Reaction of Reissert Anion with Aldimines: A New Approach to the Imidazo[5,1-*a*]isoquinoline Ring System [1]

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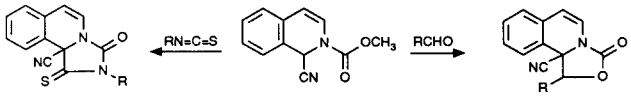
Received May 29, 1990

The carbanion derived from *N*-alkoxycarbonyl Reissert compound readily undergoes addition-cyclization reaction with aldimines to give imidazo[5,1-*a*]isoquinolines. A detailed study of this new ring annelation chemistry is described.

J. Heterocyclic Chem., **27**, 2129 (1990).

Much of the recent chemistry of Reissert compound has revolved around the study of its carbanion and has been the subject of a number of comprehensive reviews [3]. The chemistry has not only provided a versatile methodology for the modification of the heterocyclic ring but has also contributed towards annelation of a third ring which has proved an attractive synthetic methodology to a variety of ring systems [4]. Annelations are exemplified with reactions of carbanion, derived from so-called analogs of Reissert compounds **1** [3b-c], with suitable electrophiles such as heterocumulenes [5] and aldehydes [6] (Scheme 1).

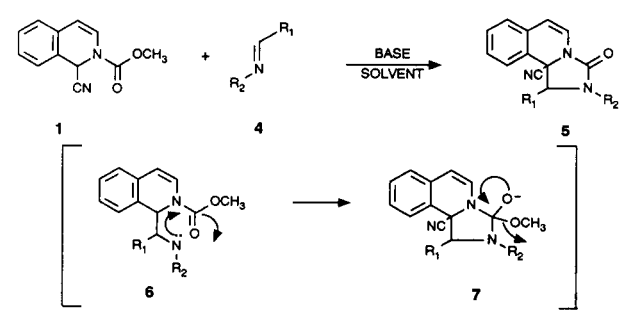
Scheme 1



3 1 2

Imines or azomethines have been exploited in organic synthesis as synthons [7]. A variety of nucleophiles readily add to the carbon atom of C=N linkage in aldimines to give addition products [8]. Recently, a stereospecific synthesis of β-lactams has also been demonstrated by utilizing enolates and aldimines [9]. It was of interest to determine whether the carbanion derived from **1** could be transformed into **5** *via* proposed intermediates **6** and **7**, by undergoing addition to aldimine followed by concomitant intramolecular ring closure by displacing alkoxy anion (Scheme 2). A successful implementation of the chemistry will provide access to imidazo[5,1-*a*]isoquinoline ring systems and would also extend the utility of Reissert compounds in organic synthesis [10]. This paper details the study of reactions between Reissert anion and various aldimines.

Scheme 2

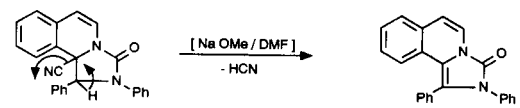


1 4 5

6 7

Aldimines were prepared according to the literature procedure by condensing amines with aldehydes [11]. Treatment of Reissert analog **1** with sodium hydride in dry dimethylformamide generated the carbanion which on reaction with benzylideneaniline (**4a**) gave a bright yellow colored compound. A mass spectrum of the product exhibited a molecular ion peak at m/z 336, instead of m/z 363, as expected from the compound **5a**. Loss of hydrogen cyanide (mass unit of 27) from **5a** would explain the molecular ion peak at m/z 336. Elimination of hydrogen cyanide was suspected during molecular analysis, however, no evidence of hydrogen cyanide (or related fragments) was recorded by the mass spectra, employing chemical ionization (ci) and electron ionization (ei) methods. Also, it was evident on the basis of "The Nitrogen Rule", the molecule contained an *even* number of nitrogens. Hence, structure **8** was tentatively assigned to the compound and was further confirmed by other spectroscopic methods, including CHN analysis. In the infrared spectrum, the product displayed a strong carbonyl absorption frequency at 1690 cm^{-1} which was indicative of a cyclic urea type of functionality [12]. The ^1H nmr spectrum of the product included two doublets at δ 7.55 and 6.35, assigned to two vinylic protons, and a multiplet between δ 7.45-7.15, allocated to 14 aromatic protons. Most

Scheme 3

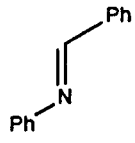
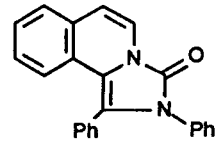
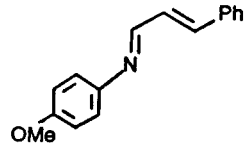
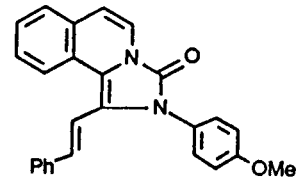
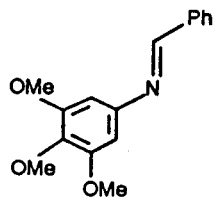
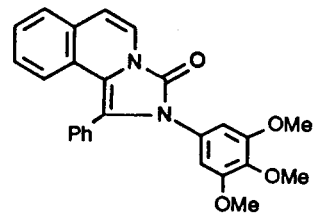
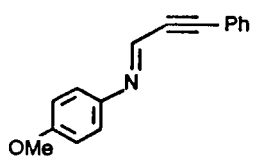
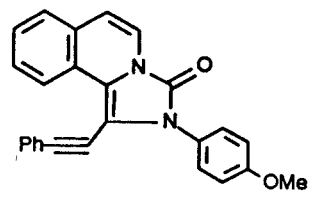


5a 8

likely, sodium methoxide generated during the reaction facilitated the elimination of hydrogen cyanide to give **8** (Scheme 3). The result was not surprising as similar base-catalyzed elimination reactions have been observed in other cyclic systems [6]. Analogously, reaction of **1** with other aldimines [13] provided a variety of imidazo[5,1-*a*]-isoquinolines in moderate yields [14] (Table 1).

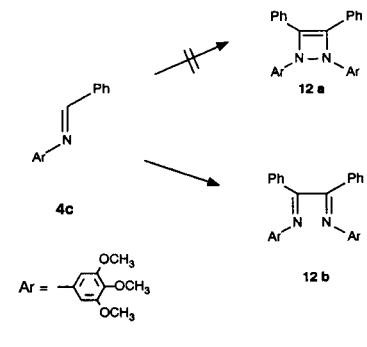
Reaction of **1** with *N*-benzylidene-3,4,5-trimethoxyphenylamine (**4c**) gave the expected cyclic diaza compound **10** along with 28% of a compound of molecular formula $C_{32}H_{32}N_2O_6$, which corresponded with the dimer of

TABLE 1

Entry	Reissert Analog	Imine	Imidazo[5,1-a]isoquinoline	Yield
1	1	 4a	 8	65%
2	1	 4b	 9	58%
3	1	 4c	 10	48%
4	1	 4d	 11	51%

4c. Imines often dimerize across C=N bonds to form four membered rings [15]. By anology, the probable structure would be 1,2-diazetidine **12a**, however, the spectroscopic evidence suggested an acyclic structure **12b** (Scheme 4). The mass spectrum of the compound exhibited a molecular ion peak at m/z 540 and a base peak at m/z 270 ($C_{16}H_{16}NO_3^+$). This fragmentation can readily be derived by the breakdown of the carbon-carbon bond in **12b**, rather than from 1,2-diazetidine system **12a**. The ^{13}C nmr spectrum of the product exhibited a prominent downfield signal at δ 165.1 which was assigned, unequivocally, to C=N moiety in **12b** [12]. Furthermore, in ^1H nmr, only one set of protons was observed which represented both monomers of the dimer.

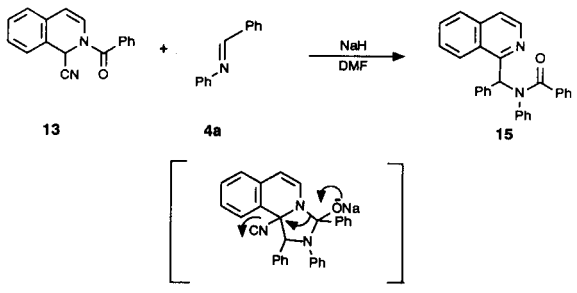
Scheme 4



The reaction of carbanion, obtained by the treatment of sodium hydride on Reissert compound **13**, with benzylide-

neaniline (**4a**) gave the expected addition product **15** *via* intermediate **14**. An important driving force in the reaction is the gain in resonance energy derived from the conversion of **14**, with its unstable cyclic hemiaminal, to the fully aromatic isoquinoline derivative (Scheme 5).

Scheme 5



13 4a 15

14

In summary, the chemistry demonstrates a new approach to the synthesis of imidazo[5,1-*a*]isoquinoline ring systems from Reissert analog. Reissert chemistry is applicable to a wide variety of heterocyclic bases, hence, this methodology is not limited to isoquinoline ring system but could certainly be directed to various mono and diaza-heterocyclic systems.

EXPERIMENTAL

The nmr data were obtained as deuteriochloroform solutions on a Varian FT-80 or XL-300 spectrometer and chemical shifts are reported in parts per million (ppm) relative to internal tetramethylsilane. Infrared spectra were obtained on a Beckmann IR-32 spectrophotometer as chloroform solutions. Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Electron impact mass spectra (eims), chemical ionization mass spectra (cims) and high resolution mass spectra (hrms) were recorded on a varian CH-5 or Ribermag R-10-10 spectrometer by Dr. Charles Judson and Mr. Robert Drake. Microanalyses were obtained on a Hewlett-Packard model 185 CHN analyser by Mr. Tho I. Nguyen at the University of Kansas. All reactions requiring anhydrous conditions were performed under a positive atmosphere of nitrogen or argon in oven-dried glassware. Chromatographic separations were performed by flash chromatography [16] on Baker silica gel (400-230). Thin layer chromatographic (tlc) comparision were done on Eastman Kodak silica gel plates with fluorescent indicator no-13181.

2-Carbmethoxy-1-cyano-1,2-dihydroisoquinoline (**1**).

The analog of the Reissert compound was prepared according to the literature procedure, ref [6a]; ^{1}H nmr: δ 3.78 (s, 3 H), 6.12 (d, J = 7.1 Hz, 1 H), 6.80-7.55 (m, 6 H); ^{13}C nmr: 45.97, 46.42, 54.27, 109.06, 116.72, 123.72, 124.35, 125.73, 126.45, 128.13, 130.07, 152.74.

Preparation of Aldimines **4a-d**.

The aldimines utilized in this study were synthesized according to the standard procedures [11]. A typical procedure is as follows: To a stirred solution of freshly distilled aldehyde (1.00 mmole) in dry ether or methylene chloride, at room temperature, was added as a 50% solution of amine in a appropriate solvent (1.00 mmole). The solution was stirred at room temperature for 8-12 hours. After completion of the reaction, as indicated by tlc, the solvent was concentrated *in vacuo*. The crude imine precipitated out and was further purified by crystallization.

N-Benzylideneaniline (**4a**).

This compound was prepared from benzaldehyde and aniline, yield 93% (crystallized from ether/hexanes); ^{1}H nmr: δ 7.05-7.95 (m, 10 H), 8.35 (s, 1 H).

N-(Cinnamylidene)-*p*-anisidine (**4b**).

This compound was prepared from *trans*-cinnamaldehyde and *p*-anisidine, yield 98% (crystallized from ether); ^{1}H nmr: δ 3.80 (s, 3 H), 6.75-7.51 (m, 11 H), 8.25 (t, J = 4.5 Hz, 1 H).

N-Benzylidene-3,4,5-trimethoxyphenylamine (**4c**).

This compound was prepared from benzaldehyde and 3,4,5-trimethoxyphenylamine, yield 76% (crystallized from ether/heptane); ^{1}H nmr: δ 3.90 (s, 9 H), 6.42 (s, 2 H), 7.45 (s, 3 H), 7.83 (s, 2 H), 8.42 (s, 1 H).

N-2-(2-Phenylpropynlidene)-*p*-anisidine (**4d**).

This compound was prepared from 3-phenyl-2-propyn-1-al and *p*-anisidine, yield 63% (crystallized from ether/hexanes); ^{1}H nmr: δ 3.70 (s, 3 H), 6.50-7.55 (m, 9 H), 7.85 (s, 1 H).

Reaction of 2-Carbmethoxy-1-cyano-1,2-dihydroisoquinoline (**1**) with Aldimines **4a-d**.

General Procedure.

To a stirred suspension of sodium hydride (98%) (1.00 mmole) in dry dimethylformamide (5.0 ml) was added **1** (1.00 mmole) at 0°. The solution was stirred for 5 minutes at 0° and an additional 10 minutes at 10°. To the red colored solution was added, dropwise, the appropriate imine (1.00 mmole) in dimethylformamide (1.0 ml) over a period of 10-15 minutes. The mixture was stirred at room temperature for 2-5 hours before quenching into 50 ml of ice-water. The aqueous layer was extracted with ethyl acetate (3 x 10 ml), washed with brine (1 x 5 ml), hydrochloric acid (5%, 1 x 5 ml), dried (magnesium sulfate), and evaporated to give a dark colored oil. The crude oil was purified by flash chromatography using 30-50% ethyl acetate in hexanes as eluents.

1,2-Diphenylimidazo[5,1-*a*]isoquinolin-3-one (**8**).

This compound was obtained in a yield of 65% (recrystallized from 95% ethanol, obtained as yellow needles), mp 202-203°; ir: 1690 cm^{-1} (C=O); ^{1}H nmr: δ 6.35 (d, J = 7.5 Hz, 1 H), 7.15-7.45 (m, 14 H), 7.55 (d, J = 7.5 Hz, 1 H); hrms: $C_{23}H_{16}N_2O$ requires m/z 336.12617; Found: 336.12660.

Anal. Calcd. for $C_{23}H_{16}N_2O$: C, 82.15; H, 4.76; N, 8.34. Found: C, 82.40; H, 4.95; N, 8.10.

1-(2-Phenylethenyl)-2-(4-methoxyphenyl)imidazo[5,1-*a*]isoquinolin-3-one (**9**).

This compound was obtained in a yield of 58% (recrystallized from 95% ethanol, obtained as yellow crystals), mp 160-161°; ir: 1690 cm^{-1} (C=O); ^{1}H nmr: δ 3.80 (s, 3 H), 6.25-6.50 (m, 2 H),

6.85-7.05 (m, 2 H), 7.10-7.55 (m, 13 H); hrms: $C_{26}H_{20}N_2O_2$ requires m/z 392.15236; Found: 392.1527.

Anal. Calcd. for $C_{26}H_{20}N_2O_2$: C, 79.57; H, 5.14; N, 7.14. Found: C, 79.57; H, 5.40; N, 6.90.

1-Phenyl-2-(3,4,5-trimethoxyphenyl)imidazo[5,1-*a*]isoquinolin-3-one (**10**).

This compound was obtained in a yield of 48% (recrystallized from ethyl acetate/hexanes, obtained as yellow plates), mp 206-207°; ir: 1690 cm^{-1} (C=O); ^1H nmr: δ 3.55 (s, 6 H), 3.75 (s, 3 H), 6.35 (s, 2 H), 6.85-7.60 (m, 11 H); hrms: $C_{26}H_{22}N_2O_4$ requires m/z 426.1578; Found: 426.1582.

Anal. Calcd. for $C_{26}H_{22}N_2O_4$: C, 73.22; H, 5.20; N, 6.57. Found: C, 73.40; H, 5.20; N, 6.20.

Also isolated was 28% of **12b** mp 237-238°; ir: 1500, 1585, 1455, 1410, 1330, 1230, 1130 cm^{-1}; ^1H nmr: δ 3.40 (s, 12 H), 3.75 (s, 6 H), 5.75 (s, 4 H), 7.42 (m, 6 H), 7.95 (m, 4 H); eims: m/z 542 (M^+).

Anal. Calcd. for $C_{32}H_{34}O_6N_2$: C, 70.83; H, 6.32; N, 5.16. Found: C, 70.86; H, 6.40; N, 5.30.

1-(2-Phenylethynyl)-2-(4-methoxyphenyl)imidazo[5,1-*a*]isoquinolin-3-one (**11**).

This compound was obtained in a yield of 51% (recrystallized from methylene chloride/heptane, obtained as light yellow plates), mp 188-189°; ir: 1690 cm^{-1} (C=O); ^1H nmr: δ 3.80 (s, 3 H), 6.45 (d, J = 8.7 Hz, 1 H), 7.05 (d, J = 8.7 Hz, 1 H), 7.20-7.75 (m, 13 H); hrms $C_{26}H_{18}N_2O_2$ requires m/z 390.13672; Found: 390.13664.

2-Benzoyl-1-cyano-1,2-dihydroisoquinoline (**13**).

The compound was prepared according to the literature procedure [17].

N-Benzoyl-*N*-phenyl-2-(1-isoquinolyl)benzylamine (**15**).

To a stirred solution of **13** (390 mg, 1.5 mmoles) in dry dimethylformamide (3.0 ml) at 0° was added sodium hydride (98%) (36 mg, 1.5 mmoles) and the solution was stirred for 15 minutes. To the red colored solution was added **4a** (326 mg, 1.8 mmoles) in dimethylformamide (0.3 ml) over a period of 10 minutes and the reaction mixture was stirred at room temperature for 2.0 hours. The reaction was quenched into 50 ml of ice-water and the *p*H of the solution adjusted to 7. Immediately, a white colored solid precipitated out which was filtered and washed with water. Recrystallization from 95% ethanol gave 447.12 mg (72%) of pure **15**, mp 180-181°; ir: 1630 cm^{-1} (C=O); ^1H nmr: δ 6.75-8.20 (m, 21 H), 8.55 (d, J = 6.25 Hz, 1 H); eims: m/z 414 (M^+).

Anal. Calcd. for $C_{29}H_{22}N_2O$: C, 84.07; H, 5.31; N, 6.76. Found: C, 83.95; H, 5.60; N, 7.00.

Acknowledgement.

The author wishes to express his thanks to Professor Gunda I. Georg of University of Kansas for providing laboratory facilities to support the investigation.

REFERENCES AND NOTES

[1] Dedicated to Professor Frank Popp (University of Missouri-Kansas City), my mentor, on the occasion of his 58th birthday.

[2] All correspondance should be addressed to the author at his present address: Chemical Process Development, Bristol-Myers Squibb Company, P.O. Box 4755, Syracuse, NY 13221.

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