Pergamon

Tetrahedron Letters, Vol. 35, No. 33, pp. 5989-5992, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $7.00+0.00

0040-4039(94)01267-9

An Efficient Synthesis of 2-Chloro-3-carboethoxy- or 2-Chloro-3-cyano- 4,5-disubstituted and 5-substituted Pyrroles

Louise H. Foley+

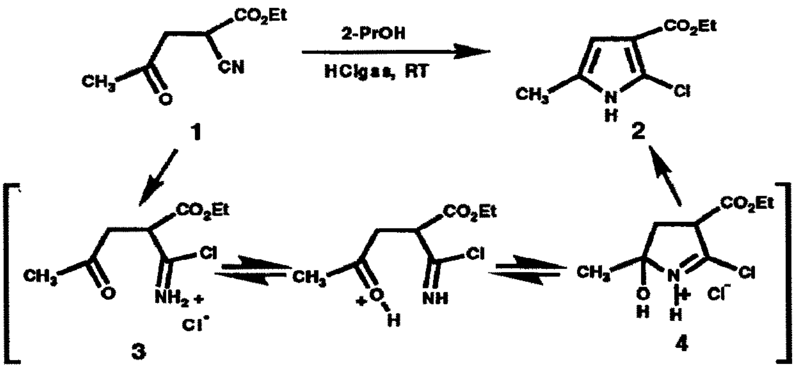
Department of Chemistry, University of New Hampshire, Durham, NH 03824
& Roche Research Center, Hoffmann-La Roche Inc., Nutley, NJ 07110

Abstract: Reaction of substituted 2-cyano-4-oxo-alkanoic acid ethyl esters or 2-cyano-4-oxo-alkanonitriles with HCl gas in 2-propanol or concentrated HCl in 2-propanol for the dinitriles provides an efficient synthesis of substituted 2-chloropyrroles from readily available starting materials and reagents.

The number of different methods available for the synthesis of pyrroles[1] is reflective of their abundance in natural products. However, only occasionally is the cyano group used for the direct preparation of pyrroles;[2] more often it serves as the precursor of a primary amine which is cyclized to afford pyrroles.[3,4] A one-step synthesis of 2-chloropyrroles containing an electron withdrawing group at C-3 from readily available acyclic keto-nitrile precursors is reported in this paper.

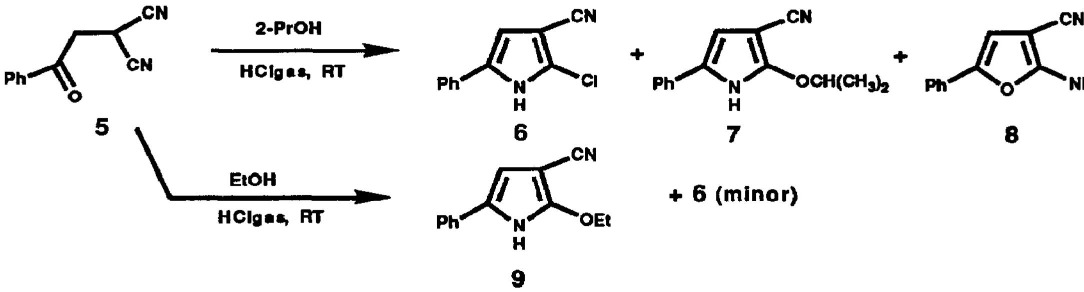
During an investigation of methods for the conversion of nitriles into amides under acidic conditions, the use of HCl gas in 2-propanol was explored. This method was used by Johnson and Crosby[5,6] to convert of α-aminonitriles and α-hydroxynitriles into the corresponding α-substituted amides. The mechanism of the reaction to afford amides, essentially the Pinner Reaction, involves conversion of the nitrile initially into the imidoyl chloride, which on reaction with 2-propanol affords the imidate. A SN2 attack by chloride ion on the propyl group of the imidate then gives the amide.[7,8]

Treatment of ethyl 2-cyano-4-oxopentanoate (1) with gaseous HCl in 2-propanol at room temperature afforded nearly a quantitative yield of the 3-carboethoxy-4-methyl-2-chloropyrrole (2),[9] with no evidence of the expected amide or 3-carboethoxy-4-methyl-2-aminofuran, which would result from acid catalyzed enolization of the 4-keto group. No intermediates or side products were detected by TLC during the course of this reaction. The formation of the pyrrole most likely involved generation of the imidoyl chloride salt **3** which then cyclized to the cyclic iminium ion **4** before it could react with 2-propanol to give the imidate. Dehydration and



deprotonation of **4** would then yield the observed pyrrole **2**.

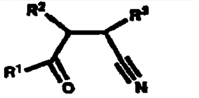
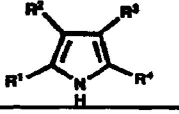
A similar reaction carried out with the aromatic ketone **5** produced the 2-chloropyrrole **6** and 2-isopropoxypyrrole **7** (ratio 3 : 1) and a trace amount of the furan **8** after 3 days in 2-propanol. When the reaction was carried out in ethanol, the 2-ethoxypyrrole **9** was isolated as the major product and **6** as the minor product (ratio 7 : 1). The 2-ethoxypyrrole **9** presumably resulted from cyclization of ethyl imidate, since treatment of **6** with HCl gas in ethanol, as expected, did not produce **9**. The slower rate of cyclization with the less reactive aromatic ketone apparently allows sufficient time for conversion of the imidoyl chloride into the imidate prior to cyclization and in the case of ethanol, a less hindered alcohol, this becomes the major pathway. Ester interchange was an additional problem when the reaction of the phenacyl derivative of ethyl cyanoacetate (exp 4) was carried out in alcoholic solvents. Thus for the aromatic ketones the use of ether as solvent leads to fewer side products and separation of the chloropyrroles from the furan side products is easily accomplished by silica gel chromatography ($CHCl_3$ - MeOH 99:1 as eluent).



Examples and yields for these and other substrates are given in the **Table**. Interestingly reaction of the dinitriles (exp 5-7) is much faster than the cyanoesters (exp 1-3), the latter taking at least 20 h at room temperature to complete, while the former only 3-6 h. The reaction of the dinitriles (exp 5-7) to give good yields of the pyrroles **13**, **14**, **15** could also be carried out in 2-propanol with concentrated HCl, in place of gaseous HCl, but required considerably longer reaction times (24-40 h). No pyrrole was generated with the cyanoester precursors or from phenacylmalononitrile with concentrated HCl over a period of 72 h. Despite giving good yields of crystalline products, the 3,4-disubstituted pyrroles prepared by the gaseous HCl method (exp 3 & 6) are highly colored, the pyrrole **11** being light red and pyrrole **14** a light blue-purple. However, the use of concentrated HCl gave the 2-chloropyrrole **14** as a white solid. Replacing gaseous HCl with HBr produced mainly decomposition from the ketone **1**. Replacement of 2-propanol with ether or ethanol in the case of reaction of the cyanoesters with HCl gas also gave 2-chloropyrroles, except with aromatic ketones as noted above, but the reactions were less clean. In all cases the substituted 2-chloropyrroles are crystalline and the alkyl pyrroles are easily separated from any unreacted starting material by a single crystallization from methanol-water; the arylpyrroles may require chromatography prior to crystallization.

The presence of an electron withdrawing group, shown here as an ester or nitrile, α to the nitrile is critical to the success of this reaction, without it mainly tars are generated (exp 11, 12), in agreement with the reported instability of halogenated pyrroles which lack an electron withdrawing group.[10,11] However, the 2-chloropyrroles prepared here are stable at room temperature for months and in a refrigerator for years. R^1 can be alkyl or phenyl, other aromatics or substituted phenyls have not been explored.

Table

Exp	 a)	Solvent	# 	Yield b) HCl gas	Yield b) conc HCl
1	R^1 = Me, R^2 = H, R^3 = CO_2Et	2-PrOH	2 R^1= Me, R^2= H, R^3=CO_2Et, R^4 = Cl	96 %	
2	R^1 = Et, R^2 = H, R^3 = CO_2Et	2-PrOH	10 R^1= Et, R^2= H, R^3=CO_2Et, R^4 = Cl	83 %	
3	R^1, R^2 = Me, R^3 = CO_2Et	2-PrOH	11 R^1, R^2 = Me, R^3 = CO_2Et, R^4 = Cl	65 %	
4	R^1 = Ph, R^2 = H, R^3 = CO_2Et	Ether	12 R^1 = Ph, R^2 = H, R^3 = CO_2Et, R^4 = Cl	65 % c)	
5	R^1 = Et, R^2 = H, R^3 = CN	2-PrOH	13 R^1 = Et, R^2 = H, R^3 = CN, R^4 = Cl	70 %	84 %
6	R^1 = R^2 = Me, R^3 = CN	2-PrOH	14 R^1 = R^2 = Me, R^3 = CN, R^4 = Cl	70 %	88 %
7	R^1, R^2 = $-(CH_2)_4-$, R^3 = CN	2-PrOH	15 R^1, R^2 = $-(CH_2)_4-$, R^3 = CN, R^4 = Cl	84 %	92 %
8	R^1 = Ph, R^2 = H, R^3 = CN	2-PrOH	6 R^1 = Ph, R^2 = H, R^3 = CN, R^4 = Cl	72 % d)	
9	R^1 = Ph, R^2 = H, R^3 = CN	Ether	6 R^1 = Ph, R^2 = H, R^3 = CN, R^4 = Cl	73 % c)	
10	R^1 = Ph, R^2 = H, R^3 = CN	EtOH	9 R^1 = Ph, R^2 = H, R^3 = CN, R^4 = OEt	72 %	
11	R^1 = Me, R^2 = R^3 = H	2-PrOH	Tars		
12	R^1, R^2 = $-(CH_2)_4-$, R^3 = H	2-PrOH	Tars		

a) Prepared according to references 3 or 12 and reference 13 for Exp 11.
b) Yields are for first crop only, additional material was always present in the mother liquors.
c) Plus 20% 2-amino-3-carboethoxy-5-phenylfuran (Exp 4) & 15% 2-amino-3-cyano-5-phenylfuran (8) (Exp 9).
d) 23% 2-isopropoxy-3-cyano-5-phenylpyrrole (7).

Although this method works better for the preparation of alkyl substituted pyrroles than for the phenyl substituted pyrroles, purification of the pyrroles by crystallization or chromatography allows isolation of pure 2-chloropyrroles in good to excellent yields. In addition to the requirement for an electron withdrawing group as noted above, a further limitation of this method is that the starting ketone can not have a conjugating group (R^2) on the adjacent carbon, since it has already been shown that the acyclic precursors can not be isolated due to their rapid cyclization to furans.[3]

The ease of preparation of the requisite starting keto-nitriles[3,12] and clean conversion to pyrroles having a removable chlorine (hydrogenolysis) and modifiable substituents make this a useful synthetic method.

General procedures: (2-propanol and HCl gas) (exp 1) A solution of the cyanoketo ester **1** (1.0 g) in 2-propanol (30 mL) was cooled in an ice-water bath while HCl gas (1.7 g) was bubbled in. After the HCl addition was complete the cooling bath was removed and the stirring continued as the solution warmed to room temperature and then at room temperature for 26 h or until TLC (silica gel $CHCl_3$-CH_3OH 99:1) showed the reaction to be complete. Nitrogen was then bubbled through the light yellow solution to remove the excess HCl and the reaction solution was concentrated to leave a cream colored solid. Recrystallization from methanol-water gave 1.06 g (96%; mp 111-112 °C) of **2**[14] as cream colored crystals.

(2-propanol and conc. HCl) (exp. 5) For 2-cyano-4-oxo-hexanenitrile (0.21 g) was dissolved in 10 mL of 2-propanol and 3 mL of concentrated HCl was carefully added. The solution was capped and left at room temperature for 20-40 h (monitored by TLC hexanes-EtOAc (8:2)). Concentration, drying, and crystallization (methanol-water) of the resulting solid afforded 0.2 g (84% yield; mp 93-94 °C) of the pyrrole **13**,[14] additional product was available from the mother liquors.

ACKNOWLEDGMENTS: The author is indebted to Professor George Büchi (M.I.T.) and Dr. Dennis Keith (Roche) for helpful comments on the manuscript.

REFERENCES AND NOTES

\+ Address correspondence to the author at: Hoffmann-La Roche Inc., 340 Kingsland St., Nutley, NJ 07110

1. A recent review of methods for preparing pyrroles can be found in: Bean, G.P. The Synthesis of 1H-Pyrroles. In *Heterocylic Compounds Vol 48 Part 1 'Pyrroles'*, Jones, R.A. Ed.; Interscience Publishers; New York, 1990; Ch. 2; p. 105-294.
2. Middleton, W.J.; Engelhardt, V.A.; Fisher, B.S. *J. Am. Chem. Soc.* **1958**, *80*, 2822-2829. Nasakin, O.E.; Alekseev, V.V.; Promonenkov, V.K.; Abramov, I.A.; Bulai, A. Kh. *Zh. Org. Khim.* **1981**, *17*, 1958-1961. (English translation 1747-1749). Zepeda, L.G.; Rojas-Gardida, M.; Morales-Rios, M.S.; Joseph-Nathan, P. *Tetrahedron* **1989**, *45*, 6439-6448.
3. Korte, F.; Trautner, K. *Chem. Ber* . **1962**, *95*, 307-318.
4. Babler, J.H.; Spina, K.P.*Tetrahedron Lett.*. **1984**, *25*, 1659-1660.
5. Johnson, H.E.; Crosby, D.G. *J. Org. Chem.* **1963**, *28*, 3255-3256.
6. Johnson, H.E.; Crosby, D.G. *J. Org. Chem.* **1962**, *27*, 798-802.
7. Stevens, C.L.; Morrow, D.; Lawson, J. *J. Amer. Chem. Soc.* **1955**, *77*, 2341-2343.
8. Cramer, F.; Baldauf, H. *Chem. Ber.* **1959**, *92*, 370-378.
9. All new compounds had IR, UV, NMR, and MS data consistent with the structures.
10. Jones, R.A.; Bean, G.P.*The Chemistry of Pyrroles* ; Academic Press, New York, 1977; Chapter 4 page 130.
11. Cordell, G.A. *J. Org. Chem.* **1975**, *40*, 3161-3169.
12. Hogan, I.; Jenkins, P.D.; Sainsbury, M. *Tetrahedron* **1990**, *46*, 2943-2964.
13. Prepared from 2-cyano-4-oxo-pentanoic acid ethyl ester using NaCl in DMSO/H_2O at reflux. Reaction carried out by M. B. Carter (UNH Undergraduate).
14. Spectra **2**: IR (nujol) 3250, 1670, 1590; NMR (200 MHz, $CDCl_3$) δ 1.33 (t, 3H), 2.19 (s, 3H), 4.27 (q, 2H), 6.25 (d, 1H, J = 1.98 becomes a singlet on D_2O exchange), 8.30 (bs, 1H, D_2O exchangeable) Spectra **13**: IR (nujol) 3230, 3160, 2230,1585; NMR (200 MHz, $CDCl_3$) δ 1.22 (t, 3H), 2.56(q, 2H), 6.08 (d, 1H, J = 2.82 becomes a singlet on D_2O exchange), 8.40 (bs, 1H, D_2O exchangeable).

(Received in USA 24 *May* 1994; *revised* 17 *June* 1994; *accepted* 21 *June* 1994)