Indian Journal of Chemistry
Vol. 43B, May 2004, pp. 1008-1011

Note

Nickel chloride hexahydrate: A novel reagent for Michael addition on α,β-unsaturated acids — A facile one-step route to 3-arylmercaptopropionic acids from thiophenols and α,β-unsaturated acids

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Received 10 March 2003; accepted (revised) 3 December 2003

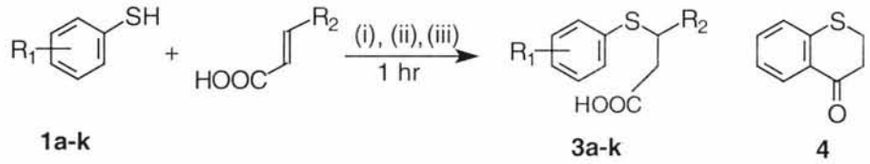
Michael additions have been successfully carried out in presence of a base, but when an α,β-unsaturated acid is a substrate, it would be most unlikely for a carboxylate ion bearing α,β-unsaturated site to undergo a Michael addition. This problem has been circumvented in the present paper by carrying out a nickel chloride hexahydrate mediated Michael addition of thiophenols **1a-k** on acrylic acid and on cinnamic acid to give 3-aryl mercaptopropionic acids **3a-k** in excellent yield.

IPC: Int.Cl.[7] C 07 G 53/00

Acid promoted cyclodehydration of 3-aryl mercaptopropionic acids **3** provides a very convenient synthetic entry to the biologically active thiochroman-4-one ring system[1]. Appropriately substituted thiochroman-4-ones for example, 7-sulphamoyl thiochroman 1,1-dioxides are effective diuretics[2], thiochroman-6-acetic acids possess anti-inflammatory, antipyretic and analgesic activity[3], phenethylamines derivatives obtained through Mannich's reaction on thiochroman-4-ones are α-sympatholytic[4] and antidepressant[5], 4-substituted aminothiochromans are active as antihypertensives, antidepressants and against angina pains[6]. Coupled with this, the claim of 3,3-dibromo-6-halo thiochroman-4-one S-oxides to exhibit antitumour characteristics[7] and substituted 4-phenyl-thiochroman-4-ols to be useful as oral antifertility agents[8] has stimulated further interest in this nucleus from yet another perspective. We required a good synthesis of 3-arylmercaptopropionic acids **3** for our studies on thiochroman-4-ones[9]. The acid **3** results from the nucleophilic displacement of a thiophenoxide ion on 3-halopropionic acids[10] or esters[11] or nucleophilic ring opening of β-propiolactone[12] or by the Michael addition to acrylate esters[13] or acrylonitrile[14] with subsequent hydrolysis. The Michael addition procedure originally developed by Tarbell[13] is by far the most simplest but as esters were employed in this procedure, two steps i.e; an additional step of the hydrolysis of ester is also required in the preparation of **3**. We describe in this note a versatile modification of Tarbell's procedure which avoids the use of acrylic esters and gives highly pure **3** in excellent yield directly from the acrylic acid (**Scheme I**).

The method involved, heating an equimolecular mixture of thiophenol **1a**, acrylic acid and $NiCl_2.6H_2O$ in quinoline:pyridine (3:1 v/v) mixture[15] for 1 hr. On addition of an excess of HCl pure **3** precipitated out from the reaction mixture in almost quantitative yield. This procedure circumvented the step of hydrolysis of the ester in Tarbell's method and opened the possibility of using acrylic acid directly in the preparation of **3**. The reaction was extended to phenyl substituted acrylic acid for example to cinnamic acid and the corresponding acid **3k** was isolated in good yield (**Table I**).

The formation of **3,** from **1** and acrylic acid in presence of nickel chloride hexahydrate and quinoline:pyridine mixture can most plausibly be



1a-k **3a-k** **4**

(i) $NiCl_2 . 6H_2O$, (ii) Quinoline:Pyridine mixture(3:1, v/v) (iii) Conc.HCl

Scheme I

rationalized in terms of the existence of six co-ordinated octahedral complexes of general formula $(Ni\text{-}O\text{-}CO\text{-}R)_2(H_2O)_2\ L_2$ (L= pyridine or quinoline) which have been shown to be formed from carboxylic acids and Ni(II) salts[16]. We presume that a six co-ordinated monomeric **5** or polymeric complex **6** of nickel is formed[15] with acrylic acid in presence of quinoline (**Figure 1**). Structure **7** shows the dispersal of the carbanion's negative charge through the parallel *d*-orbitals of nickel in this complex. We believe, it is this extrastability inherent to the carbanion, in the nickel complexed species **5** that facilitates the addition of **1** on the acrylic acid.

Table I — 3-Arylmercaptopropionic acids **3a-k** from thiophenols **1a-k**

Compd	R_1	R_2	Product[a]	Yield (%)
1a	H	H	**3a**	95
1b	3-Me	H	**3b**	90
1c	4-Me	H	**3c**	93
1d	3-OMe	H	**3d**	92
1e	4-OMe	H	**3e**	94
1f	2-Cl	H	**3f**	85
1g	3-Cl	H	**3g**	85
1h	4-Cl	H	**3h**	88
1i	3-Br	H	**3i**	85
1j	4-Br	H	**3j**	86
1k	H	Ph	**3k**	76

(a) Products were duly characterized by elemental analysis, IR and ^1H NMR spectral data and were compared with the authentic samples

Michael additions are usually carried out in presence of a base. In the event of an uncomplexed acid being the substrate, a carboxylate ion is formed and it would be most unlikely for a carboxylate ion bearing α,β-unsaturated substrate to undergo Michael addition with anionic species. This is precisely the reason why esters and not acids have been employed in the Michael addition reactions. In the present procedure the carboxylate species from acrylic acid is not available in the medium, it is grabbed by Ni(II) species to form the chelated complex **5** or **6,** or both, which facilitated Michael additions on the acid.

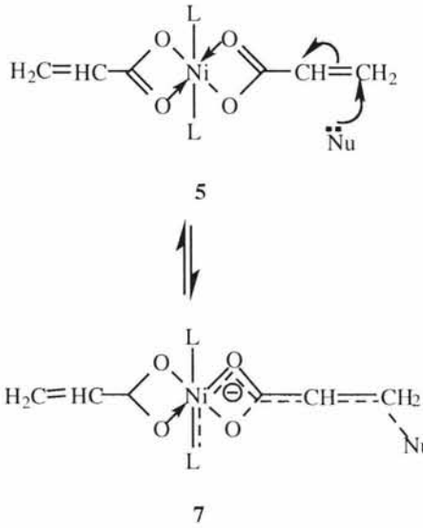
Ni(0) species form complexes with olefins[17]. Such a complex formation involving a Ni(II) species with the olefinic double bond of acrylic acid is to be ruled out.

Characterization of all the products **3a-k** was made by spectroscopic means (**Table II**) as well as by direct comparison with authentic samples prepared through known routes[18].

Experimental Section

All the melting points are uncorrected. IR spectra were recorded on Pye Unicam Model SP3-300 infracord in nujol and on KBr pellets. ^1H NMR spectra were recorded on Varian EM 360 L using $CDCl_3$ as solvent and TMS as internal reference. Lancaster make thiophenols were used, as received from the suppliers.

General procedure for preparation of 3-phenyl-mercaptopropionic acid 3a-k. Thiophenol (**1a-j**; 0.01 mole), acrylic acid (0.72 g, 0.01 mole) and



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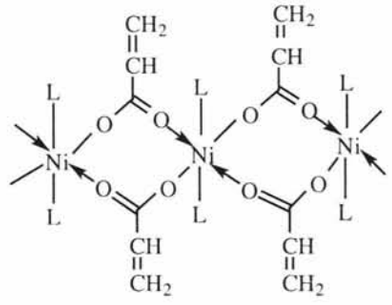

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Figure 1

Table II — Physical and spectroscopic data of the 3-arylmercaptopropionic acids **3a-k**

Compd	m.p. °C	m.p. (rep[ref])	IR (cm^{-1})	^1H NMR in $CDCl_3$(δ, ppm)
3a	58.5	(58[10a])	3300-2600, 1710, 730	12.4 (s, 1H, COOH), 7.2-7.5 (m, 5H, ArH), 4.42 (t, *J*=7.8Hz, 2H, S-CH_2), 3.35 (t, *J*=7.8Hz, 2H, C-CH_2)
3b	65	(65-6[10e])	3300-2600, 1715, 750, 1470, 1365	12.3 (s, 1H, -COOH), 7.0-7.6(m, 4H, ArH), 4.44 (t, *J*=7.8Hz, 2H, S-CH_2), 3.36 (t, *J*=7.8Hz, 2H, C-CH_2), 2.85(s, 3H, CH_3)
3c	69	(69-70[10e])	3300-2600, 1715, 750, 1470, 1365	12.3 (s, 1H, -COOH), 7.10(d, *J*=7.5Hz, 2H, ArH), 7.6(d, *J*=7.5Hz, 2H, ArH), 4.44 (t, *J*=7.8Hz, 2H, S-CH_2), 3.36 (t, *J*=7.8Hz, 2H, C-CH_2), 2.85(s, 3H, CH_3)
3d	46	(46-7[10e])	3300-2600, 1705 740, 1440, 1375	12.5 (s, 1H, -COOH), 6.82-7.35(m, 4H, ArH), 4.45 (t, *J*=7.8Hz, 2H, S-CH_2), 3.34 (t, *J*=7.8Hz, 2H, C-CH_2), 3.99(s, 3H, CH_3)
3e	81	(81-2[10e])	3300-2600, 1705, 740, 1440, 1375	12.5 (s, 1H, -COOH), 6.85(d, *J*=8Hz, 2H ArH), 7.35(d, *J*=8Hz, 2H, ArH), 4.45 (t, *J*=7.8Hz, 2H, S-CH_2), 3.34 (t, *J*=7.8Hz, 2H, C-CH_2), 3.99(s, 3H, CH_3)
3f	98.7	(98.5-99[10f])	3400-2500, 1720, 760	12.6 (s, 1H, -COOH), 7.20-7.7(m, 4H, ArH), 4.47 (t, *J*=7.8Hz, 2H, S-CH_2), 3.37 (t, *J*=7.8Hz, 2H, C-CH_2)
3g	77	(77-78[10e])	3400-2500, 1720, 760	12.6 (s, 1H, -COOH), 7.21-7.6(m, 4H, ArH), 4.47 (t, *J*=7.8Hz, 2H, S-CH_2), 3.37 (t, *J*=7.8Hz, 2H, C-CH_2)
3h	90	(90-91[10e])	3400-2500, 1720, 760	12.6 (s, 1H, -COOH), 7.10(d, *J*=8.2Hz, 2H ArH), 7.6 (d, *J*=8.2Hz, 2H, ArH), 4.47 (t, *J*=7.8Hz, 2H, S-CH_2), 3.37 (t, *J*=7.8Hz, 2H, C-CH_2)
3i	90.5	(90-91[10e])	3350-2450, 1715, 756	12.5 (s, 1H, -COOH), 7.14 -7.52(m, 4H, ArH), 4.46 (t, *J*=7.8Hz, 2H, S-CH_2), 3.35 (t, *J*=7.8Hz, 2H, C-CH_2)
3j	115	(114-15[10e])	3350-2450, 1715, 756	12.5 (s, 1H, -COOH), 7.12(d, *J*=8Hz, 2H ArH), 7.5 (d, *J*=8Hz, 2H, ArH), 4.46 (t, *J*=7.8Hz, 2H, S-CH_2), 3.35 (t, *J*=7.8Hz, 2H, C-CH_2)
3k	86	(85-6[10a])	3300-2600, 1710, 730	12.4 (s, 1H, COOH), 7.2-7.5 (m, 10H, ArH), 5.88 (t, *J*=7.8Hz, 2H, S-CH), 3.35 (d, *J*=7.8Hz, 2H, C-CH_2)

$NiCl_2.6H_2O$ (2.3 g, 0.01 mole) were refluxed in quinoline:pyridine (3:1 v/v) mixture (10 mL) for 1 hr. Cooled mixture was acidified with conc. HCl and the precipitated acid was filtered. It was dissolved in $NaHCO_3$ and reprecipitated with conc. HCl. The product was dried and recrystallized from ethanol: water (4:1 v/v) mixture. In a similar manner **3k** was obtained from cinnamic acid. Yield and melting point of the recrystallized products **3a-k** are given in **Tables I** and **II**.

Acknowledgement

The authors wish to thank CDRI, Lucknow, India, for providing micro analytical and ^1H NMR spectral data.

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