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LETTERS

Synthesis of 1,1,1-Ethanetriacetonitrile[1], Precursor of 6-Substituted-4-methyl-2-aminopyridines

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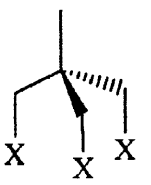
Abstract : 1,1,1-ethanetriacetonitrile **1a**, a new symmetrical tridentate ligand has been prepared from 3-methylpentenedioic acid diethylester. 6-Substituted-4-methyl-2-aminopyridines were obtained through organometallic additions on **1a**. © 1997 Published by Elsevier Science Ltd. All rights reserved.

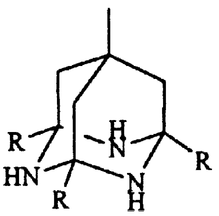
Although trinitrile **1a** has been considered for the synthesis of 2,4,9-triazaadamantane derivatives **2** through additions of organometallic compounds[2,3] or as a tridentate ligand[4], it has never been prepared. Its synthesis had been attempted, without success, from trihalogeno compound **1b** by nucleophilic substitution with cyanide[2], or from triamide **1c**[3] (from trichloride **1d**). Here we report the synthesis of 1,1,1-ethanetriacetonitrile from 3-methylpentenedioic acid diester and its transformation to 6-substitued-4-methyl-2-aminopyridine.

The first attempt to prepare **1a** by reaction of triacid **1e** with chlorosulfonyl isocyanate[5] led to 3-methyl-3-(cyanomethyl)pentanedioic anhydride **3**[6]. To the best of our knowledge, such a formation of an anhydride in this reaction has not been reported.

An other approach, from diester **4a**[7] allowed the synthesis of trinitrile **1a**[6] in three steps (**4a** → **4b** → **5** → **1a**). Conversion of **4a** to dinitrile **4b** could only be achieved in 18% yield with dimethylaluminiumamide[8] (other methods were even less successful[9]). Michael addition of methylcyanoacetate anion to **4b** gave **5** (71%)[10]. **1a** was then obtained (72%) through elimination of the carbomethoxy group of **5**[6] with paraaminothiophenol and cesium carbonate in dimethylformamide[11]. The total yield from diester **4a** was 9.2%.



1a X=CN
1b X=Br, I
1c X=$CONH_2$
1d X=COCl
1e X=CO_2H



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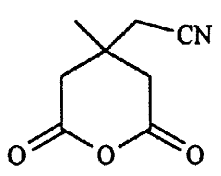

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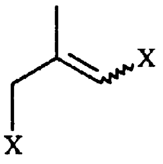
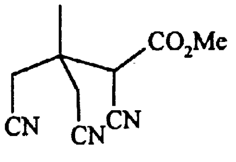


4a X=CO_2Et
4b X=CN
4c X=CO_2H
4d X=COCl



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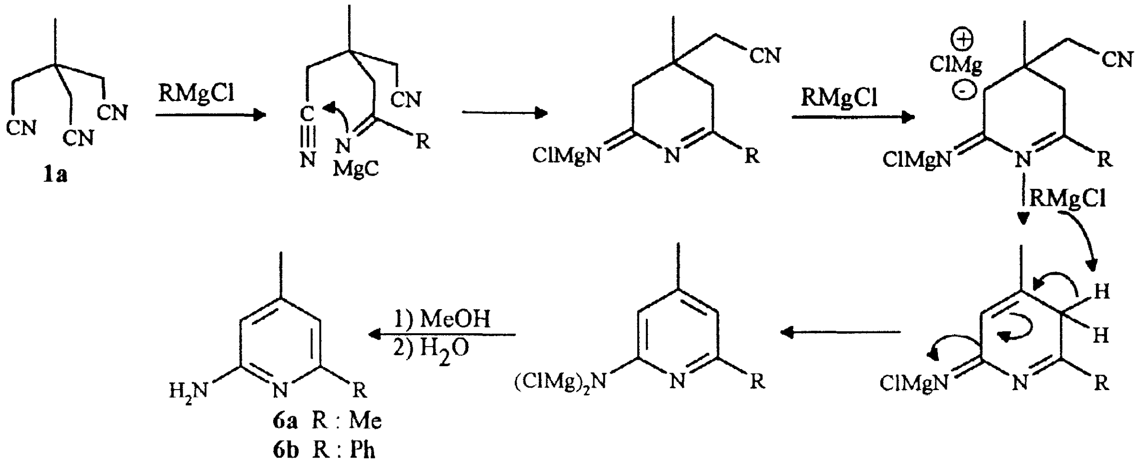
Addition of organometallic reagent led to substituted 2-aminopyridines (scheme). With methylmagnesium chloride, **6a** was isolated in 14% yield, most of the starting material undergoing a retro-Michael elimination to **4b** (44% yield); with phenylmagnesium bromide in presence of anhydrous cerium chloride, **6b**[6] was isolated in 40% yield.



References and Notes

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4. Hoskins, B.F.; Robson, R. *J. Am. Chem. Soc.* **1990**, *112*, 1546-1554.
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6. Spectral data (^{1}H and ^{13}C N.M.R., M.S.) of this new compound are in agreement with its structure.
7. Bland, N.; Thorpe, J.F. *J. Chem. Soc. Trans.* **1912**, *101*, 1557-1570.
8. Basha, A.; Lipton, M.; Weinreb, S.M. *Tetrahedron Lett.* **1977**, 4171-4174.
9. Dinitrile **4b** was obtained by reaction between 3-methylpentenedioic acid **4c** and chlorosulfonyl isocyanate in 9% yield after two chromatography on silica. Attempted preparation of 3-methylpentenedioyl dichloride **4d** from **4c** only gave 6-chloro-4-methyl-2-H-pyran-2-one (Cornforth, J.; Hawes, J.E.; Mallaby, R. *Aust. J. Chem.* **1992**, *45*, 179-185).
10. To a stirred solution of 1.24 g (23 mmol) of sodium methylate in 7.0 ml of absolute methanol were added 12.0 ml (136 mmol) of methylcyanoacetate. After 40 min 0.688 g (6.4 mmol) of 3-methylpentenedinitrile **4b** in 2 ml of absolute methanol were added with a syringe. After 19 h the reaction mixture was hydrolysed at 0°C with 20 ml of 3.5% HCl solution and extracted with ether. Organic layer was washed with brine and dried with sodium sulfate. Evaporation of the solvent gave an oil witch was heated to 100°C under 1 mmHg. The residual material was chromatographied on silica (elution with ether) yielding 0.933 g (71%) of pure **5** as a yellow oil.
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