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Modern Friedel–Crafts chemistry. Part 36. Facile synthesis of some new pyrido[3,2,1-*jk*]carbazoles *via* Friedel–Crafts cyclialkylations

HASSAN ABDOU KOTB ABD EL-AAL* and ALI ALI KHALAF

Chemistry Department, Faculty of Science, Assiut University, Assiut, 71516, Egypt

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Abstract: An efficient methodology for the synthesis of novel substituted pyrido[3,2,1-*jk*]carbazoles *via* Friedel–Crafts cyclialkylations is reported. The methodology was realized by a three-step protocol involving the addition of carbazole to 3-methylcrotononitrile. The resulting nitrile was subjected to alcoholysis to the desired ester, followed by addition of Grignard reagents to afford tertiary alcohols and/or reacted directly with different Grignard reagents to form the desired ketones. The latter ketones were converted to both secondary and tertiary alcohols by reduction with lithium aluminum hydride (LAH) and addition of Grignard reagents, respectively. These alcohols were cyclialkylated under Friedel–Crafts conditions catalyzed by $AlCl_3/CH_3NO_2$, *p*-toluenesulfonic acid (PTSA) or polyphosphoric acid (PPA) to give tri- and tetra-substituted pyrido[3,2,1-*jk*]carbazoles.

Keywords: Friedel–Crafts cyclialkylation; pyrido[3,2,1-*jk*]carbazole; heteropolycycles; heteroarylalkanols; carbocations.

INTRODUCTION

Synthesis of heteropolycycles containing pyrido[3,2,1-*jk*]carbazole scaffold is of interest because they are the core subunit often found in the heterocyclic skeleton of many natural products,[1] optoelectronics applications,[2] dye-sensitized solar cells (DSCs),[3] photochromic dyes[4] and were designed as vital precursors in the synthesis of many biologically active carbazole alkaloids.[5] Moreover, some derivatives are of interest in biomedical and pharmacological applications.[6]

A limited number of synthetic methodologies have been developed for the synthesis of pyrido[3,2,1-*jk*]carbazole derivatives. Among these synthetic approaches described in literature are the thermal condensations of malonates with carbazole,[7] Diels–Alder reaction of vinylindoles,[8] photolysis of *N*-aryltetrahydroquinolines,[9] dimerization of *N*-vinylcarbazole,[10] Fisher reaction of tetrahydro-

* Corresponding author. E-mail: hassankotb33@yahoo.com
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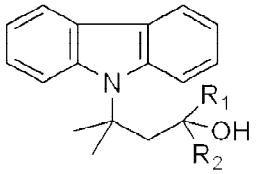
quinolines[11] and *via* intermolecular [4+2] cycloaddition of benzotriazoles with alkenes.[12]

Despite the numerous advances in the field of synthetic organic chemistry, the development of direct, concise and economic methods is currently a popular research area and has always been an attractive and challenging area for both medicinal and synthetic chemists. Among these methods, intramolecular Friedel–Crafts reaction (called cyclialkylations)[13–19] promoted by both Brönsted and Lewis acid catalysts is promising as a powerful tool offering considerable opportunities for synthetic manipulations.

In recent years, a part of our Friedel–Crafts research was devoted to the development of facile routes to approach the construction of novel bi- and higher heterocyclic systems. The previous paper of this series[19] described the synthesis of seven substituted nitrogen and nitrogen–sulfur polycycles containing fused carbazole, tetrahydrocarbazole, quinoline, tetrahydroquinoline, acridine, phenothiazine and indole moieties *via* Friedel–Crafts cyclialkylations of the corresponding heteroarylalkanols.

In connection with previous studies, herein the facile synthesis of nine unrecorded 5,6-dihydro-4*H*-pyrido[3,2,1-*jk*]carbazole derivatives *via* intramolecular cyclialkylations of suitable synthesized alcohols **1a**–**i** (Scheme 1) is described.



1 a-i

	R_1	R_2		R_1	R_2
a	Me	Me	**f**	Ph	Me
b	Et	Et	**g**	Me	H
c	Ph	Ph	**h**	Et	H
d	Me	Et	**i**	Ph	H
e	Et	Ph			

Scheme 1. Heteroarylalkanols **1a**–**i**.

RESULTS AND DISCUSSION

Synthesis of the starting alcohols

The requisite precursor 3-(9*H*-carbazol-9-yl)-3-methylbutanenitrile (**4**) was readily obtained by refluxing a solution of 3-methylcrotononitrile (**3**) and carbazole (**2**) in dioxane in the presence of a catalytic amount of triton B. Ethanolysis of **4** gave ethyl 3-(9*H*-carbazol-9-yl)-3-methylbutanoate (**5**), which was converted to tertiary alcohols **1a**–**c**, by reaction with two equivalents of the corresponding Grignard reagent.[20]

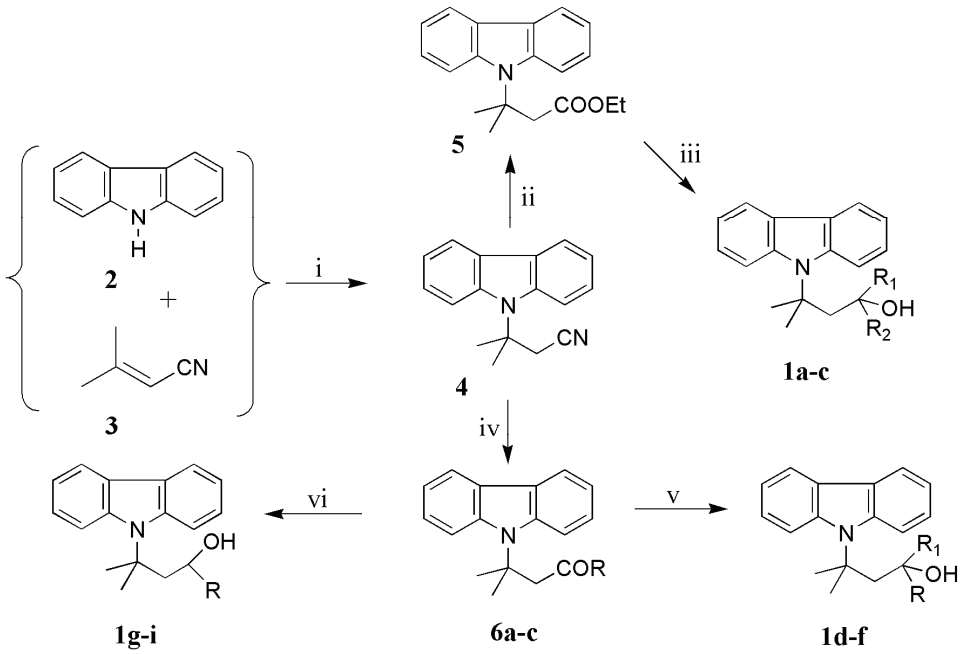
Furthermore, reaction of **4** with one equivalent of Grignard afforded ketones **6a**–**c** which were successively converted to the respective tertiary alcohols **1d**–**f** by reaction with one equivalent of the corresponding Grignard reagent and to secondary alcohols **1g**–**i** by reduction with LAH[21] The structures of all new al-

cohols were appropriately established by the usual spectroscopic methods. The results are presented in Table I and Scheme 2.

TABLE I. Synthesis of heteroarylalkanols **1a**–**i**

Entry	Substrate	R_1	R_2	Conditions[a]	Product	m.p. / °C (n_D^{25})	Yield[b] %
1	**5**	Me	Me	MeMgI, Et_2O, rt, 10 h	**1a**	122	86
2	**5**	Et	Et	EtMgBr, Et_2O, rt, 12 h	**1b**	115	92
3	**5**	Ph	Ph	PhMgBr, Et_2O, 40 °C, 12 h	**1c**	(1.542)	84
7	**6a**	Me	Et	EtMgBr, Et_2O, rt, 5 h	**1d**	(1.558)	85
8	**6b**	Et	Ph	PhMgBr, Et_2O, rt, 8 h	**1e**	112	83
9	**6c**	Ph	Me	MeMgI, Et_2O, rt, 6 h	**1f**	(1.538)	85
10	**6a**	Me	H	LAH, Et_2O, rt, 3 h	**1g**	(1.533)	84
11	**6b**	Et	H	LAH, Et_2O, rt, 2 h	**1h**	(1.536)	91
12	**6c**	Ph	H	LAH, Et_2O, rt, 3 h	**1i**	(1.541)	88

[a]All reactions were performed using 0.1 equivalent excess of RMgX and LAH, then calculated; [b]isolated yield referred to substrate



6a: R = Me; **6b**: R = Et; **6c**: R = Ph

Scheme 2. Synthesis of heteroarylalkanols **1a**–**i**; reagents and conditions: i) $BnMe_3NOH$, dioxane, 90 °C, 4 h, yield: 92.5 %, ii) EtOH, H_2SO_4, reflux 10 h, yield: 85.7 %, iii) 2RMgX, Et_2O, NH_4Cl solution, iv) RMgX, THF/Et_2O, HCl solution, v) RMgX, Et_2O, NH_4Cl solution and vi) LAH, Et_2O, room temperature (Table I).

The ^{1}H-NMR data allowed an unambiguous confirmation of the formation of the heterocyclic alkanols. Thus, the ^{1}H-NMR spectrum for alcohol **1a** displayed signals in which aromatic protons appeared at δ 7.0–7.9 ppm. The *gem*-dimethyls at C-2 and C-4 appeared as two singlets at δ 1.1 and 1.6 ppm, respectively. The third singlet at δ 2.1 ppm was assigned to the downfield CH_2 protons. A broad singlet appearing at δ 2.8 ppm was assigned to OH group. In all IR spectra, the characteristic peaks of carbonyl groups were absent. The characterization data for the synthesized compounds are given in the Supplementary material to this paper.

Cyclialkylation of heteroaryl alcohols

Cyclialkylations of alcohols **1a**–**i** were performed in the presence of $AlCl_3$/ /CH_3NO_2, polyphosphoric acid (PPA) and *p*-toluenesulfonic acid (PTSA) catalysts under varying conditions. Cyclialkylations of carbinols **1a**, **1b** and **1d**–**f** proceeded smoothly in the presence of $AlCl_3/CH_3NO_2$ for 2 h at room temperature to give the substituted 5,6-dihydro-4*H*-pyrido[3,2,1-*jk*]carbazoles **8a**, **8b** and **8d**–**f**. The results are embedded in Table II and Scheme 3.

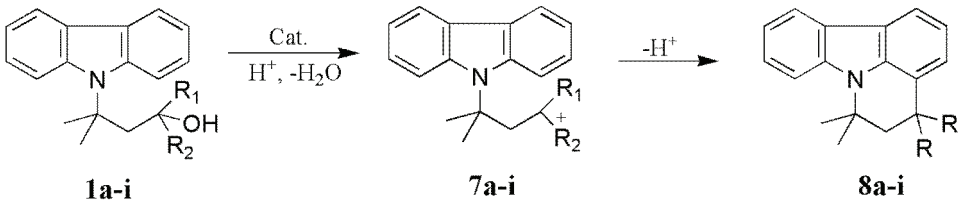
TABLE II. Cyclialkylation conditions and results for the heteroarylalkanols **1a**–**f**

Entry	Substrate	Catalyst	Product	Solvent	*t* / °C	Time, h	Yield[a], %
1	**1a**	$AlCl_3/CH_3NO_2$[b]	**8a**	DCM[c]	RT	2	82
2	**1a**	PPA[d]	**8a**	–	160	1	75
3	**1a**	PTSA[e]	**8a**	PhH	reflux	10	88
4	**1b**	$AlCl_3/CH_3NO_2$	**8b**	PE[f]	RT	2	81
5	**1b**	PPA	**8b**	–	160	1	73
6	**1c**	$AlCl_3/CH_3NO_2$	**8c**	DCM	RT	48	81
7	**1c**	PPA	**8c**	–	250	12	76
9	**1d**	$AlCl_3/CH_3NO_2$	**8d**	DCM	RT	2	79
10	**1d**	PPA	**8d**	–	160	2	74
11	**1e**	$AlCl_3/CH_3NO_2$	**8e**	PE	RT	2	84
12	**1e**	PPA	**8e**	–	160	2	74
13	**1e**	PTSA	**8e**	PhH	reflux	10	78
14	**1f**	$AlCl_3/CH_3NO_2$	**8f**	DCM	RT	4	80
15	**1f**	PPA	**8f**	–	160	4	76

[a]Isolated yield referred to substrate; [b]with $AlCl_3/CH_3NO_2$ catalyst reactant proportions were: alcohol (0.002 mol), $AlCl_3$ (0.0024 mol), CH_3NO_2 (0.024 mol), solvent (10 mL); [c]dichloromethane; [d]with PPA catalyst, the reactant proportions were: alcohol (0.5 g) and PPA (3 g); [e]with PTSA catalyst, the reactant proportions were: alcohol (0.5 g), PTSA (3 g) and solvent (10 mL); [f]petroleum ether (60–80 °C)

Intramolecular cyclization of alcohol **1c**, required more severe reaction conditions compared to its methyl-substituted analogs **1a**. Accordingly, the best results were *via* cyclialkylations of alcohol **1c** under more strenuous conditions in the presence of PPA for 12 h at 250 °C and with $AlCl_3/CH_3NO_2$ for 48 h in dichloromethane (DCM) solution at room temperature to yield 5,6-dihydro-

-6,6-dimethyl-4,4-diphenyl-4*H*-pyrido[3,2,1-*jk*]carbazole (**8c**) as the sole product (Scheme 3; Table II, Entries 6 and 7).



Scheme 3. Cyclialkylation of heteroarylalkanols **1a**–**i**.

Cyclialkylations of alcohols **1g**–**i** were performed in the presence of $AlCl_3$/ /CH_3NO_2, PPA and PTSA catalysts under different reaction conditions (Table III, Scheme 3). The closure step of the secondary alcohols required less strenuous reaction conditions than alcohol **1c**. Thus, upon treatment of such alcohols with acidic catalysts, the products were shown to be the tetracyclic amines **8g**–**i**.

TABLE III. Cyclialkylation conditions and results for heteroarylalkanols **1g**–**i**

Entry	Substrate	Catalyst	Product	Solvent	*t* / °C	Time, h	Yield, %
1	**1g**	$AlCl_3/CH_3NO_2$	**8g**	PE	RT	5	80
2	**1g**	PPA	**8g**	–	160	8	74
3	**1g**	PTSA	**8g**	PhH	reflux	15	83
4	**1h**	$AlCl_3/CH_3NO_2$	**8h**	DCM	RT	6	82
5	**1h**	PTSA	**8h**	PhH	reflux	15	80
6	**1h**	PPA	**8h**	–	160	8	75
7	**1i**	$AlCl_3/CH_3NO_2$	**8i**	PE	RT	4	79
8	**1i**	PPA	**8i**	–	160	6	76
9	**1i**	PTSA	**8i**	PhH	reflux	10	77

Examination of the data depicted in Tables II and III revealed the following significant points: *i*) most cyclialkylations could be easily achieved by $AlCl_3$/ /CH_3NO_2 in DCM and petroleum ether (60–80 °C) (PE) at room temperature, by PPA at 160 °C and by PTSA in benzene under reflux, *ii*) the only exception lies in the cyclialkylations of **1c** in which both R_1 and R_2 are phenyl groups. This reaction required much longer times with $AlCl_3/CH_3NO_2$ and much higher temperatures with PPA. Certainly, this is due to the development steric interactions exerted by both phenyls at the closure step. Similar steric observations were also noted in other reported cases.[13]

EXPERIMENTAL

Instrumentation

All reagents were purchased from Merck, Sigma or Aldrich Chemical Co. and were used without further purification. Melting points were measured on a digital Gallenkamp capillary melting point apparatus and are uncorrected. The IR spectra were recorded on a Shimadzu 470

infrared spectrophotometer using KBr wafer and thin film techniques. The ^{1}H-NMR spectra were recorded on Jeol LA 400 MHz FT-NMR (400 MHz) and Varian 90 MHz NMR spectrometers using $CDCl_3$ as the solvent with TMS as the internal standard. Elemental analyses were performed on a Perkin-Elmer 2400 Series II analyzer. The mass spectra were obtained using a JEOL JMS 600 spectrometer at an ionizing potential of 70 eV using the direct inlet system. Reactions were monitored by thin layer chromatography (TLC) using pre-coated silica plates and visualized with UV light. Flash column chromatography was performed on silica gel and basic alumina.

*Synthesis of 3-(9*H*-carbazol-9-yl)-3-methylbutanenitrile (**4**)*

An ice-cold solution of carbazole **2** (6.9 g, 40 mmol) and 3-methylcrotononitrile (**3**) (3.4 g, 42 mmol) in dioxane (30 mL) was treated with 0.7 ml of triton B. The reaction mixture was heated in a water bath for 5 h and then concentrated in *vacuo*. The pasty product was triturated with methanol (3×5 mL) and the resulting precipitate was filtered off, washed excessively with methanol and dried to yield 9.5 g (92.5 %) of the crude product. Crystallization from acetone gave (8.9 g, 86.6 %) of pure nitrile **4** in the form of white crystals.

*Synthesis of ethyl 3-(9*H*-carbazol-9-yl)-3-methylbutanoate (**5**)*

A mixture of 3-(9*H*-carbazol-9-yl)-3-methylbutanenitrile (**4**) (5 g, 20 mmol), absolute ethanol (40 mL) and 7 ml of concentrated sulfuric acid was refluxed for 10 h. Excess alcohol was then removed by distillation and the residue was diluted with cold water (50 mL), basified with Na_2CO_3 solution (20 mL, 30%) and extracted with ether (3×30 mL). The combined ethereal extracts were washed with water, dried over $MgSO_4$, filtered and finally concentrated to give 5 g (85.7 %) of crude oily ester. Purification by flash column chromatography (basic alumina, EtOAc/*n*-hexane, 2/3) gave 4.8 g (82.3 %) of pure **5** in the form of pale yellow oil.

*General procedure for the synthesis of heteroaryl ketones **6a–c***

A solution of nitrile **4** (2.5g, 10 mmol) in THF (20 mL) was added rapidly under stirring to an ice-cold Grignard reagent obtained as usual[20] from Mg turnings (0.3 g, 12 mmol) and alkyl or aryl halide (12 mmol) in diethyl ether (30 mL). After refluxing for 15 h, the mixture was poured into ice-cold hydrochloric acid (100 mL, 30 %) when the ketimine hydrochloride separated. The organic solvent was removed in *vacuo* and the cold aqueous mixture was filtered under suction. The resulting ketimine was then hydrolyzed by refluxing with a mixture of benzene, 20 mL; HCl, 10 mL; AcOH, 10 mL until the ketimine disappeared (7–9 h). The solution was cooled and the benzene layer was separated, while the aqueous layer was basified by addition of solid Na_2CO_3 under stirring and finally extracted with benzene (2×30 mL). The combined organic phases were washed with water, dried over anhydrous Na_2SO_4 and the solvent was evaporated *in vacuo* to afford the crude product that was purified by crystallization.

*General procedure for the synthesis of heteroaryl alcohols **1a–f***

To an ice-cold Grignard reagent solution obtained as usual[20] from Mg turnings (0.2 g, 8 mmol) and alkyl or aryl halide (8 mmol) in ether (25 mL), a solution of ester **5** (1.0 g, 3.6 mmol) and/or ketone **6a–c** (7.3 mmol) in ether (30 mL)was added. The reaction mixture was stirred at required temperature for appointed time (Table I) followed by decomposition with saturated NH_4Cl aqueous solution. The product was extracted with ether (3×20 mL) and combined organic phases were washed with water, dried over anhydrous Na_2SO_4 and the solvent was evaporated *in vacuo*. The residue was purified by flash column chromatography (basic alumina, EtOAc/*n*-hexane, 2/3), which gave the pure products **1a–f**.

*General procedure for the synthesis of heteroaryl alcohols **1g–i***

A solution of ketone **6a–c** (2.5 mmol) in anhydrous ether (15 mL) was added in 30 min to an ice-cold (0 °C) solution of LAH (0.10 g, 2.7 mmol)[21] in ether (15 mL). The reduction was complete after stirring for appointed time at defined temperature (Table I, TLC, 20% ethyl acetate/hexane). The cold reaction mixture was quenched at 0 °C by the sequential addition of water (2 mL), NaOH solution (10 mL, 20%) and water (10 mL). Then it was warmed to room temperature. Suction filtration removed the white precipitate of aluminum compounds, which were thoroughly triturated with ethyl acetate. The organic layer was separated, washed with water, dried over anhydrous Mg_2SO_4 and the solvent was evaporated *in vacuo* to afford crude alcohols **1g–i**. Purification of the crude products with flash column chromatography (basic alumina, EtOAc/*n*-hexane, 2/3) gave the pure products **1g–i**.

Friedel–Crafts cyclialkylations procedures

The procedures described earlier for cyclialkylation of heteroarylalkanols with $AlCl_3$/ /CH_3NO_2,[14] PTSA,[16] and PPA[19] were essentially followed and are mentioned below. In all reactions, the crude oily or solid products were purified by flash column chromatography (basic alumina, EtOAc/*n*-hexane, 1/1) giving the pure products **8a–i**. The conditions and yields for the products **8a–i** are presented in Tables II and III while the characterization data for the products are given in the Supplementary material to this paper.

Method A. Cyclialkylations using $AlCl_3/CH_3NO_2$ catalyst. To a solution of $AlCl_3$ (2.4 mmol) in CH_3NO_2 (24 mmol) was added a solution of alcohols **1a–i** (2.0 mmol) in DCM or PE (60–80 °C) (10 mL) dropwise under stirring over 10–15 min. The reaction mixture was further stirred for a certain time at room temperature and decomposed by careful addition of 10 % ice-cold hydrochloric acid solution (20 mL). The residue was extracted with diethyl ether (3×20 mL) and the combined organic phases were washed with 10 % Na_2CO_3, water and dried over anhydrous $MgSO_4$. The solvent was evaporated under reduced pressure to afford the crude products **8a–i**.

Method B. Cyclialkylations using PTSA catalyst. A solution of the carbinols **1a**, **1e** and **1g–i** (0.5 g) and PTSA (3 g) in dry benzene (10 ml) was refluxed for 10 h. After cooling to room temperature, the reaction mixture was diluted with ether (30 mL). The organic layer was separated, washed successively with a saturated solution of $NaHCO_3$, water and dried over $MgSO_4$. The solvent was evaporated under reduced pressure to afford the crude products **8a**, **8e** and **8g–i**.

Method C. Cyclialkylations using PPA catalyst. A stirred mixture of alcohols **1a–i** (0.5 g) and the PPA (3 g) was heated on an oil bath and kept at the required temperature for a certain time. Afterwards, the flask was cooled to room temperature and basified by addition of $NaHCO_3$ solution (25 ml, 30 %). The residue was extracted with diethyl ether (3×20 mL) and the combined organic phases were washed with water, dried over anhydrous Na_2SO_4 and the solvent was evaporated in *vacuo* to give the crude products **8a–i**.

CONCLUSIONS

In summary, a facile protocol was developed for the synthesis of nine new pyrido[3,2,1-*jk*]carbazole derivatives *via* the direct intramolecular Friedel–Crafts cyclization reaction of heteroarylalkanols (**1a–i**) catalyzed by $AlCl_3/CH_3NO_2$, PTSA or PPA. The simplicity of the processes, accessibility and moderate cost of the required substrates proved that Friedel–Crafts cyclialkylation could be considered as one of the most useful pathways to the synthesis of heteropolycycles.

SUPPLEMENTARY MATERIAL

Characterization data for the synthesized compounds are available electronically from http://www.shd.org.rs/JSCS/, or from the corresponding author on request.

ИЗВОД

УНАПРЕЂЕНА ФРИДЕЛ–КРАФТСОВА РЕАКЦИЈА. ДЕО 36. ЛАКА СИНТЕЗА НОВИХ ПИРИДО[3,2,1-*jk*]КАРБАЗОЛА ФРИДЕЛ–КРАФТСОВИМ ЦИКЛИАЛКИЛОВАЊЕМ

HASSAN ABDOU KOTB ABD EL-AAL И ALI ALI KHALAF

Chemistry Department, Faculty of Science, Assiut University, Assiut, 71516, Egypt

Приказана је ефикасна методологија синтезе нових супституисаних пиридо[3,2,1-*jk*]карбазола Фридел–Крафтсовим циклиалкиловањем. Поступак је реализован протоколом од три корака који укључују адицију карбазола на 3-метилкротононитрил. Новодобијени нитрил је подвргнут алкохолизи до жељеног естра, након чека су употребом Грињаревог реагенса добијени терцијарни алкохоли. Другим Грињаревим реагенсима нитрил је трансформисан у жељене кетоне који су редукцијом помоћу LAH или другим Грињаревим реагенсима преведени у одговарајуће секундарне или терцијарне алкохоле. Алкохоли су подвргнути реакцији циклиалкиловања под Фридел–Крафтсовим условима у присуству $AlCl_3/CH_3NO_2$, PTSA и PPA чиме су добијени три- и тетра-субституисани пиридо[3,2,1-*jk*]карбазоли.

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