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A New Approach to Synthesis of 3,3-Dialkyl-3,4-dihydroisoquinoline Derivatives

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ABSTRACT: *The synthesis of 3,3-dialkyl-3,4-dihydroisoquinolines via heterocyclization in three-component reaction of an activated arene with isobutyraldehyde and nitriles is described.* © 2004 Wiley Periodicals, Inc. Heteroatom Chem 15:486–493, 2004; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.20049

INTRODUCTION

Recent interest in the medicinal chemistry of partially hydrogenated isoquinoline alkaloids and their derivatives is first conditioned by high-biological activity of this class of heterocycles and their ubiquity in nature [1].

The Bishler–Napieralski reaction is of great importance in synthesizing 3,4-dihydroisoquinolines [2]. Numerous modifications of this reaction afford 1-substituted 3,4-dihydroisoquinolines with diverse substituents in the aromatic moiety of the molecule [3]. Due to recently developed methods, this type of synthesis is feasible even if electron-seeking groups such as halogens and a nitrogroup are present in the aromatic ring [4]. Compounds such as 1-substituted 3,4-dihydroisoquinolines with alkyl substituents at 3′ are rather poorly studied [5]. Methods for their synthesis have been developed and mostly published in Russian chemical journals by V. S. Shklyaev [6]. However, a few publications have lately appeared suggesting new approaches to the traditional isoquinoline synthesis, such as the synthesis of 3,3-dimethyl-3,4-dihydroisoquinoline-*N*-oxide, a potent preparation against septic and traumatic stresses [7]. Noteworthy, the author needed to use the N-activated modification of the Pickte–Spengler reaction as 2-methyl-3-phenyl-2-aminopropanes, being in a free form, gave isoquinolines in relatively low yields both in the Pickte–Spengler and in the Bishler–Napieralski reactions.

However, to obtain 3,4-dihydroisoquinoline derivatives by oxidation of tetrahydro-isoquinoline derivatives is nonpractical, and the Graaf–Ritter reaction seems to be the method of choice in this case. One of the first attempts to synthesize 1,3,3-trimethyl-3,4-dihydroisoquinoline [8] allowed the target product in low yield. V. S. Shklyaev and co-workers' contribution to the synthesis of 1-substituted 3,3-dialkyl-3,4-dihydroisoquinoline made

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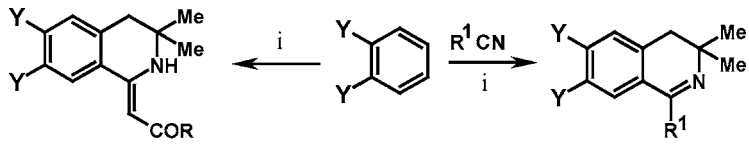


1 Y= OMe; **2** Y=Me

a: R^1 = Me, b: R^1 = SMe

c: R = OEt, d: R = NH_2

i: $(CH_3)_2CHCHO$, $NCCH_2COOEt$, H_2SO_4, 5–10 °C

SCHEME 1

it rather a routine procedure [9–12]. This method appeared to be suitable for synthesizing 1-alkyl-substituted 3,3-dialkyl-3,4-dihydroisoquinoline derivatives themselves as well as benzo[f]- and benzo[h]-3,4-dihydroisoquinolines and hexahydrophenanthridines [13–15].

The only disadvantage of the method is probably that organomagnesium synthesis is needed to obtain initial carbinol. This was overcome in a three-component "one-pot" synthesis from 1,2- or 1,4-dimethoxybenzenes, isobutylene oxide, and nitriles added in a 1:1:1 combination to concentrated H_2SO_4 [16]; however, isobutylene oxide is rather an expensive and toxic reagent.

We continue our studies of 3,3-dialkyl-3,4-dihydroisoquinolines [17], and here we report the synthesis of some novel derivatives.

RESULTS AND DISCUSSION

Basically, when isobutylene oxide is treated with sulfuric acid, isobutyraldehyde should be formed. Indeed, 3,3-dimethyl-3,4-dihydroisoquinoline derivatives could be readily synthesized by three-component condensation of activated arenes, isobutyraldehyde, and nitriles (Scheme 1).

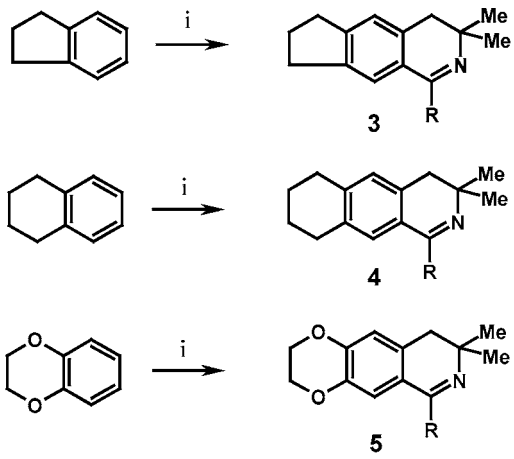
As for indan and tetralin, the reactions occurred in a similar way and resulted in products **3** and **4** (Scheme 2). No change in the reaction course was observed when benzdioxane was used as arene (^{1}H NMR, mp, formulas weight, and yields for all synthesized compounds, see Tables 1 and 2).

The effects of the aldehyde component were examined, and α-alkyl-substituted aldehyde was found to give readily 3,4-dihydroisoquinoline derivatives **6** and **7**, whereas propionic aldehyde led to 9,10-diethylanthracene **8** (Scheme 3).

The effects of the nitrile group were examined, and, as was determined, three-component synthesis occurred readily for benzyl nitrile and *p*-nitrobenzyl nitrile, acetonitrile, methylrhodane, cyanoacetic ester, cyanoacetamide, and chloroacetamide. This was not, however, true for benzyl cyanide or substituted benzyl cyanides, where the syntheses were more difficult.

Veratrole, isobutyraldehyde, and benzyl cyanide used in this reaction gave the reaction product, ^{1}H NMR spectrum of which lacked a proton signal of CH_2 benzene ring at C1, whereas its IR spectrum showed a 1600 cm^{-1} band characteristic of ketone carbonyl. MS-spectrum showed the peak of the molecular ion corresponding to 1-benzoyl-3,3,-dimethyl-3,4-dihydroisoquinoline **9** (Scheme 4).

Three-component condensation using 3,4-dimethoxybenzyl cyanide as the major reaction component led to the adduct of two molecules of the above nitrile and isobutyraldehyde (**10**), the Bayer reaction product (**11**), and ~15% isoquinoline (**12**), the latter containing a keto-group at C1 (Scheme 5).



i: $(CH_3)_2CHCHO$, $NCCH_2COOEt$, H_2SO_4, 5–10 °C

SCHEME 2

TABLE 1 Physical and Chemical Characteristics and Data Analysis for Synthesized Compounds

		Found, Calculated (%)				
	Molecular Formula	*C*	*H*	*N*	*mp (°C)*	*Yield (%)*
1a	$C_{14}H_{19}NO_2$	72.00, 72.10	8.30, 8.15	6.17, 6.01	148–150/12 mmHg	62
1b	$C_{14}H_{19}NO_2S$	63.49, 63.40	7.30, 7.17	5.00, 5.28	64–65 Hexane	51
1c	$C_{17}H_{23}NO_4$	66.70, 66.89	7.69, 7.54	4.50, 4.59	104–105 Hexane	60
1d	$C_{15}H_{20}N_2O_3$	65.10, 65.22	7.40, 7.35	10.01, 10.14	154–155 Ethylacetate	69
2a	$C_{21}H_{25}NO_3$ Salicylate	74.20, 74.34	7.45, 7.37	4.25, 4.13	150–151 Ethylacetate	33
2b	$C_{14}H_{19}NS$	72.22, 72.10	8.27, 8.15	5.88, 6.01	50–51 Hexane	43
2c	$C_{17}H_{23}NO_2$	74.61, 74.73	8.54, 8.42	5.00, 5.13	86–87 Methanol	54
2d	$C_{15}H_{20}N_2O$	73.89, 73.77	8.11, 8.20	11.53, 11.48	181–182 Ethylacetate	57
3a	$C_{22}H_{25}NO_3$ Salicylate	75.11, 75.19	7.20, 7.17	4.03, 3.99	155–157 Ethanol	32
3b	$C_{15}H_{19}NS$	73.51, 73.42	7.87, 7.80	5.63, 5.71	50,5–51,5 Hexane	50
3c	$C_{18}H_{23}NO_2$	75.70, 75.76	8.10, 8.12	5.00, 4.92	78–79 Hexane	26
3d	$C_{16}H_{20}N_2O$	75.02, 74.97	7.80, 7.68	10.84, 10.93	172–173 Ether–hexane	25
4a	$C_{23}H_{27}NO_3$ Salicylate	75.77, 75.62	7.31, 7.40	4.01, 3.84	150–151 Ethanol	43
4b	$C_{16}H_{21}NS$	74.30, 74.13	8.00, 8.11	5.55, 5.41	75–76 Hexane	59
4c	$C_{19}H_{25}NO_2$	76.41, 76.25	8.26, 8.36	4.51, 4.68	119–120 Hexane	67
4d	$C_{17}H_{22}N_2O$	75.71, 75.56	8.03, 8.15	10.49, 10.37	208–209 Ethylacetate	64
5a	$C_{14}H_{17}NO_2$	72.66, 72.70	7.53, 7.41	5.98, 6.06	97–98 Hexane-CH_2Cl_2	44
5b	$C_{14}H_{17}NO_2S$	63.80, 63.85	6.70, 6.51	5.45, 5.32	82–83 Methanol	35
5c	$C_{17}H_{21}NO_4$	67.17, 67.31	7.00, 6.98	4.50, 4.62	123–124 Ethylacetate	72
5d	$C_{15}H_{18}N_2O_3$	65.71, 65.68	6.59, 6.61	10.37, 10.21	212–214 Methanol	28
6c	$C_{20}H_{25}NO_4$	70.09, 69.95	7.46, 7.34	4.00, 4.08	126–128.5 Ethylacetate	58
7a	$C_{18}H_{27}NO_2$	74.73, 74.70	9.34, 9.40	4.89, 4.84	180–183 3 MM	39
7b	$C_{18}H_{27}NO_2S$	67.19, 67.25	8.53, 8.47	4.30, 4.36	198–205 3 mmHg	60
8	$C_{22}H_{26}O_4$	74.45, 74.55	7.31, 7.39	—	204–205 Hexane	98
9	$C_{20}H_{21}NO_3$	74.37, 74.28	6.60, 6.55	4.30, 4.33	133–135 Ethanol	40 73
12	$C_{22}H_{25}NO_5$	69.01, 68.91	6.44, 6.57	3.80, 3.65	174–176 Ethanol	15 74
13	$C_{20}H_{25}NO$	81.43, 81.31	8.48, 8.53	4.80, 4.74	107–109 Hexane	15
14	$C_{20}H_{21}NO$	82.33, 82.44	7.34, 7.26	4.96, 4.81	124–126 Heptane	13 75
17	$C_{18}H_{19}N$	86.73, 86.70	7.80, 7.68	5.72, 5.62	205–209[a] Ethylacetate	51
18	$C_{22}H_{25}NO_3$	75.23, 75.19	7.10, 7.17	4.07, 3.99	149–151 hexane	52
19	$C_{20}H_{23}N$	86.53, 86.59	8.44, 8.36	5.12, 5.05	210–211[a] Ethylacetate	55
20	$C_{20}H_{23}NO_2$	77.73, 77.64	7.60, 7.49	4.59, 4.53	209–211[a] Ethylacetate	56
21	$C_{18}H_{17}NO$	82.10, 82.10	6.51, 6.51	5.32, 5.32	160–163[a] Ethylacetate	75
23	$C_{13}H_{17}NO_3$	66.43, 66.36	7.40, 7.28	5.82, 5.95	232–234 Benzene	25
24	$C_{24}H_{29}NO_2$	79.41, 79.30	7.88, 8.04	3.72, 3.85	130–133[a] Ethylacetate	44

[a]mp hydrochloride.

Similar results were obtained for *ortho*-xylol, with some of the product **13** being formed in the reaction (Scheme 6).

Formally, the formation of **13** can be explained by the reaction of benzyl carbon cation **15** with a benzyl cyanide molecule; however, the reaction of xylol with isobutyraldehyde adduct and one molecule of benzyle cyanide **16** seems more likely (Scheme 7).

Syntheses of products by condensation of isobutyraldehyde and benzyl cyanide could be attributed to the enhanced (compared to acetonitrile, cyanoacetic ester, or methylrhodane) nucleophilic nature of the nitrile group of benzyl cyanide, and hence, isobutyraldehyde, in the protonated form, reacts rather with a nitrile group, but not with arene. In the case of homoveratric acid nitrile, the nitrile group is the main target for attack despite veratrole present and due to sufficiently increased nucleophilic reactivity of the nitrile group. To confirm this hypothesis, three-component condensation of dimethyl-(3,4-dimethyl)-benzyl carbinol with benzyl cyanide in the presence of phenylacetoacetonitrile was performed (Scheme 8).

In the reaction of benzyl cyanide with dimethylbenzyl carbinol for 15 min corresponding 1-benzyl-3,4-dihydroisoquinolines **17, 19, 20** were always formed and oxidized by the atmospheric O_2 in benzene to 1-benzoyl derivatives **12, 14**, and **21** (~75% yield, Scheme 9).

As phenylacetoacetonitrile synthesized readily 3,4-dihydroisoquinoline derivatives, we introduced nitriles of 2-phenylvalerianic acid (**21**) and 1-phenylcyclopentancarboxylic acid (**22**) in the reaction. With nitrile **21**, 3,3-dimethyl-6,7-dimethoxy-3,4-dihydro-isocarbostyryl **23** was found to be the

TABLE 2 ^{1}H NMR Data for Synthesized Compounds **1–24**

1a 1.13 (6H, s, gem-CH_3); 2.28 (3H, s, 1-CH_3); 2.55 (2H, s, 4-CH_2); 3.84 (6H, s, OCH_3); 6.58 (1H, s,5-H_{arene}); 6.93 (1H, s, 8-H_{arene})

1b Data see Ref. 18

1c 1.21 (6H, s, gem-CH_3); 1.24 (3H, t, $OCH_2\underline{CH_3}$ $J = 9$ Hz); 2.69 (2H, s, 4-CH_2); 3.83 (6H, s, 6,7-OCH_3); 4.10 (2H, q, OCH_2 $J = 10\Gamma\mu$); 4.98 (1H, s, H_{vinyl}); 6.55 (1H, s, 5-H_{arene}); 7.06 (1H, s, 8-H_{arene});

1d 1.23 (6H, s, 3-$(Me)_2$); 2.69 (2H, s, 4-CH_2); 3.65 (3H, s, 6-OMe); 3.84 (3H, s, 7-OMe); 5.03 (1H, s, CH-vinyl); 5.19 (2H, ddd C, NH_2); 6.61 (1H, s, 5-H); 7.04 (1H, s, 8-H); 9.74 (1H, br s, C, $NH_{isoquin}$).

2a 1.18 (6H, s, 3-$(Me)_2$); 2.24 (6H, s, 6,7-Me); 2.34 (3H, s, 1-Me); 2.68 (2H, s, 4-CH_2); 7.00–7.74 (6H, l.m, H-arene); 12.00 (1H, br s, OH_{phenol}).

2b 1.14 (6H, s, 3-$(Me)_2$); 2.24 (6H, s, 6,7-Me); 2.35 (3H, s, 1-SMe); 2.64 (2H, s, 4-CH_2); 7.00 (1H, s, 5-H); 7.32 (1H, s, 8-H).

2c 1.19 (3H, t, $CH_{3\,ester.}$); 1.23 (6H, s, 3-$(Me)_2$); 2.24 (6H, s, 6,7-Me); 2.74 (2H, s, 4-CH_2); 4.05 (2H, q, OCH_2); 5.03 (1H, s, CH-vinyl); 6.97 (1H, s, 5-H); 7.43 (1H, s, 8-H); 8.84 (1H, s, $NH_{isoquin}$).

2d 1.20 (6H, s, 3-$(Me)_2$); 2.23 (6H, s, 6,7-Me); 2.69 (2H, s, 4-CH_2); 5.08 (1H, s, CH-vinyl); 6.05 (2H, br s, NH_2); 6.92 (1H, s, 5-H); 7.33 (1H, s, 8-H); 9.38 (1H, br s, $NH_{isoquin}$).

3a* 1.26 (6H, s, 3-$(Me)_2$); 1.77 (4H, br s.,7-CH_2+8CH_2); 2.60 (3H,s, 1-Me); 2.77 (4H, br s, 6-CH_2+9CH_2); 2.77 (s, 2H, 4-CH_2); 6.75–7.75 (5,10H + 4H Sal)

3b 1.24 (6H, s, 3-$(Me)_2$); 1.76 (4H, br s,7-CH_2+8CH_2); 2.55 (3H,s,1-SMe); 2.75 (4H, br s., 6-CH_2+9CH_2); 2.75 (s, 2H, 4-CH_2); 6.90 (1H,s,5-H); 7.77 (1H,s,10-H)

3c 1.21 (6H, s, 3-$(Me)_2$); 1.19 (3H, t,$\underline{CH_3}$-CH_2O); 1.77 (4H, br s.,7-CH_2+8CH_2); 2.73 (4H, br s, 6-CH_2+9CH_2); 2.73 (s, 2H, 4-CH_2); 4.06 (2H, q,OCH_2); 5.03 (1H, s, CH_{vinyl}); 6.90 (1H,s, 5-H); 7.83 (1H,s,10-H); 8.88 (1H, s, NH)

3d 1.19 (6H, s, 3-$(Me)_2$); 1.77 (4H, br s, 7-CH_2+8CH_2); 2.72 (4H, br s.,6-CH_2+ 9CH_2); 2.69 (s, 2H, 4-CH_2); 5.08 (1H,s, CH_{vinyl}); 6.13 (2H, br s, NH_2); 6.86 (1H, s, 5-H); 7.57 (1H,s,10-H); 9.40 (1H,s, $NH_{isoquin}$)

4a 1.16 (6H, s, 3-$(Me)_2$); 2.06 (2H,m,7-CH_2); 2.32 (3H,s,1-Me); 2.61 (s, 2H, 4-CH_2); 2.86 (4H, qq., 6-CH_2 + 8-CH_2); 6.95 (1H,s,5-H);7.31 (1H,s,9-H)

4b 1.28 (6H, s, 3-$(Me)_2$); 2.13 (2H, m, 7-CH_2); 2.49 (3H, s, SCH_3); 2.72 (s, 2H, 4-CH_2); 2.96 (4H, q, 6-CH_2 + 8-CH_2); 7.05 (1H,s,5-H); 7.60 (1H,s,9-H)

4c 1.27 (6H, s, 3-$(Me)_2$); 1.30 (3H, t, $OCH_2\underline{CH_3}$); 2.11 (2H, m, 7-CH_2); 2.78 (s, 2H, 4-CH_2); 2.87 (4H, q, 6-CH_2 + 8-CH_2); 4.19 (2H, q, OCH_2); 5.14 (1H,s, H_{vinyl}); 7.00 (1H, s,5-H); 7.61 (1H,s,9-H); 8.99 (1H, br s, NH)

4d 1.23 (6H, s, 3-$(Me)_2$); 2.09 (2H, m, 7-CH_2); 2.76 (s, 2H, 4-CH_2); 2.89 (4H, t, 6-CH_2 + 8-CH_2); 5.00 (1H, s, H_{vinyl}); 5.07 (2H, br s, NH_2); 6.99 (1H,s,5-H); 7.46 (1H, s, 9-H); 9.51 (1H, br s, $NH_{isoquin}$)

5a 1.08 (6H, s, 3-$(Me)_2$); 2.19 (3H, s, Me); 2.47 (s, 2H, 4-CH_2); 4.25 (OCH_2CH_2O, 4H, m); 6.55 (1H, s,5-H); 6.90 (1H, s, 8-H)

5b 1.10 (6H, s, 3-$(Me)_2$); 2.32 (1 H, s, SMe); 2.49 (s, 2H, 4-CH_2); 4.17 (OCH_2CH_2O, 4H, m); 6.54 (1H,s,5-H); 7.11 (1H, s, 8-H)

5c 1.19 (3H, t, $J = 7.6$, Me); 1.20 (6H, s, 3-$(Me)_2$); 2.70 (s, 2H, 4-CH_2); 4.03 (2H, q, $J = 7.6$, OCH_2); 4.26 (OCH_2CH_2O, 4H, m); 4.94 (1H, s, =CH); 6.75 (1H,s,5-H); 7.19 (1H, s, 8-H); 8.90 (1H, s, NH)

5d 1.18 (6H, s, 3-$(Me)_2$); 2.60 (s, 2H, 4-CH_2); 4.20 (OCH_2CH_2O,4H, m); 4.82 (1 H, s, CH=) 4.85 (2 H, br s, NH_2); 6.55 (1H,s,5-H); 7.06 (1H, s, 8-H); 9.45 (1 H, s, NH)

6c 1.23 (3H, t, $J = 7.6$, Me); 1.35–1.58 (10H, m, $H_{cyclohexyl}$); 2.64 (s, 2H, 4-CH_2); 4.09 (2H, q, $J = 7.6$, OCH_2); 4.18 (OCH_2CH_2O,4H, m); 4.94 (1H, s, =CH); 6.56 (1H,s,5-H); 7.12 (1H, s, 8-H); 9.23 (1H, s, NH)

7a 0.79 (3H, t, $CH_{3\,alkyl}$); 0.80 (3H, t, $CH_{3\,alkyl}$); 1.17–1.53 (8H, lm, H_{alkyl}); 2.29 (3H, s, 1-CH_3); 2.53 (2H, s, 4-CH_2); 3.84 (6H, s, 6,7-MeO); 6.57 (1H, s, 5-H_{arene}); 6.92 (1H, s, 8-H_{arene}); 6.55 (1H, s, 5-H_{arene}); 7.08 (1H, s, 8-H_{arene})

7b 0.80 (6H, t, $CH_{3\,alkyl}$); 1.17–1.48 (8H, lm, H_{alkyl}); 2.36–2.29 (3H, s, 1-SCH_3); 2.53 (2H, s, 4-CH_2); 3.83 (6H, s, 6,7-MeO);

8 1.33 (6H, t, 2Me); 3.45 (4H, q, 2CH_2); 3.95 (12H, s, 2,3,6,7-OMe); 7.40 (4H, s, H-arene).

9 1.28 (3H, s, gem-Me); 2.74 (2H, s, 4-CH_2); 3.69 (3H, s, 6-OMe); 3.87 (3H, s,7-OMe); 6.65 (1H, s,5-H_{arene}); 6.77 (1H, s,8-H_{arene}); 7.41–7.99 (5H, m, H_{phenyl}).

12 1.25 (s,6H, gem-Me); 2.76 (s,2H, 4CH_2); 3.62–3.90 (m,12H, MeO); 6.73 (s,1H, 5H); 6.79 (s,1H, 8H); 7.05 (d,1H, 5′H); 7.51 (d,1H, 6′H), 7.54 (s, 1H, 2′-H)

13 0.69 (d, 6H, gem-Me); 1.78 (m, 1H, $Me_2\underline{CH}$); 2.12 (s, 3H, Me_{arene}); 2.19 (s, 3H, Me_{arene}); 3.51 (s, 2H, CH_2Ph); 4.60 (t, 0.5H, $\underline{CH}$-NH); 4.99 (t, 0.5H, $\underline{CH}$-NH); 5.95 (m, 1H, NH); 6.68–7.31 (m, 8H, H_{arene})

14 1.27 (s, 6H, gem-Me); 2.09 (s, 3H, 6-Me_{arene}); 2.20 (s, 3H, 7-Me_{arene}); 2.73 (s, 2H, 4-CH_2); 6.93 (d, 1H, 5-H_{arene}); 7.37–7.53 (m, 5H, H_{phenyl}); 7.97 (d, 1H, 8-H_{arene})

17 1.59 (s,6H, gem-Me); 2.14 (s,3H,6Me); 2.29 (s,3H,7Me); 2.86 (s,2H, 4CH_2); 4.70 (s,2H, $CH_{2\,benzyl}$); 7.00 (s,1H, 5H); 7.17–7.39 (m, 5H, H_{phenyl}); 7.56 (s,1H, 8H)

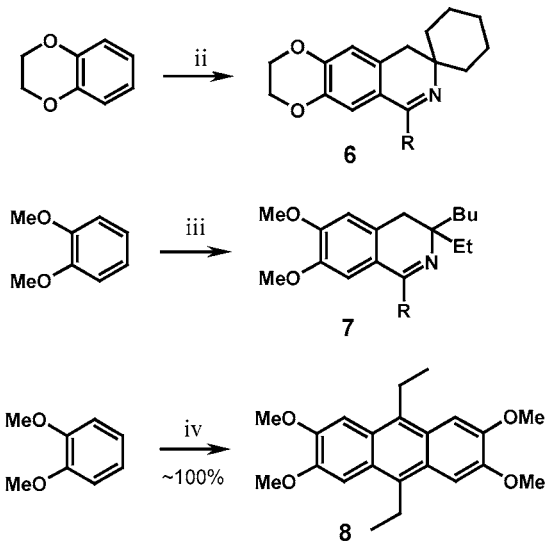
18 1.29 (s,6H, gem-Me); 1.94 (s,3H,Me_{Ac}); 2.75 (s,2H, 4CH_2); 3.12 (s,3H,6MeO); 3.85 (s,3H,7MeO); 6.28 (s,1H, 5H); 6.56 (s,1H, 8H); 7.18–7.31 (m,5H,H_{phenyl}); 13.01 (s,1H, NH)

19 1.62 (s,6H, gem-Me); 2.96 (s,2H,4CH_2); 4.76 (s,2H, CH_2 benzene); 7.15–7.39 (m, 7H, 5H 6H+H_{phenyl}); 7.58 (t,1H, 7H); 7.86 (d,1H, 8H)

20 1.60 (s,6H, gem-Me); 2.91 (c,2H, 4CH_2); 3.73 (s,3H, 6MeO); 3.90 (s,3H, 7MeO); 4.71 (s,2H, $CH_{2\,benzyl}$); 6.65 (s,1H, 5H); 6.77 (s,1H, 8H); 7.17–7.37 (m, 5H, H_{phenyl}); 14.83 (s,1H, HCl)

23 1.27 (s,6H, gem-Me); 2.80 (s, 2H, 4CH_2); 3.87 (s,6H, 6MeO 7MeO); 6.05 (br s.,1H, NH); 6.59 (s,1H, 5-H); 7.49 (s,1H, 8-H)

24 1.74–1.77 (m,10H, gem-Me + 2CH_2m.); 2.27 (m, 2H, CH_2m.); 2.76 (m, 2H,CH_2m); 2.89 (s, 2H, 4CH_2); 3.42 (s, 3H, 6MeO); 3.88 (s, 3H,7MeO); 6.66 (s,1H, 5H); 6.86 (s,1H, 8H); 7.21–7.52 (m, 5H,H_{phenyl})



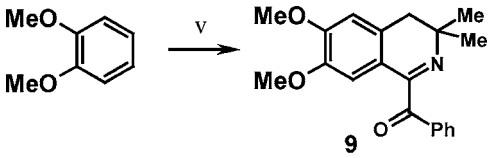
ii: cyclohexyl aldehyde, $NCCH_2COOEt$, H_2SO_4, 5–10 °C
iii: 2-ethylhexanale, $NCCH_2COOEt$ or methylrodane, H_2SO_4, 5–10 °C
iv: propionic aldehyde, RCN, H_2SO_4, 5–10 °C or propionic aldehyde only, H_2SO_4, 5–10 °C

SCHEME 3

only reaction product, whereas nitrile **22** gave the "normal" derivative **24**. Obviously, for nitrile **21**, the reaction proceeded via 1-(1′-butyl)-benzyl-3,3-dimthyl-6,7-dimethoxy-3,4-dihydroisoquinoline **25**, which was oxidized under the reaction conditions. Product **24** suggested significant influence of the possible imine–enamic tautomerism on C1—Cβ bond oxidation and, particularly, described by authors [12] conclusion on 1-butyl-substituted derivatives of 3,4-dihydroisoquinolne to be present solely in the imine form (Scheme 10).

CONCLUSIONS

Results obtained in this study show that three-component synthesis of 1-benzyl-substituted-3,3-dimethyl-3,4-dihydoisoquinoline depends significantly on the substituents at nitrile group, but does not virtually depend on the number of radicals at both position 3 and nitrile group.



v: $(CH_3)_2CHCHO$, benzyl cyanide, H_2SO_4, 5–10 °C

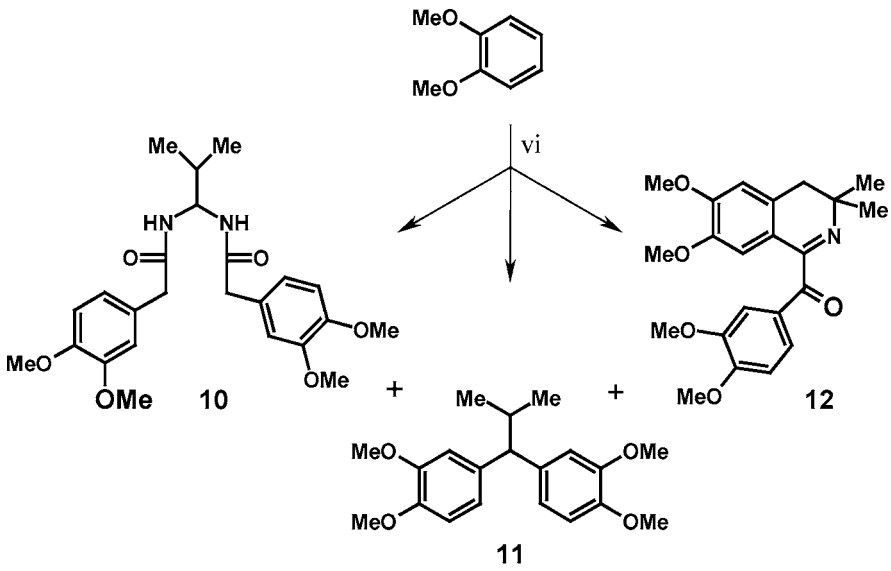
SCHEME 4

EXPERIMENTAL

Chemicals (reagent grade) and solvents were purchased from Aldrich or Merck and used as received. Melting temperatures were determined on PTP instrument and not corrected. IR spectra were recorded on UR-20 spectrophotometer in vaseline oil. ^1H NMR spectra were measured on a Bruker DRX-500 instrument (500.13 MHz) using TMS as internal standard. Mass-spectra were measured on a Finnigan MAT instrument under standard conditions (EI, 70 eV). The reaction course and the purity of the compounds were monitored by TLC on Silufol UV-254 plates in a chloroform–acetone (9:1) mixture using a 0.5% solution of chloronile in toluene for UV-visualization.

General Procedure for Synthesis of 1-Substituted 3,3-dimethyl-3,4-dihydroisoquinolines by Three-Component Condensation

A mixture of activated arene (0.1 mol), isobutyraldehyde (0.1 mol), and nitrile (0.1 mol) was added dropwise with stirring to concentrated H_2SO_4 (50 mL) for 15–20 min at 0–5°C. The mixture was stirred for 30 min, poured into water (300 mL) and extracted



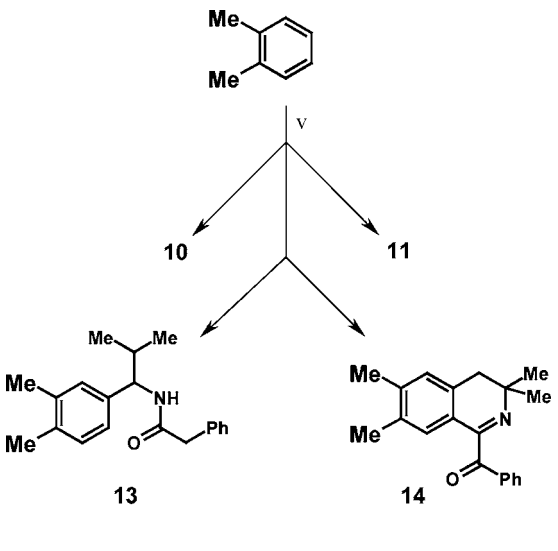
vi: $(CH_3)_2CHCHO$, 3,4-dimethoxybenzyl cyanide, H_2SO_4, 5–10 °C

SCHEME 5

with toluene (50 mL). An organic layer containing the Bayer reaction product was separated, and a water layer was basified by ammonium carbonate to pH 8–9. The precipitate was separated, washed with water, dried, and re-crystallized. In the case of oily substances, hydrochlorides were obtained. Compounds were dissolved in dry ester, and the precipitate was separated and re-crystallized from ethyl acetate.

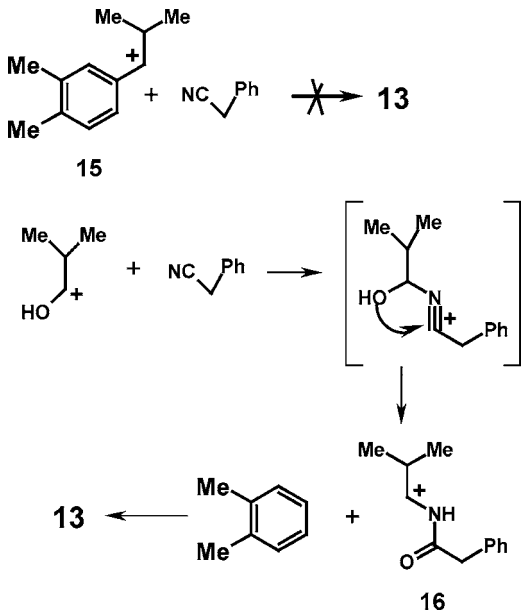
Synthesis of 1-Benzyl-3,3-dimethyl-3, 4-dihydroisoquinolines (General Procedure)

A mixture of a corresponding dimethylbenzyl carbonyl (0.1 mol) and benzyl cyanide (11.7 g, 0.1 mol) was added dropwise with stirring and cooling with water and ice to concentrated H_2SO_4(50 mL). The mixture was stirred for 15 min, poured into water

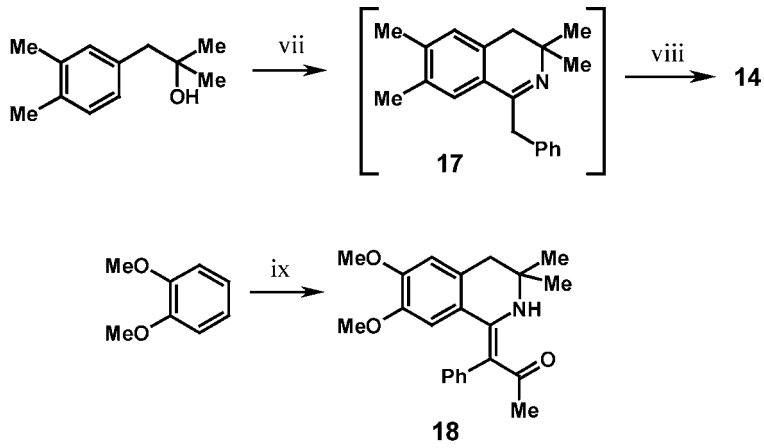


v: $(CH_3)_2CHCHO$, benzyl cyanide, H_2SO_4, 5–10 °C

SCHEME 6

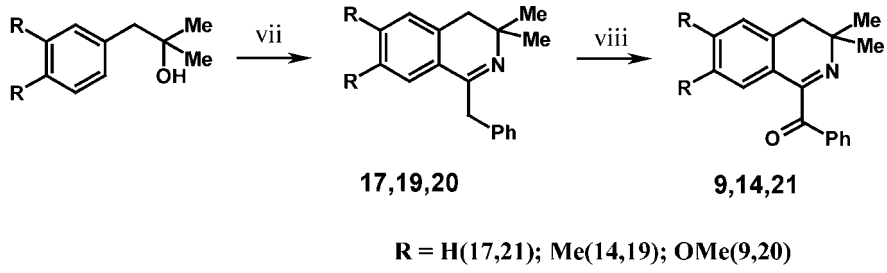


SCHEME 7



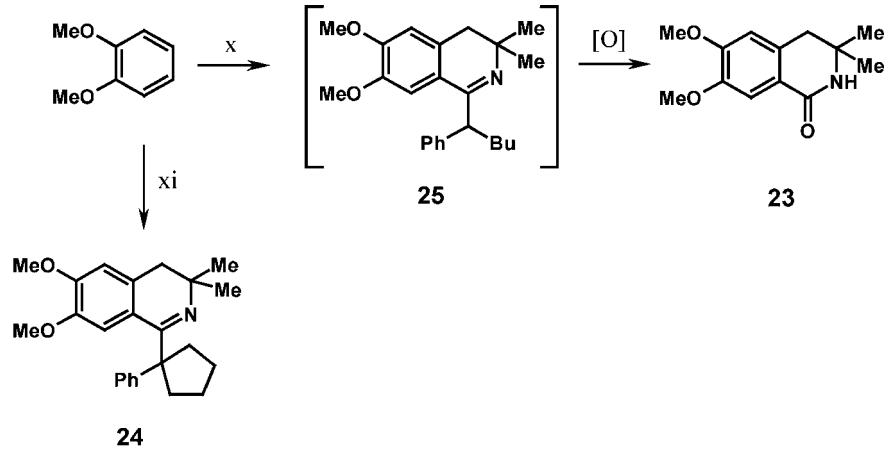
vii: benzyl cyanide, H_2SO_4, 5–10 °C
viii: air, benzene, reflux, 2 h
ix: phenylacetonitrile, H_2SO_4, 5–10 °C

SCHEME 8



vii: benzyl cyanide, H_2SO_4, 5–10 °C
viii: air, benzene, reflux, 2 h

SCHEME 9



x: 2-butylbenzyl cyanide, H_2SO_4, 5–10 °C
xi: 1-phenyl-cyclophenyl cyanide, H_2SO_4, 5–10 °C

SCHEME 10

(300 mL), and extracted with toluene (50 mL), and a water layer was basified by ammonium carbonate to pH 8. The precipitated oil was separated with methyltertbutyl ether (2 × 150 mL), dried over Na_2SO_4, and the solvent was removed on a rotary evaporator. The residue was dissolved in ester (150 mL) and exposed to dry HCL flow until the solution was completely transparent. The precipitate was re-crystallized from ethyl acetate.

General Procedure of Oxidation of 1-Benzyl-3,3-dimethyl-3,4-dihydroisoquinoline Derivatives

1-benzyl-3,3-dimethyl-3,4-dihydroisoquinoline (1 g) was dissolved in benzene (40 mL), and with heating and exposed to the air (flow) for 2 h. Major portion of isoquinoline was oxidized within approximately 40 min; the initial spot, however, disappeared completely from the TCL plate after ~2 h. Benzene was removed on a rotary evaporator, and the residue was re-crystallized from hexane. 1-benzoyl derivatives were obtained in 75% yield in the limits of the test error.

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