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Dramatically Different Photochemical Behaviour of 1-Aroyl-2-methylene Piperidine and Pyrrolidine Derivatives. An Expeditious Synthesis of Ruspolinone

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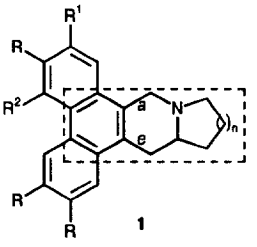
Abstract: Upon irradiation in neutral solvent, the diversely substituted 1-aroyl-2-methylenepiperidines **6a-f** give rise to photocyclized products **4a-f** while their pyrrolidine congeners **7a,c,d** afford enaminoketones **18a,c,d** products of photo-Fries rearrangement.

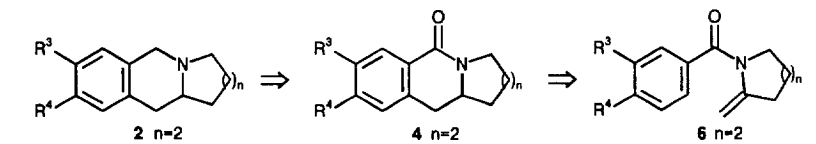
The benzo[*b*]quinolizidine and benzo[*b*]indolizidine ring systems represent the main structural subunit of highly condensed alkaloids such as tylocrebrine **1a**, tylophorine **1b**, antofine **1c** and cryptopleurine **1d** which have been shown to possess unique and interesting biological properties including vesicant,[1a] antimicrobial,[1b] antiviral[1c] and anti-cancer activities.[1d] On the other hand, several patents and articles emphasising the pharmaceutical properties of their perhydro or methoxy derivatives,[2,3a,b] and particularly their uterine stimulant activity[3c] have appeared in the literature. Consequently these heterotricyclic compounds have ellicited important synthetic efforts and several synthetic methods have been developed in recent years. The most convenient route involves the final formation of bonds *a* and *e* of the isoquinoline nucleus either by Pictet-Spengler[4] or Friedel-Crafts reaction[5] of 2-benzylpiperidine or pyrrolidine derivatives but these methods invariably require the presence of electron donors on the aromatic unit. To obviate this inconvenience diverse methods[6-9] have been proposed such as hydrogenation of acridizinium halides[9] or cyclization of 3-halogenoalkylisoquinolines[7] but they are rather restrictive in scope.



1

a n=1 R¹=H, R=R²=OMe
b n=1 R²=H, R=R¹=OMe
c n=1 R¹=R²=H, R=OMe
d n=2 R¹=R²=H, R=OMe

Paradoxically, despite the fact that the arylenamide photocyclization protocol[10] has been established as one of the most convenient method for the elaboration of the dihydroisocarbostyril framework (1-oxotetrahydroisoquinoline), the photochemical approach to the six-membered lactams **4, 5** (Scheme 1) which can serve as precursors of the targeted tricyclic compounds, **2, 3** respectively, have been neglected by the scientific community. Retrosynthetically it was deemed that the lactamic compounds **4, 5** could be easily assembled by photo-induced electrocyclic ring closure of the aromatic enamides **6** and **7** comprising a methylene function. However it was obvious that application of this strategy would be fraught with difficulties associated with access to enamides **6, 7** and with the vagarious character of enamide photocyclization. Indeed the main methods for the preparation of these conjugated compounds involve acylation of aldimines with carboxylic acid chlorides in the presence of a



Scheme 1

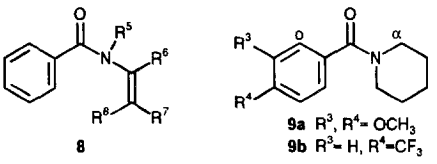
2 n=2
3 n=1

4 n=2
5 n=1

6 n=2
7 n=1

tertiary amine,[11a] the anionisation followed by alkylation and subsequent elimination of α-carbamidosulfones[11b] and the addition of an aryllithium moiety to a vinyl isocyanate.[11c] They may also be prepared by the fluoride ion induced Peterson alkenation of *N*-[C,C-bis(trimethylsilyl)methyl]amido derivatives.[11d,e] Unfortunately none of these methods could be applied to the synthesis of *N*-acylenamines **6, 7**. On the other hand the photochemical behavior of aromatic enamides with an acyclic nitrogen vinylic bond is rather erratic in nature and is strongly influenced by the nature of the substituent patterns on the olefinic moiety. Thus compounds **8** (R^6 = SR, aryl or heteroaryl, R^7 = R^8 = H) lead exclusively to cyclized products upon photolysis in neutral solvent[10] while irradiation of **8** (R^6, R^7, R^8 = alkyl) furnishes enaminoketones, products of photo-Fries rearrangement[12] under similar conditions. Actually the single exception in the later series concerns aromatic carboxamides with an appended cycloalkylidene unit (**8**, R^6 = H, R^7,R^8 = $(CH_2)_n$) which photocyclize to tricyclic spiranic compounds thus opening a promising route to sesbanine alkaloid derivatives.[13]

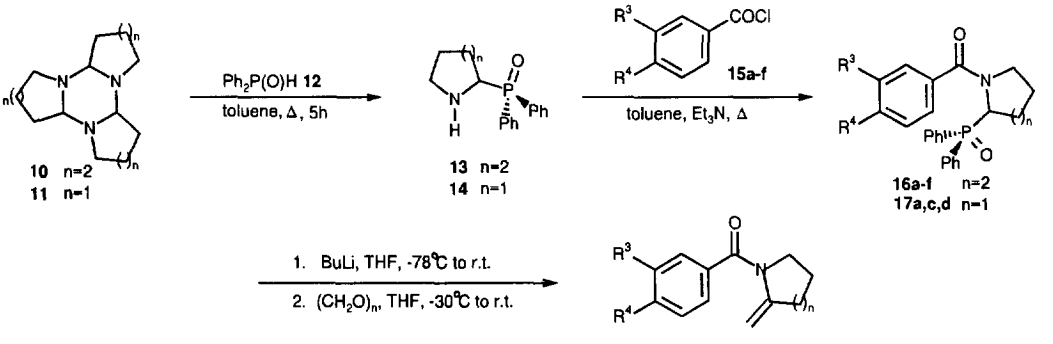
We then embarked on a dual program aimed at developing a new and general concept for the elaboration of 1-acyl-2-methylene piperidine and pyrrolidine derivatives **6, 7** and at defining their photochemical synthetic potential. Initial attempts to provoke the base-induced formation of dipole-stabilized α-aminocarbanions from the *N*-aroylpiperidine derivatives **9**[11e,14] which could be trapped with formaldehyde and subsequently dehydrated were unrewarding. Indeed the lithiated base-induced deprotonation (*sec*-BuLi, TMEDA or LiTMP, -78°C, THF) of **9a,b** was exclusively directed to the *ortho*-position on the aromatic nucleus at the expense of Cα-to-N-position which is undoubtedly due to the cooperative effects of the 1,3-interrelated ortho-directing dimethoxy and carboxamido groups and to additional inductive factors for **9a** and **9b** respectively.[15] Alteration of the profile of the molecule was inevitable in order to force metallation to occur at the α-nitrogen carbon atom. The remarkable nucleophilicity and yluric character of phosphorylated α-aminocarbanions,[16] properties cleverly used thus far for enamine derivatives[17] and *N*-alkylaminoalkylphosphine oxide syntheses,[18] prompted us to incorporate the diphenylphosphinoyl group on this position.



8

9a R^3, R^4= OCH_3
9b R^3= H, R^4=CF_3

Initially the 2-diphenylphosphinoyl piperidine and pyrrolidine, **13, 14** respectively, were easily prepared by addition of diphenylphosphine oxide **12** to the triazines **10**[19] and **11**[20] and subsequently treated with the



10 n=2
11 n=1

13 n=2
14 n=1

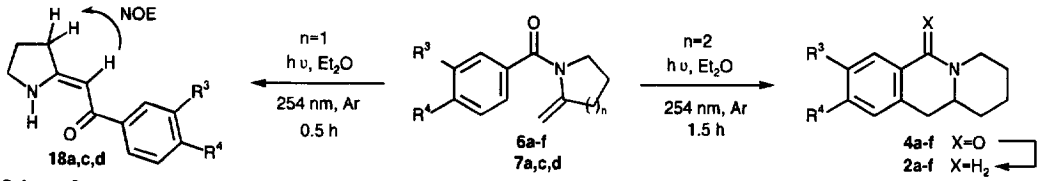
16a-f n=2
17a,c,d n=1

6a-f n=2
7a,c,d n=1

Scheme 2

suitably substituted carboxylic acid chlorides **15a-f** to afford the phosphorylated *N*-acylamines **16a-f** and **17a,c,d** in excellent yields (Scheme 2, Table). The phosphorylated amides were then smoothly deprotonated at -78°C with *n*-BuLi in THF and transferred into a pre-cooled THF solution of freshly depolymerized paraformaldehyde. Warming the reaction mixture to room temperature ensured completion of the reaction and the 1-aroyl-2-methylene piperidine and pyrrolidine derivatives, **6a-f** and **7a,c,d**, were easily obtained, albeit in moderate yield (Scheme 2, Table).[21]

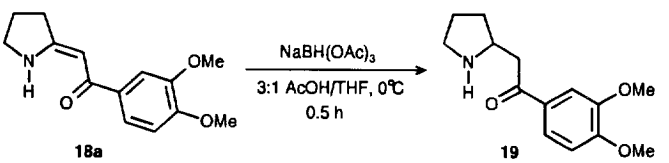
Scrutiny of the photochemical behaviour of **6a-f** and **7a,c,d** clearly revealed that the nature of the photoproducts is dramatically conditioned by the size of the heterocyclic entity in the parent models (Scheme 3). Thus irradiation of a carefully deaerated solution of **6a-f** in ether (10^{-2} M, Rayonet RPR, 254 nm, 1.5 h) in a quartz reactor led exclusively to the annulated compounds **4a-f**,[21] products of the electrocyclic ring closure of the parent 6π electron conjugated compounds **6a-f**. In contrast to precedently reported procedures this protocol is tolerant with a wide variety of substitution patterns on the aromatic unit and delivers the diversely substituted benzo[*b*]quinolizidinones **4a-f** with excellent yields (Table).



Scheme 3

The strain which would be developed during the closure of the hetero ring system of the corresponding pyrrolidine congeners **7a,c,d** probably accounts for the failure of these compounds to photocyclize under the same conditions. Actually irradiation of a degassed etheral solution of **7a,c,d** gave rise exclusively and efficiently to the enaminoketones **18a,c,d** (Scheme 3, Table) products of photo-Fries rearrangement involving 1,3-aroyl migration. The (*Z*)-stereochemistry of these vinylogous amides was inferred from the nuclear Overhauser enhancement (*c.a.* 3.5%) of the allylic hydrogens on irradiation of the vinylic hydrogen in **18a** and from the chemical shift of hydrogen atom on C-3 of the heterocyclic ring (δ 2.73 ppm) implying the lack of anisotropic through-space deshielding by the carbonyl group.

The benzo[*b*]quinolizine-6-ones **4a-f** are easily reduced ($LiAlH_4$, Et_2O, 0°C, 1 h) to afford the targeted benzoquinolizidine derivatives **2a-f** (Scheme 3, Table). Moreover the ready access to the vinylogous amides **18a,c,d** endows the photochemical procedure with interesting synthetic potential and provide a new entry to pyrrolidine alkaloids. Thus ruspolinone **19**, one of the three pyrrolidine alkaloids isolated in the racemic form from *Ruspollia hypercrateriformis*[22, 23] and possessing the pyrrolidinyl-acetophenone skeleton, can be readily obtained by chemoselective reduction of the C=C unit of the enaminone **18a** with sodium triacetoxyborohydride in a 3:1 mixture of AcOH and THF (0°C, 30 mn, 91%) (Scheme 4).



Scheme 4

Application of this strategy to the preparation of alkaloids based on the 1-aryl-2-pyrrolidin-2-ylethene structure are underway and will be reported in due course.

Table. Compounds Prepared

n	R^3	R^4	Compound, mp °C (Yield %)							
			Phosphorylated Amides **16, 17**		Enamides **6, 7**		Photoproducts **4, 5**		Reduction Products **2, 18**	
2	OMe	OMe	**16a**	156-157 (76)	**6a**	98-99 (55)	**4a**	127-128 (56)	**2a**	104-105 (77)
2	H	CF_3	**16b**	212-213 (83)	**6b**	117-118 (58)	**4b**	97-98 (68)	**2b**	- (72)
2	H	H	**16c**	176-177 (81)	**6c**	93-94 (65)	**4c**	92-93 (72)	**2c**	43-44 (80)
2	H	Me	**16d**	197-198 (78)	**6d**	109-110 (68)	**4d**	76-77 (75)	**2d**	- (83)
2	H	F	**16e**	194-195 (79)	**6e**	84-85 (62)	**4e**	78-79 (76)	**2e**	- (79)
2	H	OMe	**16f**	171-172 (83)	**6f**	88-89 (60)	**4f**	72-73 (70)	**2f**	47-48 (82)
1	OMe	OMe	**17a**	125-126 (75)	**7a**	- (59)	**18a**	141-142 (95)	**19**	- (91)
1	H	H	**17c**	150-151 (77)	**7c**	- (60)	**18c**	108-109 (92)		
1	H	Me	**17d**	165-166 (80)	**7d**	60-61 (63)	**18d**	135-136 (96)		

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21. Selected data for **16e**: ^{1}H NMR ($CDCl_3$, TMS) δ ppm: 1.21-1.42 (1H, m), 1.62-1.71 (2H, m), 1.83-2.04 (1H, m), 2.11-2.23 (1H, m), 2.40-2.65 (1H, m), 3.35-3.39 (1H, m), 3.71 (1H, dt, *J* 2, 13), 5.86 (1H, br. s), 6.76 (2H, d, *J* 8), 6.93 (2H, d, *J* 8), 7.41-7.66 (6H, m), 7.90-8.12 (4H, m); ^{13}C NMR ($CDCl_3$, TMS) δ ppm: C 169.9, 163.1 (d, *J* 257), 132.1, 130.9; CH 131.9, 131.2, 131.0, 129.8, 129.3, 128.5, 115.4 (d, *J* 22), 48.2 (d, *J* 75); CH_2 46.7, 26.2, 24.3, 20.5; ^{31}P NMR ($CDCl_3$) δ ppm: 31.3.
Selected data for **6b**: ^{1}H NMR ($CDCl_3$, TMS) δ ppm: 1.71-1.92 (4H, m), 2.27 (2H, t, *J* 6), 3.73 (2H, t, *J* 5), 4.12 (1H, s), 4.63 (1H, s), 7.51 (4H, s); ^{13}C NMR ($CDCl_3$, TMS) δ ppm: C 168.8, 143.2 (d, *J* 248), 131.2, 124.9, 121.9; CH 128.1, 125.0; CH_2 110.3, 45.9, 33.0, 26.1, 25.1.
Selected data for **4a**: ^{1}H NMR ($CDCl_3$, TMS) δ ppm: 1.39-1.55 (3H, m), 1.68-1.85 (3H, m), 2.63 (1H, dt, *J* 3, 13), 2.72 (1H, dd, *J* 9, 16), 2.97 (1H, dd, *J* 5, 16), 3.52 (1H, m), 3.87 (3H, s), 3.88 (3H, s), 4.63 (1H, m), 6.55 (1H, s), 7.59 (1H, s); ^{13}C NMR ($CDCl_3$, TMS) δ ppm: C 165.2, 152.9, 147.8, 130.3, 121.2; CH 110.6, 109.1, 55.4; CH_2 43.6, 34.3, 33.1, 24.8, 23.7; CH_3 55.9.
Selected data for **2d**: ^{1}H NMR ($CDCl_3$, TMS) δ ppm: 1.32-1.45 (2H, m), 1.55-1.81 (5H, m), 2.13 (1H, dd, *J* 11, 15), 2.21-2.26 (1H, m), 2.37 (3H, s), 2.73-2.78 (1H, m), 3.08 (1H, dd, *J* 2, 10), 3.35 (1H, d, *J* 15), 3.85 (1H, d, *J* 15), 6.93-7.15 (3H, m), 10.23 (1H, br. s); ^{13}C NMR ($CDCl_3$, TMS) δ ppm: C 133.9, 130.8, 129.5; CH 127.9, 126.1, 125.9, 58.3; CH_2 58.5, 56.3, 36.4, 33.8, 25.7, 24.3; CH_3 21.5.
Selected data for **18a**: ^{1}H NMR ($CDCl_3$, TMS) δ ppm: 2.04-2.19 (2H, m), 2.73 (2H, t, *J* 8), 3.68 (2H, t, *J* 7), 3.88 (3H, s), 3.91 (3H, s), 5.86 (1H, s), 6.79 (2H, d, *J* 8), 7.53 (1H, s), 7.56 (2H, d, *J* 8); ^{13}C NMR ($CDCl_3$, TMS) δ ppm: C 168.8, 151.2, 148.8, 133.6, 132.4; CH 123.4, 120.4, 110.3, 110.2; CH_2 47.7, 32.9, 21.5; CH_3 55.9.
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