated at refluxing condition for 4h. The residual solution was poured into crushed ice, stirred for 1h, extracted with $CHCl_3$ (3 x 50 mL), concentrated, and column chromatographed (petroleum ether:EtOAc = 8:1) to yield the corresponding products.

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