

NOVEL FUSED TRIHETEROCYCLIC SYSTEMS.

SYNTHESIS OF 6H-PYRIDO[2,3-c]PYRROLO[1,2-e]-1,2,5-TRIAZEPINES

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Abstract — The synthesis of 6H-pyrido[2,3-c]pyrrolo[1,2-e]-1,2,5-triazepines has been described:

This communication presents a facile synthetic approach to the unknown pyridine isoster of benzopyrrolotriazepine¹. This, 3-amino-2-chloropyridine (1a) was interacted with 2,5-dimethoxytetrahydrofuran in boiling acetic acid following the procedure of Clauson-Kaas² to give 2-chloro-3-(N-pyrrolyl)-pyridine (2a). The 2-chlorine atom of the latter compound was easily replaced by a hydrazino group giving the derivative (3). Heating this hydrazino derivative in acetic anhydride resulted in acetylation with concomitant cyclodehydration leading to 3-methyl-8-(N-pyrrolyl)-1,2,4-triazolo[4,3-a]pyridine (4).

Another cyclization involving the pyridine nitrogen could be realised by heating (3) with acetylacetone to give 3,5-dimethyl-10-(N-pyrrolyl)-pyrido[2,1-c]-1,2,4-triazepine (5), bp 180°C at 0.05mm, nmr ; 8.46 (1H, dd, H7, JH7-H9=1.50 Hz, JH7-H8=4.50 Hz) ; 8.08 (1H, dd, H9, JH9-H8=7.80 Hz, JH9-H7=1.50 Hz) ; 7.60 (1H, dd, H8, JH8-H7=4.50 Hz, JH8-H9=7.80 Hz) ; 5.91 (1H, s, H4) ; 6.51 (2H, t, H2', H5') ; 6.08 (2H, t, H3', H4') ; 2.18 (3H, s, CH₃) ; 1.78 (3H, s, CH₃).

The reactivity of the α -position in pyrrole towards electrophiles made it possible to apply both Vilsmeier-Haack and Friedel-Crafts reactions on compound (2a) to give the formyl and acyl derivatives (6a-c). The formyl derivative (6a) was converted into its oxime which was immediately³ treated with acetic anhydride yielding the corresponding cyano compound (6d). When compounds (6a-d) were heated under reflux with hydrazine hydrate, the title compounds (7a-d) were obtained. Acetylation of (7d) resulted in the diacetyl derivative (8). On the other hand, the 6H-8-hydrazinopyrido[2,3-c]pyrrolo[1,2-e]-1,2,5-triazepine (7e) could be obtained when 3-amino-2,5-dichloropyridine (1b) was used instead of (1a) as starting material. Further synthetic studies are in progress.

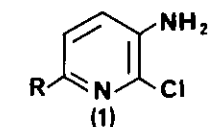
Physical and analytical data :

Compounds (1a-1b) are commercially available (ALDRICH). All elemental analyses are in accordance with the structures proposed. Nmr spectra were measured on VARIAN-EM390 90 MHz using DMSO-d₆ as a solvent and TMS as internal reference.

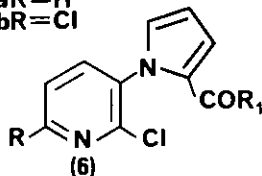
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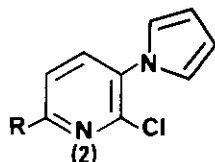
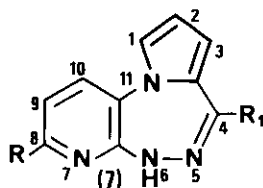
TABLE



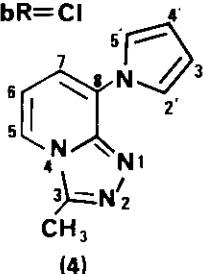
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bR=Cl



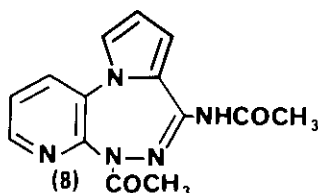
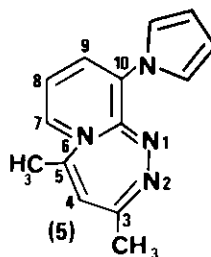
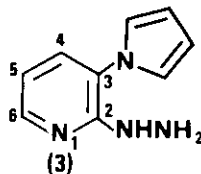
aR=H, COR₁=H
bR=H, COR₁=CH₃
cR=H, COR₁=C₂H₅
dR=H, COR₁=CN
eR=Cl, COR₁=H



aR=H
bR=Cl



aR=R₁=H
bR=H, R₁=CH₃
cR=H, R₁=C₂H₅
dR=H, R₁=NH₂
eR=NHNH₂, R₁=H



(2a), bp 154°C at 0.05mm, nmr ; 8.38 (1H, dd, H₆, JH₆-H₄=1.80 Hz, JH₆-H₅=4.5 Hz) ; 7.88 (1H, dd, H₄, JH₄-H₅=7.8 Hz) ; 7.30 (1H, dd, H₅, JH₅-H₄=7.8 Hz) ; 7.30 (2H, t, H₂'-H₅') ; 6.25 (2H, t, H₃'-H₄') ; (2b), bp 140°C at 0.05mm, nmr ; 7.35 (1H, d, H₄, JH₄-H₅=8.1 Hz) ; 7.60 (1H, d, H₅, JH₅-H₄=8.1 Hz) ; 7.00 (2H, t, H₂'-H₅') ; 6.25 (2H, t, H₃'-H₄') ; (3), mp 74°C, nmr ; 8.11 (1H, dd, H₆, JH₆-H₄=1.62 Hz, JH₆-H₅=4.8 Hz) ; 7.38 (1H, dd, H₄, JH₄-H₅=7.50 Hz) ; 6.71 (1H, dd, H₅, JH₅-H₄=7.50 Hz) ; 6.91 (2H, t, H₂'-H₅') ; 6.26 (2H, t, H₃'-H₄') ; 6.45 (1H, s, NH) ; 4.2 (2H, s, NH₂) ; (4), mp 186°C, nmr ; 8.20 (1H, dd, H₅, JH₅-H₆=6.60 Hz, JH₅-H₇=0.72 Hz) ; 7.95 (1H, dd, H₇, JH₇-H₆=7.20 Hz) ; 7.00 (1H, dd, H₆, JH₆-H₅=6.60 Hz, JH₆-H₇=7.20 Hz) ; 7.95 (2H, t, H₂'-H₅') ; 6.31 (2H, t, H₃'-H₄') ; (6a), mp 146°C, nmr ; 9.46 (1H, d, CHO, JH₅'-CHO=0.9 Hz) ; 8.48 (1H, dd, H₆, JH₆-H₄=1.8 Hz, JH₆-H₅=4.5 Hz) ; 7.95 (1H, dd, H₄, JH₄-H₆=1.8 Hz, JH₄-H₅=7.8 Hz) ; 7.55 (1H, dd, H₅, JH₅-H₆=4.5 Hz) ; 7.36 (1H, dd, H₅', JH₅'-H₃'=1.8 Hz, JH₅'-H₄'=2.7 Hz) ; 7.23 (1H, dd, H₃', JH₃'-H₅'=1.8 Hz, JH₃'-H₄'=3.9 Hz) ; 6.50 (1H, dd, H₄', JH₄'-H₃'=3.9 Hz, JH₄'-H₅'=2.7 Hz) ; (6b), mp 106°C, nmr ; 8.46 (1H, dd, H₆, JH₆-H₄=1.8 Hz, JH₆-H₅=4.5 Hz) ; 7.81 (1H, dd, H₄, JH₄-H₆=1.8 Hz, JH₄-H₅=7.8 Hz) ; 7.45 (1H, dd, H₅, JH₅-H₆=4.5 Hz, JH₅-H₄=7.8 Hz) ; 7.21 (1H, dd, H₅', JH₅'-H₃'=1.8 Hz, JH₅'-H₄'=2.7 Hz) ; 7.16 (1H, dd, H₃', JH₃'-H₄'=3.9 Hz, JH₃'-H₅'=1.8 Hz) ; 6.35 (1H, dd, H₄', JH₄'-H₃'=3.9 Hz, JH₄'-H₅'=2.7 Hz) ; 2.31 (1H, s, CH₃) ; (6c), mp 72°C, nmr ; 8.46 (1H, dd, H₆, JH₆-H₄=1.8 Hz, JH₆-H₅=4.5 Hz) ; 8.00 (1H, dd, H₄, JH₄-H₆=1.8 Hz, JH₄-H₅=7.8 Hz) ; 7.55 (1H, dd, H₅, JH₅-H₄=7.8 Hz, JH₅-H₆=4.5 Hz) ; 7.86 (1H, dd, H₅', JH₅'-H₃'=2.1 Hz, JH₅'-H₄'=1.8 Hz) ; 7.08 (1H, dd, H₃', JH₃'-H₄'=3 Hz, JH₃'-H₅'=2.1 Hz) ; 6.61 (1H, dd, H₄', JH₄'-H₃'=3 Hz, JH₄'-H₅'=1.8 Hz) ; 2.76 (2H, dd, CH₂) ; 1.05 (3H, t, CH₃) ; (6d), mp 98°C, nmr ; 8.56 (1H, dd, H₆, JH₆-H₄=1.62 Hz, JH₆-H₅=4.8 Hz) ; 8.15 (1H, dd, H₄, JH₄-H₆=1.62 Hz, JH₄-H₅=7.50 Hz) ; 7.63 (1H, dd, H₅, JH₅-H₆=4.8 Hz, JH₅-H₄=7.50 Hz) ;

7.41 (1H, dd, H5', JH5'-H3'=1.5 Hz, JH5'-H4'=2.7 Hz) ; 7.20 (1H, dd, H3', JH3'-H5'=1.5 Hz, JH3'-H4'=3.9 Hz) ; 6.41 (1H, dd, H4', JH4'-H5'=2.7 Hz, JH4'-H3'=3.9 Hz) ; (6e), mp 148°C, nmr ; 8.03 (1H, d, H4, JH4-H5=8.10 Hz) ; 7.66 (1H, d, H5, JH5-H4=8.10 Hz) ; 7.35 (1H, dd, H5', JH5'-H3'=1.8 Hz, JH5'-H4'=2.7 Hz) ; 7.21 (1H, dd, H3', JH3'-H4'=3.9 Hz, JH3'-H5'=1.8 Hz) ; 6.45 (1H, dd, H4', JH4'-H5'=2.7 Hz, JH4'-H3'=3.9 Hz) ; 9.45 (1H, s, CHO) ; (7a), mp 176°C, nmr ; 9.00 (1H, dd, H4, JH4-H1=0.6 Hz) ; 8.70 (2H, m, H8, H10) ; 8.51 (1H, m, H1) ; 8.05 (1H, s, NH) ; 7.55 (1H, dd, H9, JH9-H8=4.8 Hz, JH9-H10=7.80 Hz) ; 6.96 (2H, m, H2, H3) ; (7b), mp 142°C, nmr ; 8.50 (1H, s, NH) ; 7.95 (1H, dd, H8, JH8-H10=1.5 Hz, JH8-H9=4.8 Hz) ; 7.66 (1H, tt, H10-H8=1.5 Hz, JH10-H9=7.80 Hz, JH10-NH=0.84 Hz) ; 7.26 (1H, dd, H1, JH1-H2=2.7 Hz, JH1-H3=1.56 Hz) ; 6.95 (1H, dd, H9, JH9-H10=7.80 Hz, JH9-H8=4.8 Hz) ; 6.55 (1H, dd, H3, JH3-H1=1.56 Hz, JH3-H2=3.90 Hz) ; 6.28 (1H, dd, H2, JH2-H1=2.70, JH2-H3=3.90 Hz) ; 2.15 (3H, s, CH₃) ; (7c), mp 120°C, nmr ; 9.33 (1H, s, NH) ; 8.01 (1H, dd, H8, JH8-H10=1.5 Hz, JH8-H9=4.8 Hz) ; 7.71 (1H, tt, H10, JH10-H9=7.80 Hz, JH10-H8=1.5 Hz) ; 7.30 (1H, dd, H1, JH1-H2=2.7 Hz, JH1-H3=1.56 Hz) ; 7.00 (1H, dd, H9, JH9-H8=4.8 Hz, JH9-H10=7.80 Hz) ; 6.58 (1H, dd, H3, JH3-H2=3.90 Hz, JH3-H1=1.56 Hz) ; 5.98 (1H, dd, H2, JH2-H3=3.90 Hz, JH2-H1=2.7 Hz) ; 2.70 (2H, dd, CH₂) ; 1.10 (3H, t, CH₃) ; (7d), mp 214°C, nmr ; 8.00 (2H, m, H8, H10) ; 7.86 (1H, dd, H1, JH1-H2=2.7 Hz, JH1-H3=1.56 Hz) ; 7.25 (1H, dd, H3, JH3-H1=1.56 Hz, JH3-H2=3.90 Hz) ; 6.78 (1H, dd, H9, JH9-H8=4.8 Hz, JH9-H10=7.80 Hz) ; 6.53 (1H, dd, H2, JH2-H1=2.7 Hz, JH2-H3=3.90 Hz) ; 5.61 (2H, s, NH₂) ; 5.40 (1H, s, NH) ; (7e), mp 238°C, nmr ; 9.03 (1H, s, H4) ; 8.81 (1H, d, H10, JH10-H9=8.4 Hz) ; 8.55 (1H, dd, H1, JH1-H2=2.70 Hz, JH1-H3=1.56 Hz) ; 7.65 (1H, d, H9, JH9-H10=8.4 Hz) ; 7.40 (2H, s, NH₂) ; 7.05 (1H, dd, H3, JH3-H2=1.56 Hz, JH3-H1=1.56 Hz) ; 6.95 (1H, dd, H2, JH2-H3=3.90 Hz, JH2-H1=2.7 Hz) ; 3.45 (1H, s, NH) ; (8), mp 262°C, nmr ; 8.38 (1H, dd, H8, JH8-H10=1.50 Hz, JH8-H9=4.8 Hz) ; 8.13 (3H, m, H1, H10, NH) ; 7.20 (1H, dd, H9, JH9-H8=4.8 Hz, JH9-H10=7.80 Hz) ; 6.85 (1H, dd, H3, JH3-H1=1.56 Hz, JH3-H2=3.90 Hz) ; 6.60 (1H, dd, H2, JH2-H3=3.90 Hz, JH2-H1=2.7 Hz) ; 2.30 (3H, s, COCH₃) ; 2.08 (3H, s, COCH₃).

REFERENCES AND NOTES

- 1) G. Stefancich, M. Artico, F. Correlli, and S. Massa, *Synthesis*, 757, (1983).
- 2) N. Clauson-Kaas and Z. Tyle, *Acta Chem. Scand.*, **6**, 667, (1952) ; N. Elming and N. Clauson-Kaas, *Ibid.*, **6**, 867, (1952).
- 3) This oxime was not isolated because it decomposes with a violent explosion on standing.

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