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Unexpected and novel synthesis of spirojulolidines via intramolecular cyclization of *N*-carbethoxymethyl spirotetrahydroquinolines catalyzed by PPA

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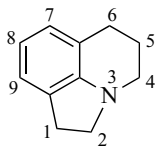
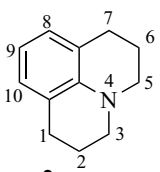
Abstract—A series of *N*-carbethoxymethyl spirotetrahydroquinolines (**6**) were prepared and subjected to cyclization. We show that cyclization of (**6**) in the presence of excess PPA results in a 50–62% yield of unexpected spirojulolidines (**7**).

The skeletons of the tricyclic compounds of the 1,2,5,6-tetrahydro-4*H*-pyrrolo[3,2,1-*ij*]quinoline and 2,3,6,7-tetrahydro-1*H*,5*H*-benzo[*ij*]quinolizine systems appear as a basic structural moieties in lilolidine[1] (**1**) and julolidine[2] (**2**) alkaloids. Their derivatives show very interesting properties that depend on functional groups.



1



2

The syntheses and biological activities of 2-oxolilolidines as well as 4-oxo- and 6-oxolilolidines have been extensively studied.[3–7] Most practical and classical construction of lilolidine and julolidine skeletons focus on the use of tetrahydroquinoline or aniline derivatives as starting materials by way of *N*-alkylation followed by intramolecular electrophilic cyclization.[8,9] Recently, Katriztky reported a convenient synthesis of julolidine derivatives in high yields by using benzotriazole methodology.[10]

In connection with our studies on the synthesis of spirotetracyclic systems containing the tetrahydroquinoline skeleton (**3**) as a basic structural unit, we have recently synthesized spiro analogs of 2-oxolilolidine (**4**)[11] and wish to prepare the 1-oxo-spirolilolidines (**5**) from *N*-carbethoxymethylspirotetrahydroquinolines (**6**). In this paper, we describe an unusual conversion of these starting materials under acidic conditions into new 7,9-disubstituted spirojulolidines (**7**).

Intramolecular Friedel–Crafts reactions promoted by Brönsted and Lewis acids are powerful methods for rapid construction of carbocyclic and heterocyclic compounds.[12] As outlined in Eq. (1), our approach to the above mentioned and unexpected spirojulolidines started from spirotetrahydroquinolines (**3**), which were easily prepared.[13] After spirotetrahydroquinolines **3a–e** were *N*-carbethoxymethylated,[14] the resulting *N*-alkylated compounds **6a–e** were formed in 56–79% yield, and NH-spiro-tetrahydroquinolines were recovered in 20–35%. Compounds **6a–e** were isolated from the reaction mixture by alumina column chromatography as maroon oils. All attempts to further improve the yields of (**6**) by extending the reaction time or by using different solvents (benzene, DMF) met with failure. The ^{1}H NMR spectra[15] of these compounds are very similar to those of precursors **3a–e**, except for the signals of the CH_3, CH_2O and N-CH_2 protons of the *N*-car-

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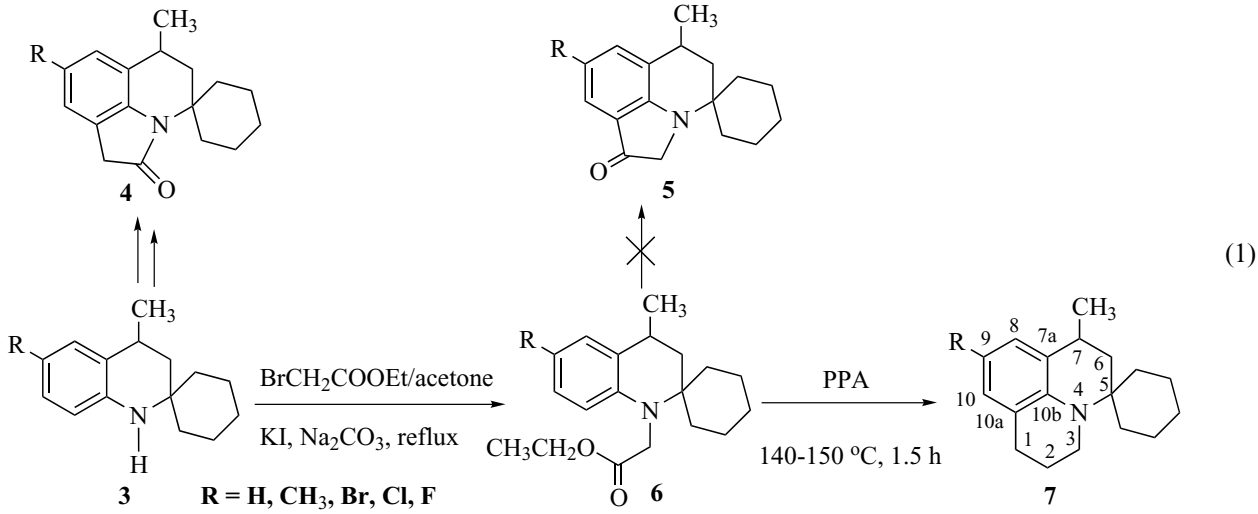

(1)

bethoxymethyl fragment, which resonated as a triplet, a quartet and a doublet of doublets at 1.19–1.27, 4.10–4.22 and 3.76–3.86 and 4.10–4.20 ppm, respectively.

Cyclization to the unexpected spirojulolidines (**7**) was achieved by heating compounds (**6**) in the presence of PPA at 140–150°C during 1.5 h. Under these reaction conditions, the spirojulolidines **7a**–**e** were obtained in 50–62% yields as red oils after NaOH work-up of the reaction mixture, extraction and alumina chromatography purification. In all cases, the expected 1-oxospirolilolidines (**5**) have not been detected. It is noteworthy that the attempted cyclization of (**6**) in the presence of concentrated H_2SO_4 led to decomposition. This result suggested that spirojulolidines (**7**) are formed as a consequence of an unusual rearrangement process of (**6**), promoted by PPA.

The structural elucidation of (**7**) was mainly based on NMR and mass spectrometry studies and elemental analyses. The ^1H and ^{13}C NMR data and 2D experiments allowed an unambiguous statement of the formation of the julolidine ring.[16] Thus, the ^1H NMR spectra displayed the signals of three (for compound **7a**) or two (for compounds **7b**–**e**) aromatic protons. The six aliphatic protons of the three methylene groups of the new piperidine ring appeared as four multiplets. In all ^{13}C NMR spectra a signal characteristic of a carbonyl group was absent.

In conclusion, the results presented here provide a novel, very attractive route to unknown spirojulolidines. The transformation of (**6**) into (**7**) apparently proceeds by an unanticipated carbethoxymethyl rearrangement, that is currently under study. This new julolidine ring system synthesis could well be general and is being further investigated in our laboratory.

Acknowledgements

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14. The alkylation of compounds (**3**) was carried out with 1.5 equiv. of ethyl bromoacetate in the presence of 0.2 equiv. of KI and 1.5 equiv. of $NaCO_3$ in acetone at reflux during 15–17 hours.

15. Selected NMR data for compounds (**6**). Data for compound **6a**: ^{1}H NMR (400 MHz, $CDCl_3$, δ): 1.20–1.82 [10H, m, $(CH_2)_5$], 1.27 (3H, t, $J=7.1$, **CH_3**-CH_2-), 1.32 (1H, t, $J=14.3$, H_{ax}-3), 1.35 (3H, d, $J=6.7$, 4-CH_3), 2.37 (1H, dd, $J=4.3$ and 13.3, H_{eq}-3), 2.82 (1H, m, H-4), 3.86 (1H, d, $J=18.5$, N-CH_B), 4.20 (1H, d, $J=18.5$, N-CH_A), 4.22 (2H, q, OCH_2), 6.32 (1H, d, $J=8.4$, H-8), 6.65 (1H, t, $J=7.7$, H-6), 7.03 (1H, t, $J=7.9$, H-7), 7.13 (1H, dd, $J=1.2$ and 7.5, H-5).

16. Selected NMR data for compounds (**7**). Data for compound **7a**: ^{1}H NMR (400 MHz, $CDCl_3$, δ): 1.16–1.90 [10H, m, $(CH_2)_5$], 1.19 (1H, t, $J=12.6$, H_{ax}-6), 1.34 (3H, d, $J=6.6$, 7-CH_3), 1.95 (2H, td, $J=4.0$ and 13.1, H-2), 2.36 (1H, dd, $J=4.5$ and 13.1, H_{eq}-6), 2.76 (2H, m, H-1), 2.77 (1H, m, H-7), 3.08 (1H, ddd, $J=4.3$, 7.6 and 11.8, H_B-3), 3.45 (1H, dt, $J=5.0$ and 10.6, H_A-3), 6.44 (1H, t, $J=7.6$, H-9), 6.83 (1H, d, $J=7.0$, H-10), 6.97 (1H, d, $J=7.6$, H-8).