

Organic Preparations and Procedures International: The New Journal for Organic Synthesis

Publication details, including instructions for authors and subscription information:

<http://www.tandfonline.com/loi/uopp20>

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

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Published online: 18 Feb 2009.

To cite this article: R. E. Chen, X. H. Zhou, W. H. Zhong & W. K. Su (2008) A NOVEL ACCESS TO SOME 1,4-DICHLOROISOQUINOLINES FROM PHENACYL AZIDES, Organic Preparations and Procedures International: The New Journal for Organic Synthesis, 40:6, 579-585, DOI: [10.1080/00304940809458125](https://doi.org/10.1080/00304940809458125)

To link to this article: <http://dx.doi.org/10.1080/00304940809458125>

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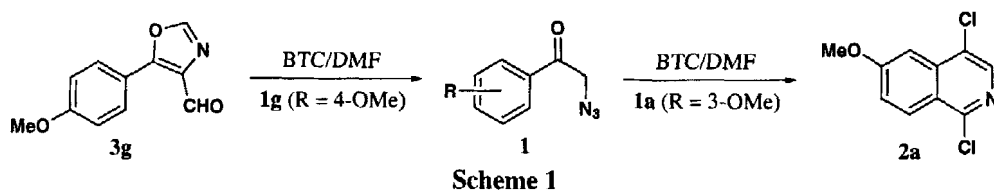
A NOVEL ACCESS TO SOME 1,4-DICHLOROISOQUINOLINES FROM PHENACYL AZIDES

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(11/01/07)

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The Vilsmeier-Haack reaction initially used for the formylation of activated aromatic substrates¹ and carbonyl compounds² has now evolved into a powerful synthetic tool for the construction of many heterocyclic compounds³ 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).



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).

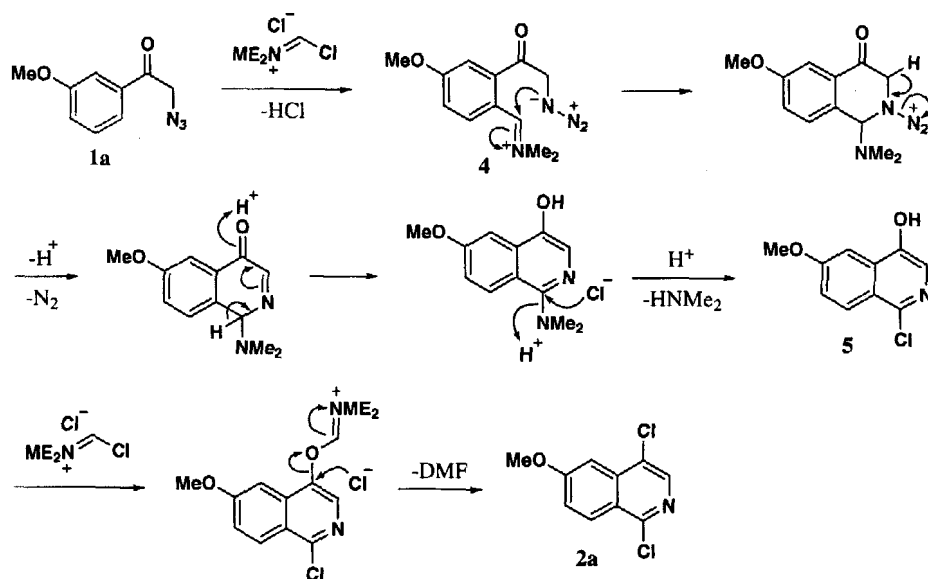
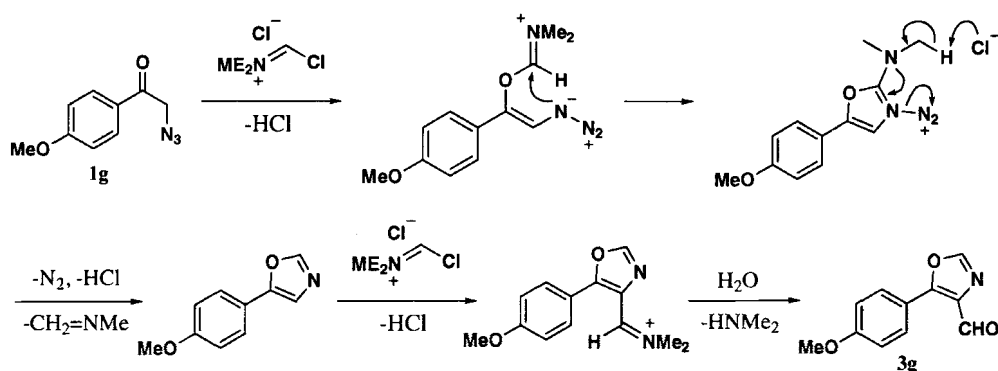


Table 1. Effect of Reagent, Solvent and Temperature on Cyclization of **1a**

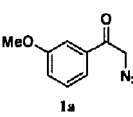
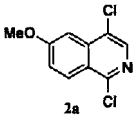
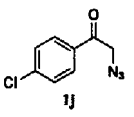
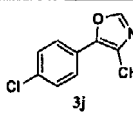
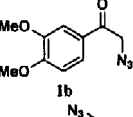
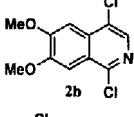
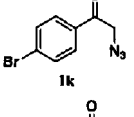
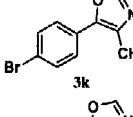
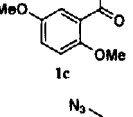
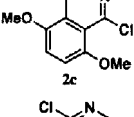
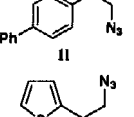

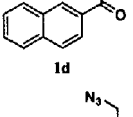
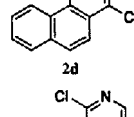
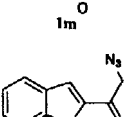
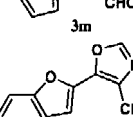
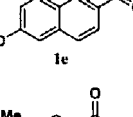
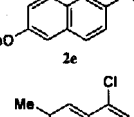
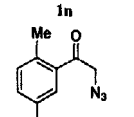
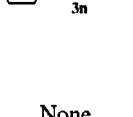
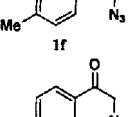
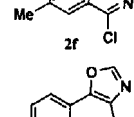
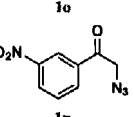
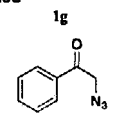
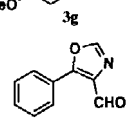
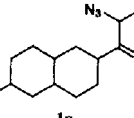
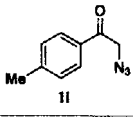
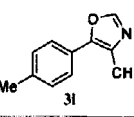

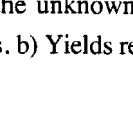
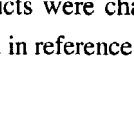
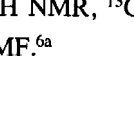
Entry	BTC (equiv.)	Solvent	Temperature (°C)	Reaction time (h)	Yield (%)
1	1.0	(CH ₂ Cl) ₂	80	4	54
2	1.0	DMF	80	4	55
3	0.67	(CH ₂ Cl) ₂	80	4	40
4	1.33	(CH ₂ Cl) ₂	80	4	55
5	1.0	(CH ₂ Cl) ₂	60	4	20
6	1.0	(CH ₂ Cl) ₂	25	12	0
7	1.0	(CH ₂ Cl) ₂	80	8	50

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 (NO₂) 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 POCl₃ by BTC provides somewhat lower yields probably due to the lower reactivity⁷ 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			54	10			30 (36 ^b)
2			75	11			38 (42 ^b)
3			42	12			40 (45 ^b)
4			8	13			trace
5			87	14			trace
6			15	15		None	---
7			62	16		None	---
8			38	17		None	---
9			33 (36 ^b)	18		None	---

a) All the unknown products were characterized by ¹H NMR, ¹³C NMR, MS and elemental analysis. b) Yields reported in reference using POCl₃/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, <i>J</i> =2.0 Hz, Ar <i>H</i>), 7.39 (s, 1H, Ar <i>H</i>), 7.87 (d, 1H, <i>J</i> =8.8 Hz, Ar <i>H</i>), 8.82 (s, 1H, Ar <i>H</i>)	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 <i>H</i>), 7.37 (s, 1H, Ar <i>H</i>), 8.72 (s, 1H, Ar <i>H</i>)	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, <i>J</i> =8.8 Hz, Ar <i>H</i>), 7.06 (d, 1H, <i>J</i> =8.8 Hz, Ar <i>H</i>), 9.26 (s, 1H, Ar <i>H</i>)	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, <i>J</i> _{1,2} = 7.2, 7.2 Hz, Ar <i>H</i>), 7.78 (dd, 1H, <i>J</i> _{1,2} = 7.2, 7.2 Hz, Ar <i>H</i>), 7.95 (d, 1H, <i>J</i> = 7.6 Hz, Ar <i>H</i>), 8.07 (dd, 2H, <i>J</i> ₁ = 9.2 Hz, <i>J</i> ₂ = 8.4 Hz, Ar <i>H</i>), 8.70 (d, 1H, <i>J</i> = 7.6 Hz, Ar <i>H</i>), 9.68 (s, 1H, Ar <i>H</i>)	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, <i>J</i> = 2.4 Hz, Ar <i>H</i>), 7.40 (dd, 1H, <i>J</i> = 9.2 Hz, 2.4 Hz, Ar <i>H</i>), 7.98 (d, 1H, <i>J</i> = 9.2 Hz, Ar <i>H</i>), 8.10 (d, 1H, <i>J</i> = 9.2 Hz, Ar <i>H</i>), 8.61 (d, 1H, <i>J</i> = 9.2 Hz, Ar <i>H</i>), 9.60 (s, 1H, Ar <i>H</i>)	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 <i>H</i>), 7.94 (s, 1 H, Ar <i>H</i>), 8.84 (s, 1 H, Ar <i>H</i>)	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, <i>J</i> = 8.4 Hz, Ar <i>H</i>), 8.04 (d, 2H, <i>J</i> = 8.8 Hz, Ar <i>H</i>), 8.28 (s, 1H, Ar <i>H</i>), 9.99 (s, 1H, CHO)	55.4, 114.3, 118.7(2 Ψ CH), 128.7(2 Ψ 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 <i>H</i>), 8.11 (d, 2H, Ar <i>H</i>), 8.33 (s, 1H, Ar <i>H</i>), 10.02 (s, 1H, CHO)	123.5, 126.9(2 Ψ CH), 129.5(2 Ψ 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, <i>J</i> = 7.6 Hz, Ar <i>H</i>), 8.00(d, 2H, <i>J</i> = 7.6 Hz, Ar <i>H</i>), 8.30 (s, 1H, Ar <i>H</i>), 10.01 (s, 1H, CHO)	----	----	----	----	----
3j	128-129 ^c	7.50 (d, 2H, <i>J</i> = 8.4 Hz, Ar <i>H</i>), 8.06 (d, 2H, <i>J</i> = 8.4 Hz, Ar <i>H</i>), 8.35 (s, 1H, Ar <i>H</i>), 10.02 (s, 1H, CHO)	----	----	----	----	----
3k	136-137 ^d	7.21 (d, 2H, <i>J</i> = 8.0 Hz, Ar <i>H</i>), 7.54 (d, 2H, <i>J</i> = 8.0 Hz, Ar <i>H</i>), 8.22 (s, 1H, Ar <i>H</i>), 9.64 (s, 1H, CHO)	----	----	----	----	----
3l	161-163 ^e	7.13-7.03 (m, 5H, Ar <i>H</i>), 7.39 (d, 2H, <i>J</i> = 8.0 Hz, Ar <i>H</i>), 7.83 (d, 2H, <i>J</i> = 8.0 Hz, Ar <i>H</i>), 8.25 (s, 1H, Ar <i>H</i>), 9.65 (s, 1H, CHO)	----	----	----	----	----

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. ¹H NMR spectra were measured on a Varian Mercur plus-400 spectrometer (400 MHz) in CDCl₃ using TMS as internal standard. ¹³C NMR spectra were determined in CDCl₃ 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 mate-

rial 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 $\text{ClCH}_2\text{CH}_2\text{Cl}$ (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 $\text{ClCH}_2\text{CH}_2\text{Cl}$ (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.

Acknowledgement.- We are grateful to the National Basic Research Program (No. 2003CB114402), National Natural Science Foundation of China (No. 20476098 and No. 20676123) for financial support.

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