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A Convenient Synthesis of *N*-Methyl-3-(2-ethenylphenyl)-1(2*H*)-isoquinolones, Key Models for the Elaboration of the Benzo[*c*]phenanthridinone and Phenanthridine Skeletons

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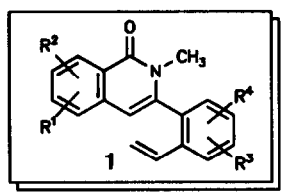
Abstract: A variety of *N*-methyl-3-(2-ethenylphenyl)-1(2*H*)-isoquinolones **1a-e** have been prepared by base-induced intramolecular cyclization of *N*-(2-ethenylbenzoyl)-*N*,2-dimethylbenzamide derivatives **2a-e**. The concomitant formation of the fused dihydro benzo[*c*]phenanthridinones **7a-e** was also observed during this process.

For the organic chemists who are embarked on sophisticated alkaloid syntheses, the elaboration of key intermediates, commonly called synthons, remains a permanent and challenging synthetic task. Indeed, such compounds display an interesting array of chemical reactivities and can easily give rise to the targeted naturally occuring alkaloids through relatively simple chemical transformations. This is notably the case of the isoquinolones **1** in which a styrene moiety is connected at the 3-position of the isocarbostyryl framework.



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These semi-condensed compounds are indeed involved in the synthesis of a variety of fully aromatic benzo[*c*]phenanthridine alkaloids which have been put in a position of biological, pharmacological and synthetic importance owing to the wide range of their physiological effects.[1] In particular, the electrocyclic ring closure of these 6π electron conjugated systems can be photochemically induced and this process represents the key step in the elaboration of oxychelerythrine and chelerythrine.[2] Alternatively, to circumvent problems arising from the photochemical formation of undesirable regioisomeric dimers, the styrene moiety of **1** can be oxy-functionnalized by treatment with thallium trinitrate and oxyterihanine,[3] oxychelerythrine[4] and oxysanguilutine[5] are readily obtained by treatment of the resulting acetals with dilute hydrochloric acid. On the other hand the reduction of the carbonyl function of suitably substituted compounds **1** furnishes anhydroprotopine and anhydrocryptopine[2a] which can be regarded as direct precursor of epicryptopirubine chloride[6] or can be easily photoconverted into sanguinarine after dehydrogenation and oxydation with DDQ of the primary photoproducts.[2a] Finally, compounds **1** can be easily cyclized with dilute hydrochloric acid to yield five membered spiro compounds.[7]

Paradoxically a litterature survey reveals the paucity of the synthetic methodologies for the elaboration of species like **1**. To our knowledge these models can only be accessible by sequential treatment of berberinium salts with KOH[8],DDQ and potassium ferricyanide[1c,3] or O_2 in basic medium.[5] We wish to report in this paper a new and convenient method for the elaboration of the isocarbostyryl framework which allows the concomitant incorporation of the desired styrene moiety. The method is tolerant with the presence of methoxy and methylenedioxy groups usually present in

benzo[*c*]phenanthridine alkaloids. Our strategy is based upon the base-induced intramolecular cyclization of the diversely substituted *N*-(2-ethenylbenzoyl)-*N*,2-dimethylbenzamide, **2a-e**.

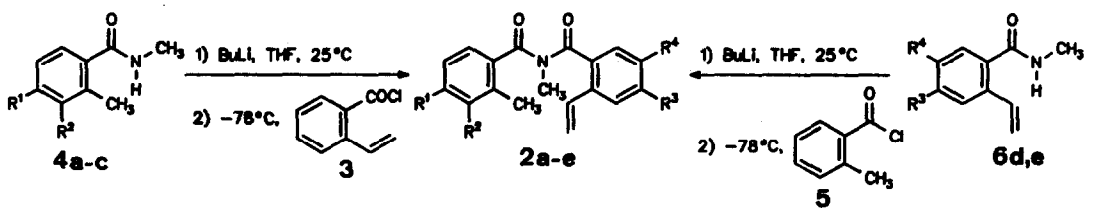
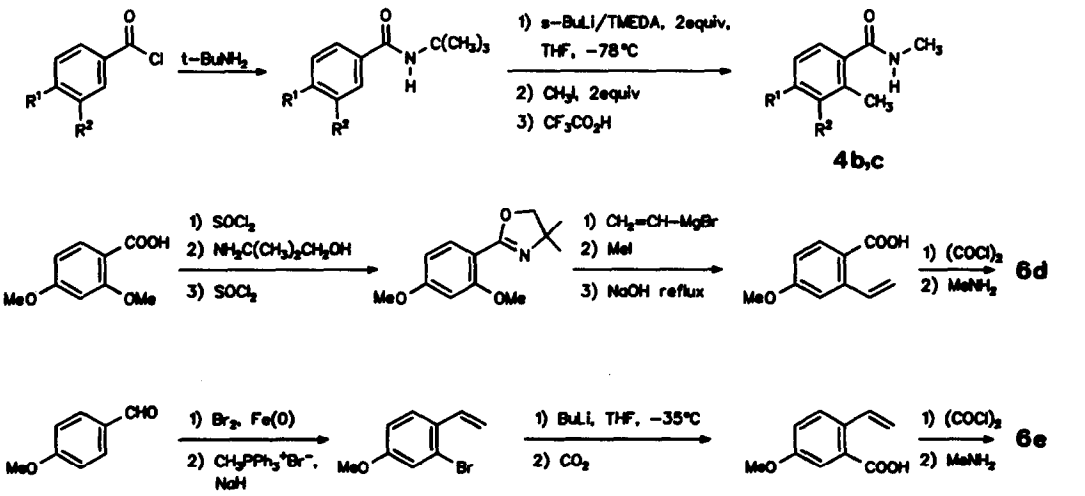


Table. Data for New Compounds Prepared.

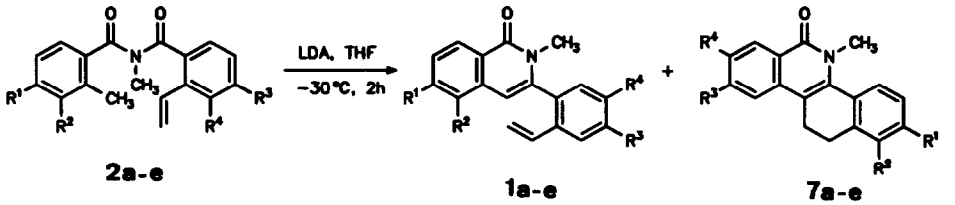
R^1	R^2	R^3	R^4	Starting Compd	m.p. (°C)	Yield* (%)	Reaction Product	m.p. (°C)	Yield* (%)	Reaction product	m.p. (°C)	Yield* (%)
H	H	H	H	**2a**	82-83	87	**1a**	120-121	41	**7a**	142-144	13
H	H	H	H	**11**	oil	95	**1a**		66	-		
CH_3O	H	H	H	**2b**	109-110	88	**1b**	130-131	43	**7b**[15]	170-171	12
-CH_2-O-CH_2-		H	H	**2c**	119-120	81	**1c**	128-129	44	**7c**	154-155	14
H	H	CH_3O	H	**2d**	84-85	78	**1d**	144-145	46	**7d**	168-169	17
H	H	H	CH_3O	**2e**	81-82	81	**1e**	149-150	47	**7e**	164-165	18
CH_3O	H	H	H	**4b****	95-96	79						
-CH_2-O-CH_2-		H	H	**4c**	125-126	82						
H	H	CH_3O	H	**6d**	128-129	47						
H	H	H	CH_3O	**6e**	64-65	53						
H	H	H	H	**10**	95-96	92						

* Evaluated after recrystallization from hexane-toluene. ** **4a** ($R^1 = R^2 = H$) commercially available.



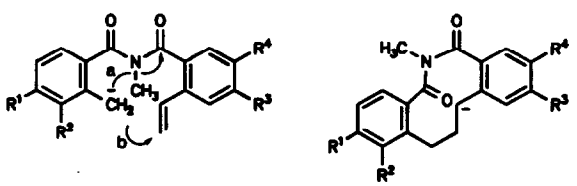
Two different protocols depending on the nature and position of the substituents in the parent models were adopted for the elaboration of the *N*-acylamides **2a-e**. The monosubstituted *o*-toluamides **4a-c** and **6d,e** were deprotonated with *n*-butyllithium in THF at room temperature and subsequently treated at -78°C with the appropriate acyl chlorides, **3**[9] and **5** respectively, to yield almost quantitatively the diacylamines **2a-e**.[10]

Initially, the *o*-toluamides **4b,c** were prepared after preliminar incorporation of the *t*-butyl group in the parent compounds. This operation allowed a double metallation reaction of the carboxamido group and of the *o*-directed position of the aromatic ring.[11] The subsequent trapping of the dilithiated species with methyl iodide and removal of the *t*-butyl group gave rise to the expected toluamides **4b,c**. Compound **6d** was obtained following the elegant method recommended by Meyers[12] for the nucleophilic displacement of *o*-methoxy group in a variety of benzoic acid derivatives and the isomeric compound **6e** was readily obtained from *p*-anisaldehyde through a four step sequence.

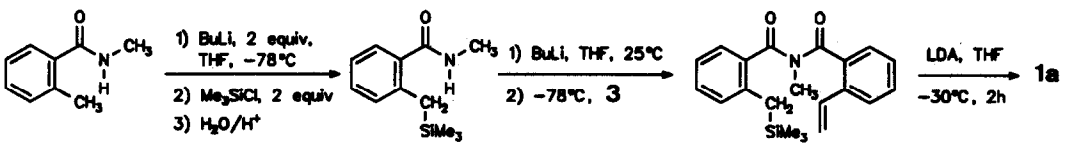


Deprotonation of the *N*-acylamides **2a-e** was effected with LDA in THF at -30°C. Stirring the reaction mixture for a few hours led to the completion of the reaction as indicated by the disappearance of the deep-red color of the benzylic anions. Results of a representative series of products obtained by this method are presented in the Table. It may be seen that this simple procedure affords good to moderate yields of the targeted 3-styrylisoquinolone derivatives **1a-e** accompanied by the dihydrophenanthridinone derivatives **7a-e**.[10] The structure of the fused compounds **7a-e** was unambiguously assigned from complementary experiments carried out on the unsubstituted model **7a** and from results observed with the parent monosubstituted acylamide **2b**. Thus the structure of **7a** was confirmed by its conversion into the known benzophenanthridinone and dihydrophenanthridine derivatives.[13] On the other hand, the basic treatment of the *N*-acylamide **2b** led to the formation of the styrylisoquinolone **1b** and to the cyclocondensed compound **7b**.[10] The latter was identified as the 2-methoxy-11,12-dihydrobenzo[*c*]phenanthridine-6-one and was identical to the product obtained by photocyclization under anaerobic conditions[7,14] of *N*-methyl-3-(2-ethenyl-4-methoxyphenyl)-1(2*H*)-isoquinolone **1d** and to the product obtained by an independant synthesis recently described by Castedo and *al.*.[15]

From a mechanistic point of view, the formation of the semi-condensed products **1a-e** can be easily explained by the intramolecular attack of the prealably generated benzylic carbanion **8** on the terminal carbonyl moiety in **2a-e** (**8**, path a). The obtention of the fully condensed products **7a-e** was more intriguing. It was assumed that such compounds would arise from the attack of the carbanion on the weakly polarized styrenic bond (**8**, path b).



The subsequent intramolecular attack of the transferred carbanion **9** on the vicinal carbonyl group followed by dehydration would afford the fused compounds **7a-e**. It was then anticipated that the incorporation of a trimethylsilyl group on the benzylic position of a parent model would favour the exclusive attack of the anionic species on the carbonyl moiety under the well-known Peterson olefination conditions.[16] To this end, the monosilylated *N*-acylamide **11** was synthetized from *o*-trimethylsilylmethyl-*N*-methyl benzamide **10** easily obtained by regioselective monosilylation of *N*-methyl-*o*-toluamide. As anticipated, the basic treatment of **11** under the conditions used for **2a-e** gave rise exclusively to the styrylisoquinolone **1a** and this result corroborated the mechanistic hypothesis framed to account for the formation of the condensed products **7a-e**.



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In conclusion, the method presented here represents a new approach to the interesting 3-styrylisoquinolone synthons and sets the basis of a new methodology for the construction of the benzo[*c*]phenanthridine skeleton.

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10. All new compounds gave satisfactory spectroscopic and analytical data. Representative data for selected compounds;
    2b; IR (KBr) 1692, 1645 (ν_{CO}); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.18 (3H, s, CH_3), 3.45 (3H, s, NCH_3), 3.65 (3H, s, OCH_3), 5.30 (1H, dd, *J*= 11.0, 1.0 Hz, H_2C=), 5.56 (1H, dd, *J*= 17.5, 1.0 Hz, H_2C=), 6.37-6.47 (2H, m), 6.82 (1H, dd, *J*= 11.0, 17.5 Hz, HC=), 7.02-7.14 (4H, m), 7.30 (1H, dd, *J*= 0.5, 7.8 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 19.89 (q, CH_3), 32.78 (q, NCH_3), 55.09 (q, OCH_3), 110.40 (d), 116.45 (d), 116.80 (t, H_2C=), 125.61 (d), 126.83 (d), 126.95 (d), 128.93 (s), 129.96 (d), 130.08 (d), 133.63 (d), 135.58 (s), 135.98 (s), 139.54 (s), 160.88 (s), 173.48 (s, CO), 173.75 (s, CO); MS *m/z* 309 (M^+, 3), 149 (100); *Anal.* Calcd for $C_{19}H_{19}NO_3$: C 73.76; H 6.19; N 4.53; O 15.52; Found: C 73.89; H 6.16; N 4.67; O 15.46.
    1b; IR (KBr) 1639 (ν_{CO}); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.22 (3H, s, NCH_3), 3.87 (3H, s, OCH_3), 5.21 (1H, dd, *J*= 11.0, 1.0 Hz, H_2C=), 5.73 (1H, dd, *J*= 17.4, 1.0 Hz, H_2C=),6.35 (1H, s, H-4), 6.51 (1H, dd, *J*= 11.0, 17.4 Hz, HC=), 6.82 (1H, m), 7.05 (1H, m), 7.25-7.47 (3H, m), 7.67 (1H, d, *J*= 7.7 Hz), 8.36 (1H, d, *J*=8.9 Hz, H_{peri}); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 32.79 (q, NCH_3), 55.46 (q, OCH_3), 106.40 (d), 107.32 (d), 116.38 (d), 116.67 (t, H_2C=), 118.94 (s), 125.27 (d), 128.00 (d), 129.45 (d), 129.59 (d), 129.93 (d), 133.64 (d), 134.53 (s), 136.55 (s), 138.37 (s), 143.09 (s), 166.77 (s, CO); MS *m/z* 291 (M^+, 96), 290 (100), 276 (24); *Anal.* Calcd for $C_{19}H_{17}NO_2$: C 78.33; H 5.88; N 4.81; O 10.98; Found: C 78.28; H 5.90; N 4.90; O 10.85.
    7b; IR (KBr) 1638 (ν_{CO}); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.83 (4H, m, CH_2), 3.76 (3H, s, NCH_3), 3.85 (3H, s, OCH_3), 6.81-6.86 (2H, m), 7.39-7.48 (2H, m), 7.62-7.72 (2H, m), 8.47 (1H, dd, *J*= 1.0, 7.5 Hz, H_{peri}); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 23.42 (t), 29.42 (t), 37.87 (q, NCH_3), 55.36 (q, OCH_3), 111.23 (d), 113.50 (d), 114.90 (s), 121.87 (d), 123.42 (s), 124.64 (s), 126.37 (d), 127.41 (d), 128.25 (d), 132.26 (d), 135.67 (s), 137.74 (s), 140.67 (s), 159.11 (s), 164.25 (s, CO).
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