[2.2]Paracyclophane Substituted Indolizines

LAURA GABRIELA SARBU[1], ELENA BICU[1], HENNING HOPF[2], MIHAIL LUCIAN BIRSA[1]*
[1] "Al. I. Cuza" University of Iasi, Department of Chemistry, 11 Carol I Blvd., 700506, Iasi, Romania
[2] Institute of Organic Chemistry, Technical University of Braunschweig, Hagenring 30, D-38106 Braunschweig, Germany

Novel [2.2]paracyclophane substituted indolizines have been synthesized by dipolar cycloaddition of various substituted pyridinium ylides with an activated triple bond derived from [2.2]paracyclophane. The latter compound has been synthesized from the reaction of 4-formyl[2.2]paracyclophane with ethynyl magnesium chloride, followed by the oxidation of the propargylic alcohol.

Keywords: indolizines, [2.2]paracyclophanes, pyridinium ylids, propargylic alcohols

Synthetic and biosynthetic heterocycles are known to have a large variety of therapeutic uses [1-5]. Between them, sulphur and nitrogen-containing heterocyclic compounds have maintained the continuous interest of researchers [6-14]. Indolizines constitute a class of heteroaromatic compounds containing two condensed rings (5- and 6-membered) and a bridging nitrogen atom. The aromatic indolizine does not appear to occur in nature, but the reduced derivatives are commonly encountered in nature [15]. A great interest derived from the presence of these heterocyclic structures in several alkaloids isolated from the skin extracts of Neotropical frogs. Indolizine derivatives exhibit valuable biological activities and have been studied for their psychotropic anti-inflammatory, analgesic, antimicrobial, antiexudative, anti-inflammatory, and anti-tumour agents [16]. Many substituted indolizines are the subject of extensive research due to biological and other useful applications. Synthetic indolizines are widely used in drug design and pharmaceutical research [17].

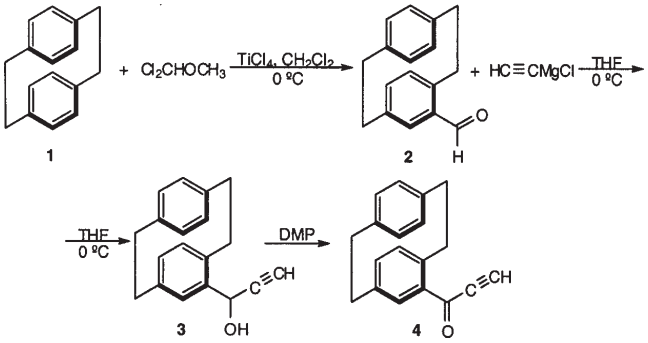
[2.2]Paracyclophanes constitute an intriguing class of compounds, which have attracted a particular interest since their first appearance in the literature [18-20]. So far, most studies have involved the structural characteristics of [2.2]paracyclophanes, particularly their geometry and steric properties, transanular interactions, and ring strain; further investigations have concerned the electronic interactions between the parallel aromatic rings, their influence on reactivity in electrophilic aromatic substitution reactions, and their implications for charge-transfer complex formation [21-24]. A great deal of attention is focused on developing new synthetic methods for synthesizing functionalized [2.2]paracyclophanes designing appropriately substituted [2.2]paracyclophanes that can serve as polycyclic hydrocarbon precursors or as chiral templates or auxiliaries [25]. Prompted by the above facts, we decided to investigate the synthesis of a combined system containing indolizine and [2.2] paracyclophane cores.

Experimental part

Analysis methods

Melting points were obtained on a Mel-Temp II apparatus. IR spectra were recorded on a Bruker Tensor 27 instrument. UV-Vis spectra were recorded on a Varian BioCarry 100 Spectrophotometer. NMR spectra were recorded on a Bruker DPX-300 Spectrometer. Chemical shifts are reported in ppm downfield from TMS. Mass spectra were recorded on a Finnigan MAT 90X spectrometer. Elemental analyses (C, H, N, S) were conducted using a CE440 Elemental Analyser; the results were found to be in good agreement (±0.25%) with the calculated values.

Synthesis



Scheme 1. Synthesis of activated acetylene **4**

*Propargylic alcohol **3***

To a solution of 4-formyl[2.2]paracyclophane (**2**, 2.62g, 11.10mmoles) in anhydrous THF (50mL), ethynyl magnesium chloride (0.6M in THF/toluene, 2.8mL, 16.8mmoles) was slowly added at 0°C. After 1h, the reaction mixture was brought to room temperature and quenched with a saturated solution of NH_4Cl. The aqueous layer was extracted with CH_2Cl_2 and the combined extracts were washed with water and brine, then dried over $MgSO_4$, and concentrated under vacuum. Crystallization from ethanol gave the pure propargylic alcohol **3** as a white solid. M.p. 101–103 °C, yield 2.77 g (95%). Analytical and spectral data of this compound are presented in table 1.

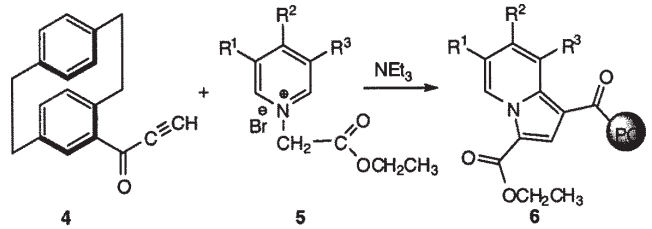
*Ethynyl [2.2]paracyclophanyl ketone **4***

To a solution of propargylic alcohol **3** (2.8g, 10.68mmoles) in CH_2Cl_2 (100 mL), DMP (6.61g, 16.04mmoles) was added and the resulting mixture was stirred at room temperature for 12h. A solution of $Na_2S_2O_3$ and a solution of $NaHCO_3$ were then added and the aqueous layer was extracted with CH_2Cl_2. The combined extracts

* email: lbirsa@uaic.ro; Tel.: (+40) 232201349

	M.p., °C	η, %	IR-ATR, cm^{-1}	NMR ($CDCl_3$)
3	101–103	95	3536, 3415, 3277, 2116	*^1H NMR* δ : 2.13 (1H, d, CH), 2.55 (1H, d, OH), 2.89-3.17 (8H, m, $4CH_2$), 5.38 (1H, dd, CHOH), 6.39-6.70 (7H, m). *^{13}C NMR* δ : 32.9, 34.4, 35.1, 35.2, 62.2, 73.9, 84.1, 129.0, 130.1, 132.5, 132.8, 132.9, 133.1, 135.4, 136.3, 138.2, 139.1, 139.6, 140.4.
4	129–131	66	3250, 2090, 1729	*^1H NMR* δ : 2.05 (1H, d, CH), 2.78-3.23 (8H, m, $4CH_2$), 6.43-6.73 (6H, m), 7.43 (1H, d, CH). *^{13}C NMR* δ : 34.4, 35.0, 35.2, 35.8, 79.1, 81.1, 131.7, 132.2, 132.9, 133.1, 136.5, 136.6, 137.8, 138.1, 139.2, 140.1, 140.2, 143.2, 178.2.

Table 1
ANALYTICAL AND SPECTRAL DATA OF COMPOUNDS **3** AND **4**



PC = [2.2]paracyclophan-4-yl

Scheme 2. Synthesis of indolizines **6**

5, 6	R^1	R^2	R^3
a	H	H	H
b	H	CH_3	H
c	CH_3	H	CH_3

	M.p., °C	η, %	IR-ATR, cm^{-1}	NMR ($CDCl_3$)
6a	144–146	33	1692, 1614, 1504, 1206	*^1H NMR* δ : 1.32 (3H, t, CH_3), 2.85-3.37 (7H, m), 3.38-3.50 (1H, m), 4.26 (2H, q, CH_2), 6.33-6.46 (1H, m), 6.54-6.58 (1H, m), 6.58-6.62 (2H, m), 6.62-6.71 (1H, m), 6.72-6.82 (1H, m), 6.83-6.92 (1H, m), 6.98-7.13 (1H, m), 7.38-7.47 (2H, m), 8.60-8.72 (1H, m), 9.50-9.60 (1H, m). *^{13}C NMR* δ : 14.4, 34.9, 35.2, 35.2, 35.7, 60.2, 114.4, 115.2, 120.5, 126.1, 126.7, 127.9, 131.7, 132.1, 132.5, 132.8, 133.1, 135.2, 135.6, 138.1, 139.2, 139.4, 139.9, 140.0, 161.2, 191.1.
6b	yellow oil	66	1688, 1615, 1507	*^1H NMR* δ : 1.26 (3H, t, CH_3), 2.45 (3H, s, CH_3), 2.83-3.16 (6H, m), 3.24-3.49 (2H, m), 4.25 (2H, q, CH_2), 6.36 (1H, d), 6.50 (1H, d), 6.54 (2H, d), 6.60 (1H, d), 6.75 (1H, d), 6.82 (1H, d), 6.90 (1H, d), 7.31 (1H, m), 8.51 (1H, m), 9.37 (1H, d). *^{13}C NMR* δ : 14.4, 21.4, 34.8, 35.1, 35.2, 35.7, 60.0, 113.3, 114.0, 117.6, 119.3, 126.3, 127.2, 131.7, 132.1, 132.5, 132.8, 133.0, 135.1, 135.5, 138.1, 138.4, 139.1, 139.2, 139.7, 139.8, 139.9, 161.1, 190.9.
6c	yellow oil	69	1688, 1615, 1507	*^1H NMR* δ : 1.31 (3H, t, CH_3), 2.39 (3H, s, CH_3), 2.78 (3H, s, CH_3), 2.83-3.07 (3H, m), 3.07-3.23 (3H, m), 3.23-3.39 (1H, m), 3.57-3.74 (1H, m), 4.29 (2H, q, CH_2), 6.43 (1H, d), 6.57 (3H, m), 6.69 (1H, d), 6.80 (1H, d), 6.92 (1H, m), 7.03 (1H, m), 7.30 (1H, m), 9.39 (1H, m). *^{13}C NMR* δ : 14.5, 18.3, 21.5, 35.1, 35.2, 35.5, 35.6, 60.0, 113.2, 117.7, 123.8, 124.4, 126.4, 129.5, 130.0, 131.1, 132.5, 132.8, 135.2, 135.7, 135.8, 136.8, 139.0, 139.3, 139.3, 139.9, 141.7, 161.2, 190.7.

Table 2
ANALYTICAL AND SPECTRAL DATA OF INDOLIZINES **6a-c**

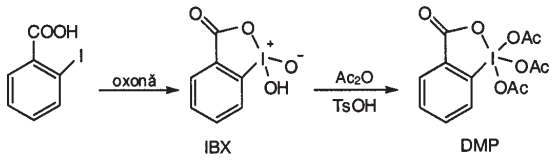
were washed with water and brine, dried over $MgSO_4$ and concentrated under vacuum. Purification by flash chromatography (silica gel, CH_2Cl_2/pentan = 1:1) gave the pure product, ketone **4**, as a yellow solid. M.p. 129–131 °C, yield 1.83 g (66%). Analytical and spectral data of this compound are presented in table 1.

*Indolizine **6a** ($R^1 = R^1 = R^1 = H$)*
General Procedure

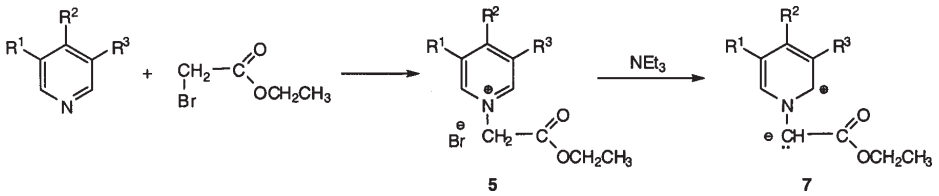
To a suspension of **5a** (0.246g, 1mmole) in CH_2Cl_2 (10mL), triethylamine (0.14mL, 1mmole) and a solution of ketone **4** (0.26g, 1mmole) in CH_2Cl_2 (5mL) were added. The reaction mixture was stirred at room temperature for 1h and then concentrated under vacuum. Crystallization from ethanol gave the pure indolizine **6a** as a yellow solid. M.p. 144–146 °C, yield 0.14 g (33%). Analytical and spectral data of indolizines **6a-c** are presented in table 2.

Results and discussions

4-Formyl[2.2]paracyclophane (**2**) has been synthesized according to the reported procedure using α,α-dichloromethyl methyl ether and $TiCl_4$ (Rieche formylation) [26, 27]. Addition of ethynyl magnesium chloride to the carbonyl function of **2** in anhydrous THF, at 0°C, leads to the corresponding propargylic alcohol **3**. The structure of this compound has been proved by spectral data (table 1). The disappearance of the absorption band of the carbonyl group from the IR spectrum and of the characteristic signals from the NMR spectra indicates the addition of the ethynyl anion. Moreover, the new signals corresponding to the propargylic carbon atom and the triple bond atoms revealed the presence of the propargyl moiety. Oxidation of the propargylic alcohol to the corresponding ketone **4** has been performed using Dess-Martin periodane reagent (DMP) (scheme 3) [28, 29]. The spectral data (table 1) confirm the structure of ketone **4**. Again, the NMR data provided



Scheme 3. Synthesis of DMP



Scheme 4. Synthesis of pyridinium salts **5** and of corresponding ylids

important structural information, like the disappearance of the signal for the propargylic alcohol carbon atom from 62.2 ppm and the appearance of a new signal at 178.2 ppm for the ketone carbon atom.

Pyridinium salts **5a-c** have been prepared by reacting - bromo ethyl acetate with different substituted pyridines (scheme 4) [30]. Under basic conditions, the pyridinium salts provide the corresponding type **7** ylids *in situ*, which further react with dipolarophiles as described in scheme 2.

The structure of indolizines **6a-c** has been proved by analytical and spectral data, as described in table 2. The NMR spectra indicate the presence of both indolizine and [2.2]paracyclophane moieties.

Conclusions

The synthesis of a new class of indolizines substituted with [2.2]paracyclophane has been accomplished by dipolar cycloaddition of pyridinium ylides with an activated triple bond derived from [2.2]paracyclophane. The latter compound has been synthesized from 4-formyl [2.2]paracyclophane following an addition-oxidation reaction sequence. Biological application of these indolizine derivatives are under investigation.

Acknowledgments : This work was supported by a grant of the Romanian National Authority for Scientific Research, CNDI– UEFISCDI, project number 51/2012.

References

1. DUA, R., SHRIVASTAVA, S., SONWANE, S. K., SRIVASTAVA, S. K., Adv. Biolog. Res., **5**, 2008, p. 120.
2. NORMAN, S. R., Drug Develop. Res., **69**, 2008, p. 15.
3.BRAVERMAN, S., CHERKINSKY, M., BIRSA, M. L., ZAFRANI, Y., Eur. J. Org. Chem., 2002, p. 3198.
4.BRAVERMAN, S., CHERKINSKY, M., BIRSA, M. L., GOTTLIEB, H. E., Synthesis, 2003,p. 849.
5.BELEI, D., BICU, E., JONES, P. G., BIRSA, M. L., Synlett, 2010, p. 931.
6.LUNGU, N. C., SANDU, I., CHIRITA, P., BIRSA, M. L., Rev. Chim. (Bucharest), **64**, no. 7, 2013, p. 697.
7.BUHACEANU, R., LUNGU, N. C., FORNA, N. C., ASAFTEI, I. V., CHIRITA, P., BIRSA, M. L., Rev. Chim. (Bucharest), **64**, no. 8, 2013, p. 803
8.BUHACEANU, R., LUNGU, N. C., FORNA, N. C., ASAFTEI, I. V., CHIRITA, P., BIRSA, M. L., Rev. Chim. (Bucharest), **64**, no. 9, 2013, p. 960.
9. CHIRITA, P., SCHLEGEL, M. L., Chem. Geol., **334**, 2012, p. 131.
10.CHIRITA, P., SAMIDE, A., RUSU, O., PREDA, M., BERDAN, I., Rev. Chim. (Bucharest), **55**, no. 2, 2004, p. 227.
11. CHIRITA, P., SAMIDE, A., RUSU, O., PREDA, M., Rev. Chim. (Bucharest), **54**, no. 12, 2003, p. 950.
12. CHIRITA, P., BERDAN, I., Rev. Chim. (Bucharest), **56**, no. 5, 2005, p. 477.
13.SAMIDE, A., CHIRITA, P., RUSU, O., PREDA, M., Rev. Chim. (Bucharest), **55**, no. 12, 2004, p. 1022.
14. CHIRITA, P., Surf. Interface Anal., **41**, 2009, p. 405.
15. SINGH, G. S., MMATLI, E. E., Eur. J. Med. Chem., **46**, 2011, p. 5237.
16.VEMULA, V. R., VURUKONDA, S., BAIRI, C. K., Int. J. Pharm. Sci. Rev. Res., **11**, 2011, p. 159
17. FLITSCH, W., in Comprehensive Heterocyclic Chemistry, KATRITZKY, A. R., REES, C. W., Eds., Pergamon Press, Oxford, **4**, 1984, p. 443.
18. BROWN, C. J., FARTHING, A. C., Nature (London), **164**, 1949, p. 915.
19.CRAM, D. J., STEINBERG, H., J. Am. Chem. Soc., **73**, 1951, p. 5691.
20.VÖGTLE, F., NEUMANN, P., Synthesis, 1973, p. 85.
21.STAAB, H. A., KNAUS, G. H., HENKE, H.-E., KRIEGER, C., Chem. Ber., 116, 1983, p. 2785.
22.BOEKELHEIDE, V., Top. Curr. Chem., 113, 1983, p. 87.
23.HOPF, H., MARQUARD, C., in Strain and its Implications in Organic Chemistry, de MEIJERE, A.; BLECHERT, S., Eds., Kluwer, Dordrecht, 1983, p. 297.
24.VÖGTLE, F., Cyclophane Chemistry, Synthesis, Structure and Reactions, Wiley, Chichester, 1993, p. 71.
25.ROZENBERG, V. I., SERGEEVA, E. V., HOPF, H., in Modern Cyclophane Chemistry, GLEITER, R; HOPF, H. Eds., Wiley-VCH: Weinheim, 2004, p. 435.
26.RIECHE, A., GROSS, H., HÖFT, E., Chem. Ber., **93**, 1960, p. 88.
27.DALTON, M. H., CRAM, D. J., J. Am. Chem. Soc., **94**, 1972, p. 2471.
28. DESS, D. B., MARTIN, J. C., J. Org. Chem., **48**, 1983, p. 4155.
29. DESS, D. B., MARTIN, J. C., J. Am. Chem. Soc., **113**, 1991, p. 7277.
30. SARKUNAM, K., NALLU, M., J. Heterocyclic Chem., **42**, 2005, p. 5

Manuscript received: 3.10.2013