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Graphical Abstract

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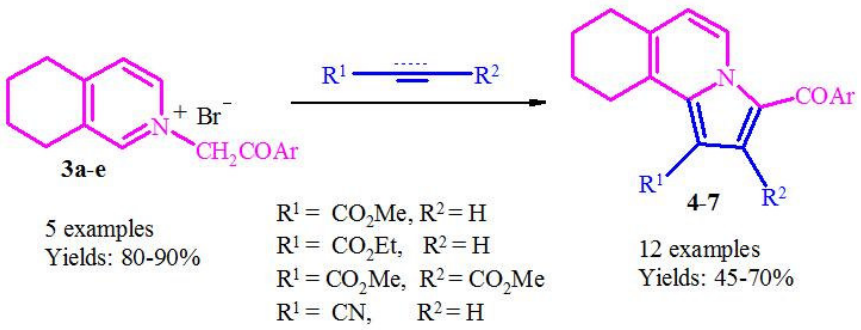

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7,8,.9,10-Tetrahydropyrrolo[2,1-*a*]isoquinolines in searching for new indolizine derivatives

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ABSTRACT

7,8,9,10-Tetrahydropyrrolo[2,1-*a*]isoquinolines were obtained by 1,3-dipolar cycloaddition reactions of their corresponding *N*-ylides with olefinic (acrylonitrile) and symmetrical or non-symmetrical acetylenic dipolarophiles (methyl/ethyl propiolate, dimethyl acetylenedicarboxylate). Also, stable 5,6,7,8-tetrahydroisoquinolinium dicyanomethylide was isolated and characterized by X-ray diffraction analysis.

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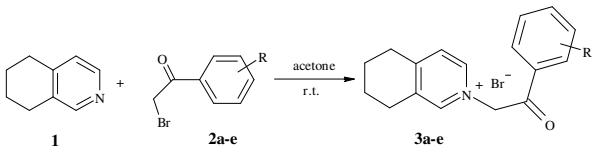
The indolizine core has attracted much interest due to its biological activity[1-5] and physico-chemical properties such as fluorescence.[6-9] Also, benzoindolizine frameworks such as pyrrolo[1,2-*a*]quinoline and pyrrolo[2,1-*a*]isoquinoline are found as the building blocks of a number of alkaloids such as gephyrotoxin[10] and lamellarins,[11,12] which are of medicinal importance.[11] For medicinal reasons the hydrogenated or partially hydrogenated pyrrolo[2,1-*a*]isoquinoline framework was of interest with a special focus on obtaining lamellarin analogs with biological activity (e.g. lamellarin D)[13] and similar compounds possessing a dihydrogenated pyridine moiety.[14]

As the 1,3-dipolar cycloaddition reaction has proved to be a very convenient route to the class of pyrroloazine compounds,[15-19] we have extended our studies to obtaining 7,8,9,10-tetrahydropyrrolo[2,1-*a*]isoquinolines *via* the 1,3-dipolar cycloaddition reaction of the corresponding 5,6,7,8-tetrahydroisoquinolinium *N*-ylides by different approaches.

Herein we present the synthesis and characterization of new partially hydrogenated pyrrolo[2,1-*a*]isoquinoline derivatives, which might be of potential synthetic interest for medicinal purposes and/or optical applications.

To our knowledge only one example of a 7,8,9,10-tetrahydropyrrolo[2,1-*a*]isoquinoline has been reported by Babaev et al.,[20] but it was obtained by an alternative method starting from the corresponding oxazolo[3,2-*a*]isoquinolinium salt.

The new 7,8,9,10-tetrahydropyrrolo[2,1-*a*]isoquinoline derivatives were obtained by 1,3-dipolar cycloaddition of the corresponding *N*-ylides with olefinic or acetylenic dipolarophiles. The ylides were generated *in situ* from the corresponding tetrahydroisoquinolinium bromides **3a-e**, which were easily obtained in 80-90% yields by reacting 5,6,7,8-tetrahydroisoquinoline (**1**) with different bromoacetophenones **2a-e** in acetone at room temperature (Scheme 1).[21]



1 **2a-e** **3a-e**

Scheme 1. Synthesis of tetrahydroisoquinolinium bromides **3a-e**

The synthetic route to the new 7,8,9,10-tetrahydropyrrolo[2,1-*a*]isoquinolines was investigated in order to obtain optimum conditions and simple work-up procedures. Scheme 2 depicts the synthesis of the new compounds by different pathways. The reaction mechanism of the 1,3-dipolar cycloaddition briefly involves the generation of the *N*-ylide *in situ* by the action of a base,[15] or other deprotonation agent acting as a base,[16] on the corresponding cycloiminium bromide and subsequent

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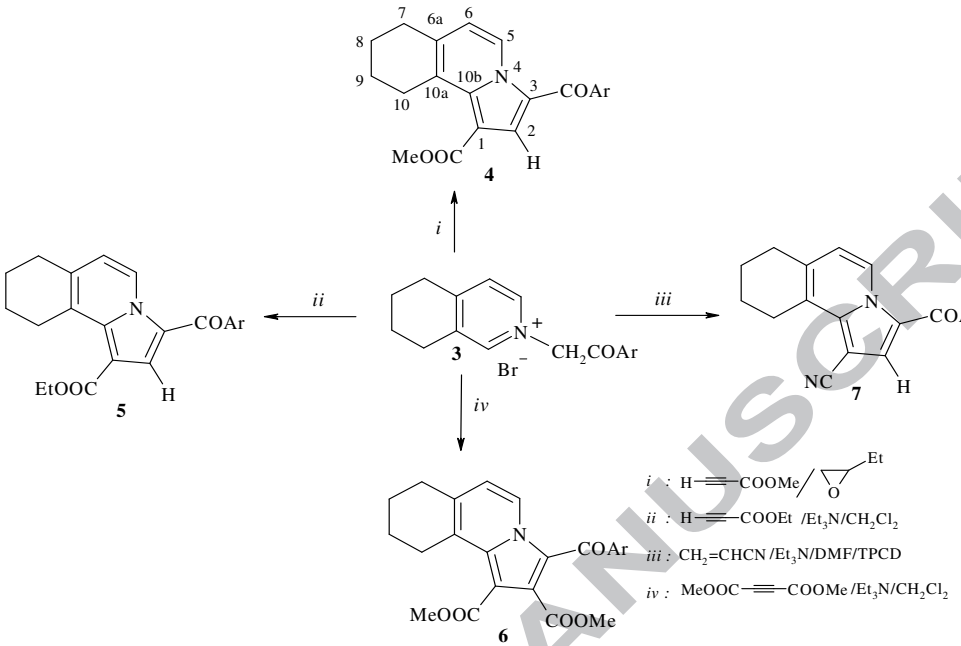
cycloaddition of the *N*-ylide to the olefinic or acetylenic dipolarophile, thus leading to the generation of new condensed five-membered ring systems (Scheme 2).



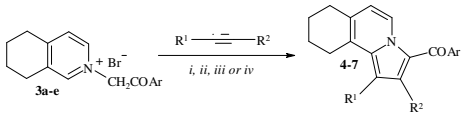
Scheme 2. Synthesis of the new 7,8,9,10-tetrahydropyrrolo[2,1-*a*]isoquinolines **4-7**

Thus compounds **4** were obtained[22] using 1,2-epoxybutane as the reaction medium and agent for the generation of the ylide *in situ* starting from the bromides **3** in the presence of methyl acetylenecarboxylate. The reaction was also carried out by using methylene chloride as the solvent and triethylamine as the base for the generation of the ylides, as in the case of compounds **5** and **6** obtained by reacting 5,6,7,8-tetrahydroisoquinolinium bromides **3** with ethyl propiolate or DMAD (Scheme 2).

Compounds **7** were obtained using acrylonitrile as the olefinic dipolarophile and TPCD (tetrakispyridineCo(II)dichromate)[15] as the oxidant in order to direct the reaction to the desired aromatic compounds.

It is noteworthy that either reaction pathway works for each dipolarophile employed with yields ranging from medium to good, and could be also extended to other dipolarophiles. The new compounds are presented in Table 1.

Table 1. The new tetrahydroisoquinolinium salts **3a-e** and the new 7,8,9,10-tetrahydropyrrolo[2,1-*a*]isoquinolines **4-7**



	R^1	R^2	Ar	m.p. (°C)	Yield (%)
3a	-	-	C_6H_5	213-215	93
3b	-	-	4-$C_6H_5C_6H_4$	219-222	90
3c	-	-	4-BrC_6H_4	260-262	87
3d	-	-	4-$MeOC_6H_4$	195-198	89
3e	-	-	3-$O_2NC_6H_4$	222-224	84
4a	COOMe	H	C_6H_5	135-136	45
4b	COOMe	H	4-$MeOC_6H_4$	129-132	60
4c	COOMe	H	3-$O_2NC_6H_4$	190-192	52
5a	COOEt	H	4-BrC_6H_4	137-139	65
5b	COOEt	H	4-$MeOC_6H_4$	140-142	54
5c	COOEt	H	3-$O_2NC_6H_4$	148-150	69
6a	COOMe	COOMe	C_6H_5	152-154	50
6b	COOMe	COOMe	4-$C_6H_5C_6H_4$	98-100	58
6c	COOMe	COOMe	4-BrC_6H_4	163-166	65
7a	CN	H	4-BrC_6H_4	149-152	60
7b	CN	H	4-$MeOC_6H_4$	175-177	63
7c	CN	H	3- $O_2NC_6H_4$	189-191	55

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The new compounds were characterized by NMR spectroscopy, and for the representative compounds **3e** and **5b**, single crystal X-ray diffraction analysis was performed.[23]

The NMR spectra of all the compounds presented the expected signals. The intermediate salts **3** were also investigated by NMR and X-ray (**3a**) analysis and their structures were confirmed.

Figure 1 shows the X-ray structure of the new salt **3e**. This is the first structural elucidation of a 5,6,7,8-tetrahydroisoquinolinium salt in which there are no substituents other than hydrogen at positions 5-8. The dihedral angle C7-C8-C9-C10 is 58.6(3)°, indicating a half-chair conformation for the partially saturated ring, while the plane of the ring N1→C6 is nearly orthogonal to the phenyl ring [interplanar angle 82.2(1)°]. Crystal cohesion is maintained by three C-H···Br^- hydrogen bonds and π-stacking of inversion-related phenyl rings with a centroid···centroid distance of 3.834 Å.

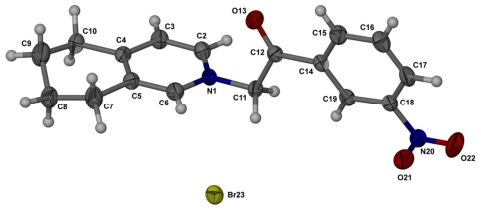


Figure 1. X-ray structure of **3e** with thermal ellipsoids for non-H atoms drawn at the 50% probability level.

The most characteristic ^{1}H-NMR signals of compounds **4-7** were the H-5 and H-6 hydrogens which appeared as two doublets with $J_{5,6}$= 7.1 Hz. In the case of the unsymmetrical dipolarophiles (ethyl propiolate, methyl propiolate and acrylonitrile), the regioselectivity of the reaction was proved by the singlet assigned to H-2 at ~7.60 ppm and confirmed by X-ray diffraction analysis. The main spectral ^{13}C-NMR features were the signals of the CO groups in the benzoyl and carboxylate moieties for compounds **4, 5** and **6**, and the CN group for compounds **7**. Carbon C-1 appeared highly shielded in compounds **7** due to the shielding effect of the attached CN group.

Figure 2 shows the X-ray structure of compound **5b**, a representative of the new 7,8,9,10-tetrahydropyrrolo[2,1-*a*]isoquinolines. The condensed ring system is rare, and as alluded to earlier, the only other known compound in this class, the X-ray structure of which had been reported, is 2-(4-bromophenyl)-5-methoxy-7,8,9,10-tetrahydropyrrolo[2,1-*a*]isoquinoline (Cambridge Structural Database refcode XIDKEB).[20] However, some structural features of **5b** are distinctly different from those reported for XIDKEB. For example, at the low temperature of the X-ray analysis, the partially saturated ring in **5b** is ordered, adopting a half-chair conformation with a C8-C9-C10-C11 dihedral angle of 61.5(4)°, with the five formal single C-C bonds being close to 1.50 Å (consistent with the results for **3e** above), whereas the equivalent dihedral angle in XIDKEB has a magnitude of only ~33°, with the distance equivalent to C9-C10 being abnormally low at ~1.33 Å. (These discrepancies are possibly due to disorder in the latter case, so further detailed comparison is not warranted). In addition, the overall conformation of **5b** is uniquely maintained by the two intramolecular C-H···O hydrogen bonds shown in Figure 2. The crystal structure is further stabilized by three intermolecular H-bonds with C···O distances in the range 3.327(3)-3.446(3) Å, π-stacking (minimum centroid···centroid distance 3.575 Å) and a C-H···π(phenyl) interaction with the H···centroid distance being 2.78 Å.

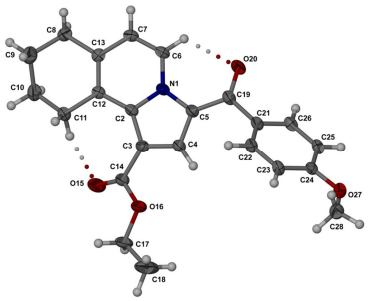
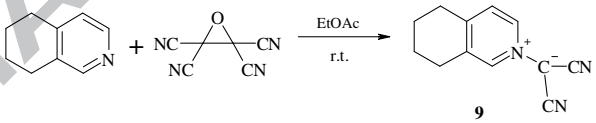


Figure 2. X-ray structure of **5b** with thermal ellipsoids for non-H atoms drawn at the 50% probability level. Dotted lines represent intramolecular C-H···O hydrogen bonds.

The isolation and characterization of stable dicyanopyridinium ylides has been of interest for many years since their first synthesis,[24] as their reactions have been employed in obtaining indolizines.[25,26] Thus, by reacting 5,6,7,8-tetrahydroisoquinoline with tetracyanomethyleneoxide, we obtained the corresponding dicyanomethylide **9** (Scheme 3), as the first stable *N*-ylide of a tetrahydroisoquinoline, which was investigated by NMR spectroscopy and X-ray analysis.



9

Scheme 3. Synthesis of novel 5,6,7,8-tetrahydroisoquinolinium dicyanomethylide **9**

The NMR spectrum showed the expected signals. In the aromatic region two multiplets with integrals of 2:1 corresponding to the three aromatic protons in the pyridine moiety were present. The ^{13}C-NMR spectrum also exhibited the expected signals, the main one being that of the exocyclic carbanion C atom which appeared at 59 ppm [the signal was resolved by adding chromium(III) acetylacetonate ($Cr(acac)_3$) to the sample].

The IR spectrum showed two distinct bands for the two CN groups at 2129 and 2171 cm^{-1}. The stable ylide **9** could be employed in further 1,3-dipolar cycloaddition reactions with the aim of conferring structural variations on the 7,8,9,10-tetrahydropyrrolo[2,1-*a*]isoquinoline framework.

Figure 3 shows the X-ray structure[23] of the new dicyanomethylide **9**. The saturated residue again adopts a half-chair conformation, as found for **3e** and **5b**, with a dihedral angle magnitude of 62.5(2)°. The six atoms comprising the dicyanomethylide unit are co-planar, with a maximum deviation from their least-squares plane of 0.006(2) Å (atom N2). The interplanar angle between this unit and the aromatic ring is 19.4(1)°. Pertinent bond lengths (listed in the caption to Figure 3) indicate a highly symmetrical arrangement about the $N2^+$-$C11^-$ axis. These are in accord with those reported in the crystal of pyridinium-1-dicyanomethylide.[27] While the two C≡N bond lengths in **9** do not differ significantly (difference ~2.6 combined standard deviations), the environments of atoms N13 and N15 in the crystal are distinct, atom N13 being the acceptor of an intermolecular hydrogen bond [C3-H3···$N13^i$ (i = *x*, *-1+y*, *z*)

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with H···N 2.47 Å, C···N 3.165(3) Å and C-H···N angle 131°], and N15 instead not engaged in hydrogen bonding. We infer that this structural difference may account for the appearance of two distinct infrared peaks in the range expected for the CN stretching vibration. In the crystal, the pyridinium rings of two inversion-related molecules of **9** engage in offset π-stacking with a centroid···centroid distance of 3.688 Å.

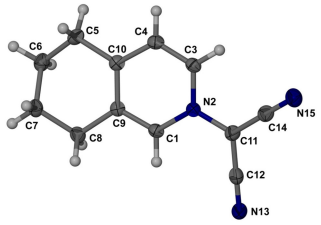

Figure 3. X-ray structure of **9** with thermal ellipsoids for non-H atoms drawn at the 50% probability level. Selected bond distances (Å): C1-N2 1.354(3), N2-C3 1.356(3), N2-C11 1.418(3), C11-C12 1.397(3), C11-C14 1.396(3), C12-N13 1.146(3), C14-N15 1.157(3).

In conclusion, we have investigated the efficient synthesis of new 7,8,9,10-tetrahydropyrrolo[2,1-*a*]isoquinolines **4**-**7** formed *via* 1,3-dipolar cycloaddition reaction of the corresponding ylides. The compounds were characterized by NMR spectroscopy as well as X-ray diffraction in the case of the representative compounds **3e** and **5a**. In addition, we were interested in investigating the stable ylides corresponding to 5,6,7,8-tetrahydroisoquinoline, and we subsequently isolated, and characterized by X-ray analysis, the corresponding tetrahydroisoquinolinium dicyanomethylide **9**. The new compounds could be of relevant synthetic and medicinal interest and show promising optical properties.

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Supplementary data

Supplementary data associated with this article can be found in the online version at DOI:

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21. The 5,6,7,8-tetrahydroisoquinoline **1** (8 mmol) and substituted bromoacetophenone **2** (8 mmol) were stirred in acetone for 6 h. The precipitated compounds **3** (see Supporting Information) obtained were filtered and were used further in the synthesis of compounds **4**-**7**. **2-[2-Phenyl-2-oxoethyl]-5,6,7,8-tetrahydroisoquinolinium bromide (3a).** Colorless crystals, with m.p. 213-215 °C, 93%. Anal. Calcd. $C_{17}H_{18}BrNO$: C 61.46, H 5.46, Br 24.05, N 4.22. Found: C 61.75, H 5.72, Br 24.42, N 4.43. ^{1}H-NMR (300 MHz, $CDCl_3$, δ): 1.83-1.88 (m, 4H, $2CH_2$); 2.90, 2.98 (2t, *J* = 6.0 Hz, 4H, $2CH_2$); 6.90 (s, 2H, CH_2-N); 7.41-7.47 (m, 2H, H-3′, H-5′); 7.55-7.58 (m, 1H, H-4′); 7.64 (d, *J* = 6.3 Hz, 1H, H-4); 8.07-8.11 (m, 2H, H-2′, H-6′); 8.89 (d, *J* = 6.3 Hz,1H, H-3); 9.02 (s, 1H, H-1). ^{13}C-NMR (75 MHz, $CDCl_3$, δ): 21.0 ($2CH_2$); 26.2, 29.7 ($2CH_2$); 65.9 (CH_2-N); 127.3 (C-4); 128.8, 129.0 (C-2′, C-3′, C-5′, C-6′); 133.5, 137.9, 142.2 (C-4a, C-8a, C-1′); 134.7 (C-4′); 145.6 (C-1); 158.4 (C-3); 190.8 (COAr).
22. To isoquinolinium bromide **3** (3 mmol) was added methyl propiolate (4 mmol) and the reactiom mixture was stirred under reflux in 1,2-epoxybutane for 12 h. After the evaporation of the solvent the residue was treated with ethanol and the crystalline compound **4** was filtered and washed with a small amount of cold ethanol on the filter paper. Compounds **4** were crystallized from ethanol. **Methyl 3-benzoyl-7,8,9,10-tetrahydropyrrolo[2,1-*a*]isoquinoline-1-carboxylate (4a)** Yellow crystals, m.p. 135-136 °C, 45% yield. Anal. Calcd. $C_{21}H_{19}NO_3$: C 75.66, H 5.74, N 4.20. Found: C 75.85, H 5.51, N 4.48. ^{1}H-NMR (300 MHz, $CDCl_3$, δ): 1.83-1.87 (m, 4H, $2CH_2$); 2.84, 3.20 (2t, *J* = 6.0 Hz, 4H, CH_2); 3.82 (s, 3H, Me); 6.79 (d, *J* = 7.1 Hz, 1H, H-6); 7.47-7.54 (m, 3H, H-3′, H-4′, H-5′); 7.72 (s, 1H, H-2); 7.77-7.80 (m, 2H, H-2′, H-6′); 9.76 (d, *J* = 7.1 Hz,1H, H-5).^{13}C-NMR (75 MHz, $CDCl_3$, δ): 21.9, 22.6 ($2CH_2$); 27.5, 29.9 ($2CH_2$); 51.6 (Me); 128.4, 129.0 (C-2′, C-3′, C-3′, C-6′); 117.9, 126.2, 131.3, 131.4 (C-2, C-5, C-6, C-4′); 107.2, 121.5, 128.1, 137.9, 139.2, 140.4 (C-1, C-3, C-6a, C-10a, C-10b, C-1′); 164.9 (COOMe); 185.1 (COAr). (For compounds **5**-**7** see the Supporting Information associated with this paper).
23. Crystallographic data (excluding structure factors) for the structures in this paper (**3e**, **5b** and **9**) have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC **3e**: 1000508; **5b**: 1000509; **9**: 1000510. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).
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