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New synthesis of alpha-methyl-2-thiopheneacetic acid, a key intermediate of tiaprofenic acid and process related impurity

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ABSTRACT

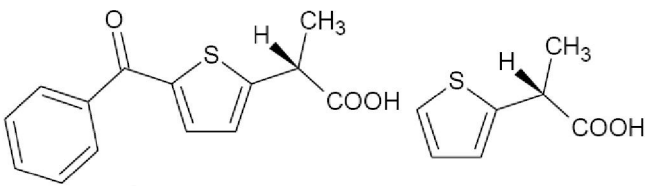
An industrially efficient method was developed to synthesize alpha-methyl-2-thiopheneacetic acid, a key intermediate of tiaprofenic acid (5-benzoyl-alpha-methyl-2-thiopheneacetic acid) which is a very important pharmaceutical compound having anti-inflammatory and analgesic activity. Sodium-2-bromopropionate is reacted with 2-thienylmagnesiumbromide and further acidification to give alpha-methyl-2-thiopheneacetic acid. One known impurity was synthesized and characterized.

KEYWORDS

Magnesium metal;
2-Thienylmagnesiumbromide;
Impurity;
Tiaprofenic acid;
NSAID.

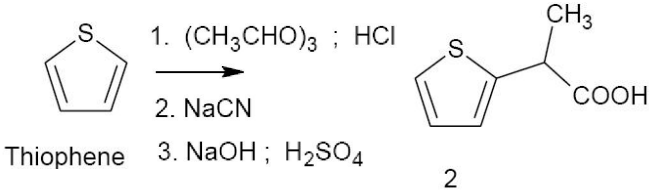
INTRODUCTION

Tiaprofenic Acid (1) is NSAID (non-steroidalantinflammatory drug), similar to ibuprofen. It reduces inflammation and fever and relieves pain. Tiaprofenic Acid (1) is also used in the treatment of arthritis, headaches and menstrual cramps. Several processes for the preparation of the alpha-methyl-2-thiopheneacetic acid (2) derivatives are known.



1 **2**

All the known processes[1-3] (Scheme 1) use the alpha-methyl-2-thiopheneacetic acid (2) as intermediate product The preparation of said intermediate shows several drawbacks being based on very laborious and low yield processes contemplating very expensive or very dangerous reactants such as sodium cyanide. We wish to report to use Grignard reagent[4], which is easy to handle even at the production scale, and the reaction temperature reported was room temperature.

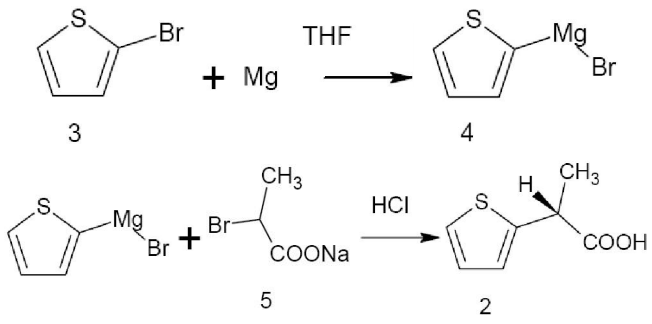


Scheme 1

RESULTS AND DISCUSSION

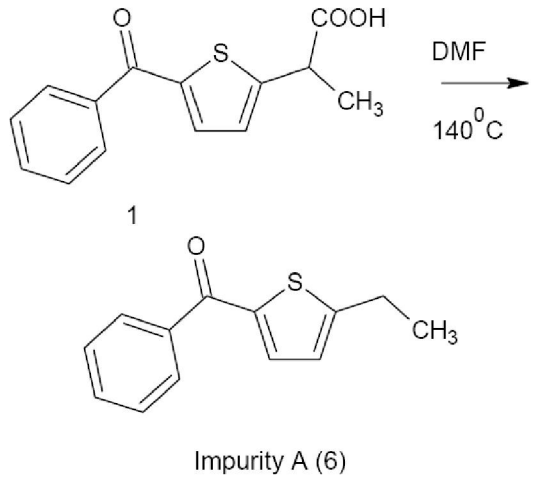
We present an economically and industrially viable synthesis of alpha-methyl-2-thiopheneacetic acid, which is obtained from 2-Bromothiophene (3) in two steps by employing commercially available, less expensive, nontoxic raw materials by simplified experimental con-

ditions and isolation procedures. sodium salt of 2-bromopropionic acid is reacted with an thienylmagnesiumbromide, yield of alpha-methyl-2-thiopheneacetic acid (2) was obtained. (Scheme 2)



Scheme 2

The British Pharmacopoeia[5] specifies that individual impurity is not more than 0.1% and total impurity is not more than 0.3%. During the process development of Tiaprofenic acid three known were identified in the analysis of different batches whose percent area ranged from 0.05-0.3% by HPLC. One known impurity was synthesized and characterized (Scheme 3). To the best of our knowledge, synthesis route of impurity is new and not reported in literature. Due to the importance of regulatory authorities and all the impurities should be at the level of >0.1% must identify and characterized.



Impurity A (6)

Scheme 3

Structure elucidation of (5-ethyl thiophene-2yl)phenyl methanone (6) or impurity A

Sample was analyzed by HPLC and its purity was found to be 98.14%, molecular weight of is impurity A is 216. The protonated molecular ion at m/z 217 (M+1) confirms the mass as 216 corresponding to molecular formula of $C_{13}H_{12}OS$. IR spectrum displayed characteristic absorptions at 3110, 3072, 2936, & 1735 cm-1 corresponding to aromatic >CH and carbonyl stretching. The peaks at 1518.65 & 1432.52 cm^{-1} in IR spectrum is indicative of >C=C< ring stretching.

^{1}H NMR (300 MHz, $CDCl_3$): 1.37 (t, 3H); 2.92 (m, 2H); 3.70-4.0 (m, 3H); 6.85 (d, 1H); 7.45 (m, 3H); 7.57 (t, 1H); 7.82 (d, 2H).

^{13}C NMR (70 MHz, $CDCl_3$): 15.5, 24.0, 124.8, 128.3, 129.0, 131.9, 135.4, 138.3, 140.9, 157.9, 187.9.

EXPERIMENTAL

2-Bromothiophene and sodium salt of 2-bromopropionic acid are obtained from commercial source.

Mass spectrometry

Electrospray ionization mass spectroscopy was performed using an ion trap mass spectrometer (Model 6310 Agilent). The positive and negative eletrospray MS data was obtained by switching the capillary voltage between n+5000 and -4500V respectively.

NMR spectroscopy

The NMR experiments were performed on Brukeravance II 400 MH_Z. The ^{1}H chemical shift values were reported in the δ scale in ppm, relative to TMS (δ=0.00) and the ^{13}C chemical shift values were reported relative to $CDCl_3$ (δ = 77.00 ppm) and DMSO, d6 (δ=39.50 ppm) as internal standards.

FT-IR spectroscopy

The IR spectra were recorded in the solid state as KBr dispersion medium using perkin Elmer spectrum 100 FT-IR spectrophotometer.

Preparation of thienylmagnesiumbromide (4)

10 gr (0.416) of magnesium turnings is placed in the flask and covered with 200 ml of dry THF. Ten milliliters of a solution of 50 grm of 2-bromothiophene in 60 ml. of dry THF is added at reflux, the Grignard reaction is (0.3067) started by gently warming the reaction flask, and the remainder of the solution is added dropwise during 45 minutes at reflux. The mixture is stirred for 6 hours at reflux. The reactor mass was

cooled to room temperature and collected THF layer into the addition funnel U/N_2.

Preparation of alpha-methyl-2-thiopheneacetic acid (2)

Sodium 2-bromopropionate (53.6 gm, 0.3067 mol) was suspended in THF (30ml) and cooled to 10-15° C. Added grignard reagent (2-Thienylmagnesiumbromide in THF) for 1 hr at 10-15°C and maintained for 2 hr. Reaction was monitored by GC. The reaction mixture was cooled to 0-5^{0}C. Added Con HCl (50 gm, 0.5mol) and stir for 30min. THF was then evaporated under reduced pressure and extracted with methylene dichloride (2 X 100ml). The dichloro methane layer was then evaporated under reduced pressure and cooled to room temperature to get light yellow oil. (30 gr, 62%)

NMR ($CDCl_3$): 1.6(d,3H), 4.02(q, 1H), 6.92 (t, 1H), 6.96 (brd, 1H), 7.22 (dd, 1H)

Impurity synthesis

Preparation of (5-ethyl thiophene-2yl)phenyl methanone (6) or impurity A

Tiaprofenic acid (10 gm, 0.038 mol) was suspended in DMF (40ml) at 25-35° C. Heated to 140-150°C and maintained for 3 hr. Reaction was monitored by HPLC. The reaction mixture was cooled to 20-25^{0}C, diluted with water (200 ml) and extracted with methylene dichloride (2 X 100ml). The dichloro methane layer was then evaporated under reduced pressure and cooled to room temperature to get reddish oil. (7gr, 84%)

CONCLUSION

The research paper describes the synthesis of alpha-methyl-2-thiopheneacetic acid, a key intermediate of tiaprofenic acid (5-benzoyl-alpha-methyl-2-thiopheneacetic acid) and related impurities structure elucidation. The synthesis of impurity was also discussed.

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