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A NEW SYNTHETIC ROUTE TO 2-METHYL-3-(ARYL OR ALKYL)-1-OXO-1,2-DIHYDROISOQUINOLINES *via* AN INTRAMOLECULAR WITTIG REACTION

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Abstract: *2-Methyl-3-(aryl or alkyl)-1-oxo-1,2-dihydroisoquinolines* **6a-g** *have been prepared via an intramolecular Wittig olefination reaction from the N-acyl-N-methyl-o-triphenylphosphoniomethylbenzamide bromides* **5a-g**.

Isoquinolinones (1-oxo-1,2-dihydroisoquinolines) are a class of fused heterocycles that are of increasing interest in pharmaceutical chemistry[1] and can be regarded as intermediates for the synthesis of isoquinoline and dihydroisoquinoline ring systems which display a large spectrum of biological activity.[2] The isocarbostyril skeleton is also a common building block of a wide variety of benzo[*c*]phenanthridine alkaloids.[3]

To date numerous processes for the elaboration of this heterobicyclic framework have been reported but few have demonstrated broad synthetic utility.[2] The classical synthetic routes involve the treatment of appropriate isocoumarins with alkylamines,[4] the reaction of dilithiated

N,2-dimethyl benzamides with *N*,*N*-dimethylcarboxamides,[5] the transformation of homophtalic acids[6] or the condensation of the homophtalic anhydrides with imidates.[7] Different synthetic photochemical approaches have also been reported such as the arylation of chloroisoquinolones,[8] the SRN_1 reactions of *o*-halogenobenzamides with ketone enolates[9] and the photolysis of isoquinoline *N*-oxides.[10] We recently reported a new methodology for the synthesis of diverse isoquinolinones and dihydro derivatives by photolysis of appropriate aromatic enamides in neutral solvent[11] or in basic ethanolic solution.[12] However these methods are rather restrictive, especially with regards to the eventual introduction of various substitution patterns in the six-membered heterocyclic moiety.

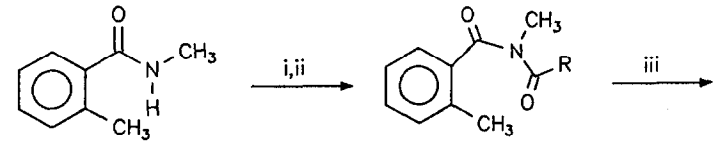
On the other hand, the Wittig reaction, considered as a condensation between a phosphorus ylide and a carbonyl compound giving rise to an olefin, undoubtedly represents one of the most synthetically useful chemical processes to the organic chemist. Indeed this olefination reaction with aldehydes and ketones[13] or a wide variety of carbonyl functions[14] has been amply reviewed. Recently, the applications to heterocyclic synthesis of intramolecular variants of the Wittig reaction have been reported and reviewed by Le Corre.[15] In this article, we wish to extend significantly the scope of these reactions to include the preparation of a series of 3-aryl-, heteroaryl- and alkyl-1-oxo-dihydroisoquinolines (isocarbostyrils) from previously unknown diacylamines.

Our strategy consists of inducing the intramolecular reaction between the triphenylmethylphosphonium bromide function and the terminal carbonyl moiety in the different diacylamines salts **5a-g** by appropriate basic treatment. These salts are efficiently prepared by alkylation of triphenylphosphine with the brominated compounds **4a-g**, readily accessible from the corresponding *N*-acyl-*N*-methyl-*o*-toluamides **3a-g** by photostimulated bromination in carbon tetrachloride (Table 1, scheme).

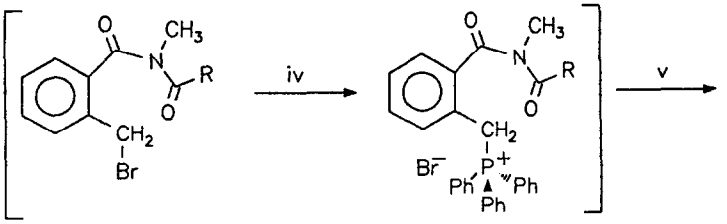
Table 1. Analytical data for the *N*-acyl-*N*-methyl-*o*-toluamides **3a-g** [a,b]

Compound	Yield (%)	M.p. (°C)	^{1}H NMR (δ)[c]	MS[d] *m/z* (%)
3a	87	53	2.28 (3H, s, CH_3), 3.47 (3H, s, N-CH_3), 7.02-7.31 (9H, m, H_{arom})	253 (M^+, 22), 119 (100), 105 (37), 91 (35)
3b	81	69	2.26 (3H, s, CH_3), 3.45 (3H, s, N-CH_3), 3.74 (3H, s, OCH_3), 6.52-7.26 (8H, m, H_{arom})	283 (M^+, 15), 135 (100), 119 (50), 91 (40)
3c	82	75	2.32 (3H, s, CH_3), 3.47 (3H, s, N-CH_3), 6.9-7.65 (8H, m, H_{arom})	289 (M^+, 11), 287 (M^+, 3), 119 (100), 91 (48)
3d	84	79	2.34 (3H, s, CH_3), 3.46 (3H, s, N-CH_3), 5.91 (2H, s, O-CH_2-O), 6.55-7.30 (7H, m, H_{arom})	297 (M^+, 24), 149 (83), 119 (100), 91 (52)
3e	76	70	2.40 (3H, s, CH_3), 3.49 (3H, s, N-CH_3), 6.8-7.5 (7H, m, H_{arom} + $H_{thienyl}$)	259 (M^+, 12), 119 (100), 91 (52)
3f	68	36	1.15 (6H, d, *J* 6.8, CH_3), 2.38 (3H, s, CH_3), 3.21 (3H, s, N-CH_3), 3.32 (1H, m, *J* 6.8, CH), 7.28 (4H, m, H_{arom})	219 (M^+, 8), 204 (15), 176 (16), 119 (100), 91 (61)
3g	79	53	2.43 (3H, s, CH_3), 3.32 (3H, s, N-CH_3), 6.71 (1H, d, *J* 15.4, H_{styryl}), 7.31 (9H, m, H_{arom}), 7.63 (1H, d, *J* 15.4, H_{styryl})	279 (M^+, 78), 119 (100), 91 (74)

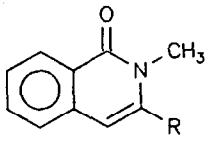
[a] All new compounds gave satisfactory combustion analysis. [b] ν_{max} (KBr) cm^{-1} 1698, 1660 and 1595. [c] Spectra were recorded in $CDCl_3$ on a Brucker WP 80 spectrometer; *J* values are given in Hz. [d] Obtained on a Riber 10-10 spectrometer (70 eV).



1 3a–g



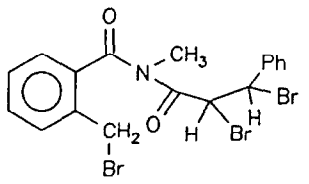
4a–f,4g 5a–g



6a–g

Compounds 2,3,4,5,6	R
a	Ph
b	o–$OMeC_6H_4$
c	p–ClC_6H_4
d	$(O CH_2O)C_6H_3$
e	2–thienyl
f	isopropyl
g	styryl

Scheme ***Reagents and conditions:*** i, n–BuLi, THF, room temperature; ii, RCOCl (**2a–g**), THF, −60 °C; iii, Br_2, CCl_4, hυ, 2 h, reflux; iv Ph_3P, toluene, 1 h, reflux; v, Et_3N, toluene, 1 h, reflux



4g

The *N*-acyl-*N*-methyl-*o*-toluamides **3a-g** were prepared by reacting the appropriate carboxylic acid chlorides **2a-g** with the anion of *N*-methyl-*o*-toluamide **1**. The amide function of **1** was deprotonated with *n*-butyllithium in tetrahydrofuran (THF) at room temperature. Due to the presence of two deprotonation sites in **1** this step was assumed to be complete when a deep red colour, characteristic of benzylic anions, appeared in the solution. This protocol has already been applied to aromatic amides of rather similar structure for the titration of organolithium reagents.[16] The addition of the acid chlorides **2a-g** must be performed at -70°C. Since the bromination step and the synthesis of the triphenylphosphonium bromides are nearly quantitative and owing to the air sensitivity of **4a-g** and to the hygroscopic nature of the intermediates **5a-g**, the conversion of the *N*-acyl-*N*-methyl-*o*-toluamides **3a-g** into the fused isoquinolones **6a-g** can be carried out in a one-pot reaction. The results of a representative series of products obtained by this sequence of reactions are presented in Table 2 where it may be seen that this simple procedure affords generally good yields of the 3-aryl-, heteroaryl- and alkyl-1-oxo-dihydro-isoquinolines **6a-g**.

This chemical behaviour is not sensitive to structural variations of the *N*-acyl group in **3**. However it was observed that bromination of the styryl derivative **3g** gave rise to the tribrominated compound **4g**. Since tertiary phosphines are known to give products of stereospecific ß-elimination from 1,2-dibromides[17] it was anticipated that the reaction of **4g** with 2 molar equiv. of triphenylphosphine and subsequent treatment with triethylamine would lead to the expected cyclocondensation product **6g**. Compound **6g** was indeed obtained by this procedure in 86% yield.

In conclusion, the procedure described here provides a convenient, simple and versatile access to 2-methyl isoquinolinones variously substituted at the 3-position of the six-membered heteronucleus. Moreover they broaden the scope of the intramolecular variant of the Wittig

Table 2. Analytical data for the 3-substituted-2-methyl-1-oxo-dihydro-isoquinolines **6a-g** [a,b]

Compound	Yield[c] (%)	M.p. (°C)	^{1}H NMR (δ)[d]	MS[e] *m/z* (%)
6a	84 (91)	63 (68-70)[f]	3.42 (3H, s, N-CH_3), 6.45 (1H, s, 4-H), 7.26-7.61 (8H, m, H_{arom}), 8.45 (1H, d, *J* 7.5, 8-H)	235 (M^+, 100), 178 (10)
6b	85 (89)	65	3.37 (3H, s, N-CH_3), 3.80 (3H, s, OCH_3), 6.45 (1H, s, 4-H), 6.92-7.55 (7H, m, H_{arom}), 8.48 (1H, d, *J* 9.0, 8-H)	265 (M^+, 100)
6c	84 (89)	142	3.42 (3H, s, N-CH_3), 6.44 (1H, s, 4-H), 7.28-7.57 (7H, m, H_{arom}), 8.46 (1H, d, *J* 7.7, 8-H)	271 (M^+, 28), 269 (M^+, 100)
6d	71 (78)	115	3.45 (3H, s, N-CH_3), 6.06 (2H, s, O-CH_2-O), 6.45 (1H, s, 4-H), 6.90-7.58 (6H, m, H_{arom}), 8.45 (1H, d, *J* 7.5, 8-H)	279 (M^+, 100), 220 (21)
6e	88 (92)	90	3.56 (3H, s, N-CH_3), 6.56 (1H, s, 4-H), 7.11-7.78 (6H, m, H_{arom} + $H_{thienyl}$), 8.46 (1H, d, *J* 7.5, 8-H)	241 (M^+, 100), 184 (16)
6f	69 (76)	84	1.31 (6H, d, *J* 6.6, CH_3), 3.08 (1H, m, J 6.6, CH), 3.65 (3H, s, N-CH_3), 6.40 (1H, s, 4-H), 7.40-7.59 (3H, m, H_{arom}), 8.39 (1H, d, *J* 7.9, 8-H)	201 (M^+, 74), 186 (100), 173 (21)
6g	80 (86)	119	3.38 (3H, s, N-CH_3), 6.47 (1H, s, 4-H), 6.83-7.84 (10H, m, H_{arom} + H_{vinyl}), 8.35 (1H, d, *J* 8.4, 8-H)	261 (M^+, 100), 184 (63)

[a] All new compounds gave satisfactory combustion analysis. [b] ν_{max} (KBr) cm^{-1} 1650, 1620 and 1595. [c] Yields after crystallization. Yields in brackets are the products obtained from chromatography. [d] Spectra were recorded in $CDCl_3$ on a Bruker WP 80 spectrometer; *J* values are given in Hz. [e] Obtained on a Riber 10-10 spectrometer (70 eV). [f] Ref. 18.

reaction and the easy availability of the starting materials renders this method particularly attractive for the construction of the isocarbostyril framework.

EXPERIMENTAL

Typical procedure for the preparation of *N*-acyl-*N*-methyl-*o*-toluamides 3a-g. A solution of N-methyl-*o*-toluamide (5.07 g, 34 mmol) in anhydrous tetrahydrofuran (180 ml) was stirred under Ar at room temperature and a solution of *n*-butyllithium in hexane (1.6 M, 35 mmol, 21.9 ml) was slowly added until the appearance of a deep red colour in the solution. The mixture was stirred for 30 mn, then cooled to -60°C and a solution of the carboxylic acid chlorides **2a-g** (35 mmol) in THF was added dropwise over a period of 15 mn. The mixture was stirred for an additional 15 mn and then allowed to warm to room temperature. Stirring was maintained for 2 h. Diethyl ether (100 ml) was added and the reaction mixture was washed with aqueous saturated $NaHCO_3$ solution. The aqueous phase was extracted with AcOEt (2 x 50 ml) and the combined organic layers were washed successively with brine (50 ml), water (50 ml) and then dried ($MgSO_4$). After elimination of the solvents the crude product was finally recrystallized from hexane/toluene (Table 1).

Typical procedure for the preparation of *N*-acyl-*N*-methyl-2-bromomethylbenzamides 4a-g. A solution of compounds **3a-g** (5 mmol) in freshly distilled carbon tetrachloride was gently refluxed under Ar and a solution of bromine (810 mg, 5 mmol for **3a-f**; 10 mmol for **3g**) in CCl_4 (5 ml) was added dropwise under UV irradiation. The mixture was refluxed for 2 h until complete decolouration. The solvent was removed under vacuum. The ^1H NMR spectrum unambiguously indicated the exclusive presence of the brominated compounds **4a-g**[19] which were used in the next step without further purification.

Typical procedure for the preparation of the *N*-acyl-*N*-methyl-*o*-triphenylphosphoniomethylbenzamide bromides 5a-g. The crude brominated derivatives **4a-g** obtained from the corresponding N-acyl-N-methyl-*o*-toluamides (5 mmol) were dissolved in toluene (20 ml) in the presence of triphenylphosphine (1.5 g, 7 mmol). The mixture was refluxed under stirring for 1 h, during which time a precipitate appeared. After cooling the toluene was pumped from the flask under Ar. The precipitate was washed twice with anhydrous diethyl ether which was removed in the same manner. The resulting solid was dried by passing a stream of dry Ar in the flask and was used as such in the next step.[19]

3-(Aryl, heteroaryl or alkyl)-2-methyl-1-oxo-dihydroisoquinolines 6a-g; General Procedure. A solution of freshly over KOH distilled triethylamine (1.01 g, 10 mmol for **5a-f** and 2.02 g, 20 mmol for **5g**) in anhydrous toluene (20 ml) was added to the salts obtained as described above and the mixture was gently refluxed with stirring under Ar for 1 h. After cooling, the precipitated triphenylphosphine oxide was filtered off and washed with AcOEt (10 ml). The organic layer was then treated successively with 10% HCl solution, brine, water and dried ($MgSO_4$). Evaporation of the solvent afforded the crude product which was finally purified by column chromatography on silica gel using AcOEt/hexane as eluent and ultimately recrystallized from EtOH. The yields before and after recrystallization are reported in Table 2.

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19. ^{1}H NMR spectra of several representative intermediates ($CDCl_3$, TMS); **4a**: δ = 3.46 (3H, s, N-CH_3), 4.59 (2H, s, CH_2Br), 7.09-7.57 (9H, m, H_{arom}); **4g**: δ = 3.23 (3H, s, N-CH_3), 4.72 (2H, s, CH_2Br), 5.60 (1H, d, *J* 11.5, BrCH-Ph), 6.19 (1H, d, *J* 11.5, BrCH-CO), 7.17-7.57 (9H, m, H_{arom}); **5a**: δ = 3.26 (3H, s, N-CH_3), 5.40 (2H, d, *J* 14.6, CH_2P), 7.17-7.72 (24H, m, H_{arom}); **5g**: δ = 3.23 (3H, s, N-CH_3), 5.37 (2H, d, *J* 15, CH_2P), 7.21-7.99 (26H, m, H_{arom} + H_{vinyl}).