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Intramolecular Peterson olefination of *ortho*-trimethylsilylmethyl-*N*-acyl-*N*-alkylbenzamides. A new route to 2-alkyl-1(2*H*)isoquinolones

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Abstract

A variety of 2-alkyl-1(2*H*)isoquinolones has been efficiently synthesized by intramolecular Peterson olefination of *ortho*-trimethylsilylmethyl-*N*-acyl-*N*-alkylbenzamides.

Introduction

Reactions leading to the formation of carbon–carbon double bonds are of fundamental importance for organic chemists and a wide variety of synthetic methods has been developed for this purpose. A large number of strategies described in the literature involves an elimination reaction from β -heterosubstituted alcohols and alcoholates. The most extensively used reactions of this type are undoubtedly the Wittig reactions *via* β -alkoxyphosphorus derivatives [1–3] but an impressive number of important reactions has also been described with β -substituted alcoholates with varied patterns containing heteroatoms such as sulphur [4], selenium [5], and lead [6]. The Peterson olefination [7] reaction has also enriched the reaction repertoire and has received much attention since, besides being generally competitive with other similar reactions, this method is particularly useful in the synthesis of functionalized and strained alkenes [8]. This olefination procedure is the cumulative reaction of an α -silyl carbanion with a carbonyl compound to form a β -hydroxy silane, followed by the spontaneous elimination of the silyl and hydroxy leaving groups which leads to the ultimate formation of a carbon–carbon double bond.

Recently the Peterson olefination reaction, along with its inter- and intramolecular variant and its application to heterocyclic synthesis has been reviewed [7a] and in this article we wish to extend significantly the scope of this reaction to include the preparation of 3-substituted-2-alkyl-1(2*H*)isoquinolones (isocarbostyrls).

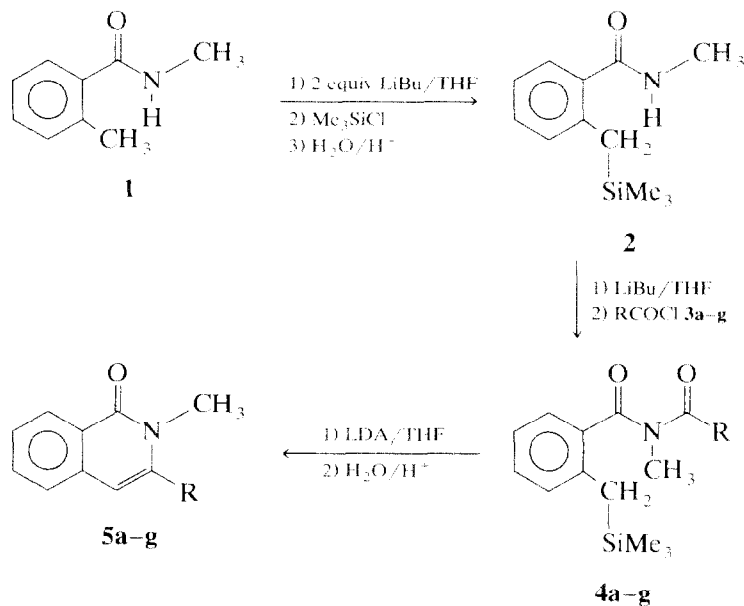
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These heterocyclic compounds are of increasing interest in pharmaceutical chemistry [9] and the isocarbostryl skeleton represents the common building block of a wide variety of benzo[*c*]phenanthridine alkaloids [10]. The numerous synthetic methodologies devised for the elaboration of this heterobicyclic framework generally involve the transformation of homophthalic acids [11], the condensation of the homophthalic anhydrides with imidates [12], the substitution reaction by primary amines on the corresponding isocoumarins [13] or the treatment of dilithiated *N*,2-dimethylbenzamides with *N*,*N*-dimethylcarboxamides [14]. Different photochemical methods have been also reported, such as ring enlargement and rearrangement of isoquinoline *N*-oxides [15], the arylation of halogenoisoquinolinones [16] or the $S_{RN}1$ reactions of *ortho*-halogenobenzamides with ketone enolates [17]. Our group has recently taken advantage of the hexatrienic character of various aromatic enamides to induce their photoelectrocyclic ring closure in neutral solvent [18] or in basic ethanolic solution [19] and thus give access to a variety of isoquinolones and dihydroderivatives previously inaccessible by classical methods. Different 3-substituted 1(2*H*)isoquinolones have been also prepared by treatment of dilithiated *N*,2-dimethylbenzamide with appropriate nitriles [20] but the method is restricted to *N*-unsubstituted compounds. A variety of aza-analogues of 2,3-disubstituted isoquinolones was also found to be accessible by acid hydrolysis of enaminnicotinamides [21].

Results and discussion

Our strategy consists of inducing the intramolecular cyclization of lithiated *ortho*-trimethylsilylmethyl-*N*-acyl-*N*-methylbenzamides (**4a–g**) (Scheme, Table I).

Initially *N*,2-dimethylbenzamide (**1**) was deprotonated with 2 mol equiv. of *n*-butyllithium in tetrahydrofuran (THF) at -60°C and subsequently treated with



Scheme 1.

Table 1
Properties of *ortho*-trimethylsilyl-*N*-methylbenzamide **2** and of its *N*-acyl derivatives **4a-g**

R	yield (%)	M.p. ^a (°C)	Anal. (Found (calcd.)) (%)				MS <i>m/z</i> (rel.int)	¹ H NMR (<i>J</i> in Hz) ^b
			C	H	N	Si		
2	92	95–96	65.20 (65.11)	8.60 (8.65)	6.46 (6.33)	12.50 (12.69)	221 (<i>M</i> ⁺ , 10), 220 (20), 206 (100)	δ 0.2 (s, 9H, CH ₃), 2.45 (s, 2H, CH ₂), 3.0 (d, <i>J</i> = 4.8, 3H, NCH ₃), 5.8 (m, 1H, NH), 7.0–7.4 (m, 4H, Ar) δ 0.2 (s, 9H, CH ₃), 2.1 (s, 2H, CH ₂), 3.5 (s, 3H, NCH ₃), 6.7–7.4 (m, 9H, Ar) δ 0.2 (s, 9H, CH ₃), 2.05 (s, 2H, CH ₂), 2.25 (s, 3H, CH ₃), 3.5 (s, 3H, NCH ₃), 6.8–7.2 (m, 8H, Ar)
4a	90	–	69.95 (70.11)	7.21 (7.12)	4.13 (4.30)	8.97 (8.63)	325 (<i>M</i> ⁺ , 6), 248 (60), 118 (100), 105 (83)	δ 0.2 (s, 9H, CH ₃), 2.1 (s, 2H, CH ₂), 3.5 (s, 3H, NCH ₃), 6.7–7.9 (m, 8H, Ar) δ 0.2 (s, 9H, CH ₃), 2.1 (s, 2H, CH ₂), 3.5 (s, 3H, NCH ₃), 3.75 (s, 3H, OCH ₃), 6.7–7.3 (m, 8H, Ar) δ 0.2 (s, 9H, CH ₃), 2.15 (s, 2H, CH ₂), 3.45 (s, 3H, NCH ₃), 3.75 (s, 3H, OCH ₃), 6.7 (d, <i>J</i> = 9, 2H, Ar), 6.9–7.3 (m, 4H, Ar), 7.4 (d, <i>J</i> = 9, 2H, Ar)
4b	86	–	70.58 (70.75)	7.56 (7.42)	4.01 (4.13)	8.39 (8.27)	339 (<i>M</i> ⁺ , 8), 248 (11), 119 (100)	δ 0.2 (s, 9H, CH ₃), 2.05 (s, 2H, CH ₂), 2.25 (s, 3H, CH ₃), 3.5 (s, 3H, NCH ₃), 6.8–7.2 (m, 8H, Ar)
4c	81	–	67.40 (67.57)	7.10 (7.09)	4.06 (3.94)	7.75 (7.90)	355 (<i>M</i> ⁺ , 18), 248 (92), 135 (100), 107 (48)	δ 0.2 (s, 9H, CH ₃), 2.1 (s, 2H, CH ₂), 3.5 (s, 3H, NCH ₃), 3.75 (s, 3H, OCH ₃), 6.7–7.9 (m, 8H, Ar) δ 0.2 (s, 9H, CH ₃), 2.1 (s, 2H, CH ₂), 3.5 (s, 3H, NCH ₃), 3.75 (s, 3H, OCH ₃), 6.7–7.3 (m, 8H, Ar)
4d	84	78–79	67.83 (67.57)	7.26 (7.09)	3.67 (3.94)	7.48 (7.90)	355 (<i>M</i> ⁺ , 7), 248 (15), 135 (100)	δ 0.2 (s, 9H, CH ₃), 2.1 (s, 2H, CH ₂), 3.5 (s, 3H, NCH ₃), 3.75 (s, 3H, OCH ₃), 6.7–7.3 (m, 8H, Ar) δ 0.2 (s, 9H, CH ₃), 2.15 (s, 2H, CH ₂), 3.45 (s, 3H, NCH ₃), 3.75 (s, 3H, OCH ₃), 6.7 (d, <i>J</i> = 9, 2H, Ar), 6.9–7.3 (m, 4H, Ar), 7.4 (d, <i>J</i> = 9, 2H, Ar)
4e	86	–	67.82 (67.57)	7.25 (7.09)	3.73 (3.94)	7.40 (7.90)	355 (<i>M</i> ⁺ , 6), 248 (9), 135 (100)	δ 0.2 (s, 9H, CH ₃), 2.15 (s, 2H, CH ₂), 3.45 (s, 3H, NCH ₃), 3.75 (s, 3H, OCH ₃), 6.7 (d, <i>J</i> = 9, 2H, Ar), 6.9–7.3 (m, 4H, Ar), 7.4 (d, <i>J</i> = 9, 2H, Ar)
4f	85	77–78	68.43 (68.44)	7.80 (7.66)	7.48 (7.60)	7.75 (7.62)	368 (<i>M</i> ⁺ , 8), 148 (100)	δ 0.2 (s, 9H, CH ₃), 2.0 (s, 2H, CH ₂), 2.95 (s, 6H, N(CH ₃) ₂), 3.40 (s, 3H, NCH ₃), 6.45 (d, <i>J</i> = 9, 2H, Ar), 7.0–7.25 (m, 4H, Ar), 7.45 (d, <i>J</i> = 9, 2H, Ar)
4g	87	64–65	72.01 (71.75)	7.17 (7.17)	3.79 (3.98)	8.43 (7.99)	351 (<i>M</i> ⁺ , 2), 260 (41), 220 (36), 206 (100)	δ 0.2 (s, 9H, CH ₃), 2.2 (s, 2H, CH ₂), 3.27 (s, 3H, NCH ₃), 6.7 (d, <i>J</i> = 15.5, 1H, CH=), 7.15–7.3 (m, 9H, Ar), 7.6 (d, <i>J</i> = 15.5, 1H, =CH)

^a Uncorrected. ^b 80 MHz (CDCl₃ solution).

chlorotrimethylsilane (2 mol equiv.) at the same temperature. Classical acidic work-up furnished solely the *ortho*-trimethylsilylmethyl-*N*-methyl benzamide **2**. Due to the presence of two deprotonation sites in **2**, the exclusive deprotonation of the amide function in **2** was effected by adapting a recently reported procedure for the titration of organolithium reagents [22]. Thus, an accurately controlled amount of *n*-butyllithium was added to a solution of **2** in THF at -60°C until the appearance of a red-wine colour signifying the formation of the α -silyl benzylic carbanion and thus indicating the NH deprotonation end-point.

Different carboxylic acid chlorides **3a–g** were then added, leading to the expected *ortho*-trimethylsilylmethyl-*N*-acyl-*N*-methylbenzamides **4a–g** in nearly quantitative yields.

After experimenting with a variety of conditions and methods it was found that the best result for the ultimate cyclization step which gives rise to the cyclocondensation products **5a–g** was obtained by use of lithium diisopropylamide (LDA) as the base in THF at -60°C . The yields were not noticeably improved by applying the different procedures recommended for the preparation of phenylalkenes from benzyltrimethylsilane and carbonyl compounds (*n*-butyllithium/HMPT [23], *n*-butyllithium/TMEDA [24]). Results of a representative series of reactions are presented in Table 2, where it may be seen that this simple procedure generally affords high yields of 2-methyl-1(2*H*)isoquinolones with different patterns of substitution at position 3.

It is noteworthy that the metallation of unsilylated compounds under the same conditions also gives rise to annelation products, but the yields are noticeably inferior (*e.g.* 56% for **5e**) and they are generally accompanied by products arising from the basic cleavage of the starting *N*-acylamides.

In conclusion, the low-temperature intramolecular cyclization of carbanions of *ortho*-trimethylsilyl-*N*-acyl-*N*-alkylbenzamides offers a convenient and effective synthetic route to 2-alkyl-3-aryl-1(2*H*)isoquinolones. The reactions reported here significantly broaden the scope of the Peterson olefination reaction. The advantage of the incorporation of the trimethylsilylmethyl group for the synthesis of heterocyclic compounds has been already demonstrated, especially for the synthesis of *N*-methylindoles from *ortho*-trimethylsilylmethyl anilides [25]. The simplicity of the process, the availability of the starting materials, and the easy removal of undesired siloxane by-products by simple evaporation make this strategy a sensible choice.

Experimental

Preparation of ortho-trimethylsilylmethyl-N-methylbenzamide (2)

A commercial solution of *n*-butyllithium in hexane (1.6 *M*, 26.6 mL, 42 mmol) was slowly added at 0°C under Ar to a solution of *N*,2-dimethylbenzamide (**1**) (2.98 g, 20 mmol) in anhydrous THF (40 mL). The red mixture was stirred for 30 min, cooled to -60°C and transferred dropwise under Ar into a solution of Me_3SiCl (4.35 g, 40 mmol) in THF (20 mL) cooled to -60°C . The reaction mixture was stirred for an additional 30 min, warmed to room temperature, and finally hydrolyzed with dilute HCl. The aqueous layer was extracted twice with CH_2Cl_2 (2×30 mL) and the combined organic layers were then dried (MgSO_4). Removal

Table 2

Properties of 2-methyl-3-substituted-1(2*H*)isoquinolones **5a–g**

R	Yield (%)	M.p. ^a (°C)	Anal. (Found (calcd.) (%))				MS <i>m/z</i> (rel. int)	¹ H NMR ^b
			C	H	N	O		
5a C ₆ H ₅	70	62–63 ^c	–	–	–	–	235 (M ⁺ , 88), 234 (100), 178 (10)	δ 3.4 (s, 3H, NCH ₃), 6.45 (s, 1H, H-4), 7.25–7.6 (m, 8H, Ar), 8.45 (d, <i>J</i> = 7.5, 1H, H _{peri})
5b <i>o</i> -CH ₃ C ₆ H ₄	71	79–80	82.06 (81.90)	6.27 (6.06)	5.44 (5.62)	6.72 (6.42)	249 (M ⁺ , 42), 248 (32), 234 (26)	δ 2.2 (s, 3H, CH ₃), 3.3 (s, 3H, NCH ₃), 6.4 (s, 1H, H-4), 7.2–7.7 (m, 7H, Ar), 8.5 (d, <i>J</i> = 8, 1H, H _{peri})
5c <i>o</i> -CH ₃ OC ₆ H ₄	71	65–66	76.67 (76.96)	5.77 (5.70)	5.22 (5.28)	12.26 (12.06)	265 (M ⁺ , 100), 264 (56), 249 (15)	δ 3.4 (s, 3H, NCH ₃), 3.8 (s, 3H, OCH ₃), 6.45 (s, 1H, H-4), 6.9–7.55 (m, 7H, Ar), 8.5 (d, <i>J</i> = 9, 1H, H _{peri})
5d <i>m</i> -CH ₃ OC ₆ H ₄	69	98–99	76.76 (76.96)	5.70 (5.70)	5.35 (5.28)	12.21 (12.06)	265 (M ⁺ , 100), 264 (97), 249 (13)	δ 3.45 (s, 3H, NCH ₃), 3.85 (s, 3H, OCH ₃), 6.45 (s, 1H, H-4), 6.9–7.6 (m, 7H, Ar), 8.5 (d, <i>J</i> = 10, 1H, H _{peri})
5e <i>p</i> -CH ₃ OC ₆ H ₄	70	135–136 ^d	–	–	–	–	265 (M ⁺ , 90), 264 (100), 249 (11)	δ 3.45 (s, 3H, NCH ₃), 3.85 (s, 3H, OCH ₃), 6.4 (s, 1H, H-4), 7.05–7.55 (m, 7H, Ar), 8.45 (d, <i>J</i> = 8, 1H, H _{peri})
5f <i>p</i> -(CH ₃) ₂ NC ₆ H ₄	69	89–90	77.53 (77.67)	6.56 (6.52)	9.80 (10.06)	6.02 (5.75)	278 (M ⁺ , 100), 277 (80), 261 (10)	δ 3.05 (s, 6H, N(CH ₃) ₂), 3.5 (s, 3H, NCH ₃), 6.45 (s, 1H, H-4), 6.75–7.55 (m, 7H, Ar), 8.5 (d, <i>J</i> = 8, 1H, H _{peri})
5g styryl	65	118–119	82.63 (82.73)	5.82 (5.79)	5.29 (5.36)	6.27 (6.12)	261 (M ⁺ , 100), 260 (50), 184 (63)	δ 3.4 (s, 3H, NCH ₃), 6.5 (s, 1H, H-4), 6.8–7.9 (m, 10H, Ar + H _{styryl}), 8.35 (d, <i>J</i> = 8.5, 1H, H _{peri})

^a Uncorrected. ^b 80 MHz (CDCl₃ solution). ^c Ref. 26: 58–70. ^d Ref. 27: 136.

of the solvents furnished a crude solid (4.07 g, 92%) which was finally purified by recrystallization from hexane-toluene (Table 1).

Preparation of ortho-trimethylsilylmethyl-N-acyl-N-methyl benzamides (4a-g)

The monolithiated derivative of compound **2** was prepared by the dropwise addition with stirring under Ar at -60°C of *n*-butyllithium (1.6 M in hexane, 15 mmol, 9.5 mL) to a solution of **2** (3.3 g, 15 mmol) in THF (60 mL). This produced a colourless solution of the *N*-lithiated amide **2** and was immediately stopped when a drop of the solution of *n*-butyllithium gave an intense orange-yellow colour due to the formation of the dianion. The mixture was stirred at -60°C for 10 min and a solution of the appropriate carboxylic acid chloride **3a-g** (15 mmol) in 10 mL of THF was added dropwise at such a rate as to maintain the internal temperature below -50°C . The reaction mixture was stirred under Ar for an additional 30 min. The cooling bath was removed and the mixture was warmed to ambient temperature and stirred for 1 h. An aqueous NaHCO_3 solution was added and the organic layer separated. The aqueous solution was extracted with AcOEt (2×50 mL) and the combined organic layers were washed with water and dried (Na_2SO_4). Evaporation of the solvent furnished an oily product which was purified by column chromatography on silica gel using AcOEt/hexane (30:70) as eluent (Table 1).

Preparation of 2-methyl-3-aryl-1(2H)isoquinolones (5a-g)

A solution of LDA was prepared at -78°C by addition, with stirring and under Ar, of a solution of diisopropylamine (1.7 mL, 10 mmol) in 10 mL of THF to 6.3 mL of 1.6 M *n*-butyllithium in hexane diluted with 10 mL of anhydrous THF. The mixture was gently warmed to -30°C and a solution of compounds **4a-g** (10 mmol) in THF (10 mL) added dropwise. The reaction mixture was stirred at -30°C for 2 h, warmed to ambient temperature and treated with dilute HCl (10%). The aqueous phase was extracted twice with CH_2Cl_2 and the combined organic extracts were washed with water, dried (Na_2SO_4), and evaporated to give the desired isoquinolinones **5a-g**, which were finally purified by column chromatography on silica gel using a mixture AcOEt-hexane (40:60). The yields reported in Table 2 were determined before recrystallization in EtOH.

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