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A Long Chain Alcohol as Support in Solid Phase Organic Synthesis

(Alkohol Rantai Panjang sebagai Penyokong dalam Sintesis Organik Fasa Pepejal)

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ABSTRACT

The solid phase synthesis is a method by which organic compound synthesis are performed on a support. With this method, the purification can be carried out easily by simple filtration and washing procedures. Long-chain alcohol (C-100 alcohol) can be used as a support because of its insolubility in organic solvents and its simple structure which enables it to be stable in various reaction conditions. In this study, a 4-aminopyridine derivative has been synthesized from C-100 β-keto ester and a cyano enamine using tin(VI)chloride as catalyst. C-100 β-keto ester was obtained by transesterification of long chain alcohol (the support) with ethyl acetoacetate using boric acid protocol. The cyano enamine was successfully synthesized by Thorpe-Ziegler cyclization initiated by sodium hydride. The 4-aminopyridine derivative was successfully cleaved from the support using sodium isopropoxide in refluxing isopropanol. From the ^{1}H-NMR spectrum at ~ 120°C, it was found that the cleaved support has the same spectrum with the long-chain alcohol used in the beginning of reaction, thus, this long chain alcohol can be reused for other reactions.

Keywords: 4-aminopyridine; C-100 alcohol support; Thorpe-Ziegler cyclization; transesterification

ABSTRAK

Sintesis organik fasa padat merupakan suatu kaedah sintesis sebatian organik yang dilakukan dengan bantuan suatu fasa pendukung. Dengan kaedah ini penulenan menjadi mudah kerana dilakukan hanya dengan penurasan dan pencucian. Alkohol rantai panjang boleh digunakan sebagai fasa pendukung kerana tidak larut dalam pelarut organik dan memiliki struktur yang sederhana sehingga dapat stabil dalam berbagai keadaan tindak balas. Dalam kajian ini, turunan 4-aminopiridin disintesis daripada β-keto ester C-100 dan suatu siano menggunakan stanum (VI) klorida sebagai katalis. β-keto ester C-100 diperoleh dengan transesterifikasi alkohol rantai panjang dengan etil asetoasetat menggunakan katalis asid borat. Siano enaminnya telah disintesis menggunakan siklisasi Thorpe-Ziegler yang dimulakan dengan natrium hidrida. Langkah terakhir, produk 4-amino piridin telah dihasilkan daripada fasa pendukung menggunakan natrium isopropoksida dalam isopropanol reflux. Daripada ^{1}H-NMR pada suhu ~120°C, fasa pendukung produk memiliki spektrum ^{1}H-NMR yang sama dengan alkohol rantai panjang yang digunakan sebagai fasa pendukung pada awal tindak balas. Dengan demikian, alkohol rantai panjang hasil reaksi ini boleh digunakan kembali untuk tindak balas yang lain.

Kata kunci: 4-amino piridin; fasa pendukung alkohol C-100; siklisasi Thorpe- Ziegler; transesterifikasi

INTRODUCTION

The solid phase synthesis (SPS) is a process by which organic compound synthesis are performed on a support. With SPS, starting molecules are bound to a solid support, which is usually a polystyrene based resin (Lejeune et al. 2003), and synthesized step by step (see Figure 1). If the target molecule has been synthesized on the solid support, the last step is the final cleavage of product from the resin, and in some cases, the resin can be regenerated for other reactions (Vitre et al. 2003).

The SPS technique offers advantages compared to normal liquid phase synthesis due to its convenient work-up and purification procedures. Any unreacted reagents and byproducts (unbound impurities) left at the end of any synthetic steps can easily be removed by a simple washing procedure. Thus, SPS is particularly advantageous for multi-step iterative synthesis. The solid phase synthesis also allows the use of excess reagents since they can easily be removed. In this way reactions can be driven to completion in order to get high yield (Gordon & Balasubramanian 1999).

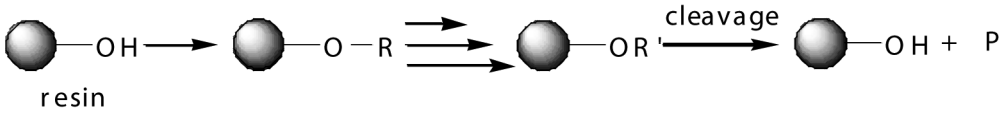

FIGURE 1. Solid phase synthesis

Another advantage offered by SPS compared to solution phase synthesis is the ease for automation. In an automated SPS system, the reactions are carried out under continuous flow. It means the reagents are passed through a reaction chamber containing the resin support. The reagents can be circulated back into the chamber or taken away to a waste collection container. Thus, the resin can be washed with clean of excess reagents which push reaction steps to completion (Figure 1). Various solid-phase automated synthesizers have been developed and are now commercially available.

Solid phase synthesis technique was first developed by Merrifield (1963) to synthesize polypeptides in 1963. Merrifield solid phase synthesis concept has spread radically (Yang 2007) not only in the field of biopolymer synthesis –peptides (Garcı´a et al. 2003), oligonucleotides (Bleczinski & Richet 2000) but also in other fields of organic synthesis including heterocyclic compound synthesis (Makino et al. 2003). Among the libraries of heterocyclic compounds, pyridine derivatives were the most frequently cited (Izumi 2006). The pyridine nucleus is a key feature found in various drugs -antihistamines, antiseptic, antirheumatic, etc. (Dallinger et al. 2004). One pyridine derivative which has been a compound of particular interest in medicinal chemistry is 4-aminopyridine derivatives. These pyridine derivatives are well-known as multiple sclerosis medicine. In this study, solid phase synthesis of a 4-aminopyridine analogue is described.

The use of SPS is not without its disadvantages as there are still limitations in the use of SPS. Firstly, most of the solid supports are aromatic compounds (Wang 1973) thus certain reactions which are reactive to aromatic compounds cannot be performed on such solid supports. Another major disadvantage is the difficulty in monitoring the reaction and determination of the product coupled to the resin at the end of synthetic steps. NMR analysis cannot be performed directly on such solid supports due to their insoluble properties. In order to find out which product is coupled to a resin, partial work-up is needed at the end of a synthetic step. A small sample is taken from which the product is cleaved off from the resins after every step, and worked-up to give the intermediate, which can then be analyzed. This analysis process is of course time and product consuming.

Long chain alcohols (C-100 alcohol) have the possibility of overcoming various disadvantages present in solid phase synthesis due to its simple structure. The long carbon chain is chemically inert to a wide range of reaction conditions including various reaction conditions which will show reaction with aromatic compounds. The reactive part of this long chain alcohol is only the methylene next to the hydroxyl group. Difficulties in reaction monitoring and determination of the product coupled to the resin at the end of synthetic steps can also be solved by this long chain alcohol. NMR analysis can be directly performed on the long chain alcohol because it can be melted at about ~120°C. Thus, the structure of synthetic intermediates can be determined utilizing high temperature NMR measurement using tetrachloroethane ($C_2D_2Cl_4$) as solvent.

This long chain alcohol was prepared by polymerization of ethylene using coordination polymerization, well known as Ziegler-Natta polymerization (Figure 2). The structure of long chain alcohol can be confirmed by ^{1}H-NMR measurement ~120°C (Figure 3). The doublet signal at 0.9 ppm corresponds to the two end methyl groups. The huge signal at 1.2 ppm corresponds to methylene of the long chain while the triplet signal at 3.5 ppm corresponds to the methylene next to the hydroxyl group.

Thus, the aim of this research was to introduce a long chain alcohol (C-100 alcohol) as a new support in solid phase organic synthesis and performing application of this new support in the synthesis of a 4-aminopyridine derivative.

Materials and Methods

All reagents were purchased from Aldrich, Across Organic, and Fluka. Long chain alcohol was obtained from Winfried Kretschmer, Inorganic Department of Stratingh Institute for Chemistry, RuG.

NMR analysis was performed with an NMR instrument Varian 300 MHz. Melting point measurements were performed on melting point apparatus. Mass spectra were recorded using JEOL MSRoute instrument.

B-keto ester of long chain alcohol (C-100)

Long chain alcohols (1.5 g), boric acid (12 mg, 20 mol %), and ethyl acetoacetate (0.6 mL, 5 eq) was heated to reflux (T=140°C) in 150 mL of toluene. Ethanol produced during the reaction was continuously removed using a Dean stark apparatus. The reaction mixture was allowed to react for 20 h and then cooled down to ambient temperature. The resulting suspension was filtered and the residue was washed with methanol (5 × 20 mL). The product was dried overnight in a vacuum oven to give β-keto ester (1.452 g). ^{1}H-NMR ($C_2D_2Cl_4$, 300 MHz, 120°C) δ (ppm) = 4.12 (t, J = 6.6 Hz, 2H, –O–CH_2), 3.34 (s, 2H, CH_2), 2.21 (s, 3H, CH_3), 0.87 (d, J = 6.6 Hz, 6H, 2CH_3).

2-Aminocyclopent-1-ene carbonitrile

To slurry of sodium hydride (50% in oil, 1.26 g, and 26 mmol) was added 30 mL of anhydrous toluene after which adiponitrile/1,4-dicyano butane (2.85 mL, 25 mmol) was added. The reaction mixture was then heated to reflux (125°C) for 15 h. After that, ethanol (5 mL), demineralized water (35 mL) and acetic acid (5 mL) were respectively added and the organic phase was then separated. The aqueous phase was extracted with ethyl acetate (3 × 50 mL). The combined organic phase was washed with demineralized water (50 mL) and brine solution (50 mL), dried over magnesium sulfate for 15 min and then filtered. The filtrate was concentrated under reduced pressure. The crude product was dissolved in hot toluene (100 mL) and then added drop by drop of heptane until it recrystallized out. 2-Aminocyclopent-1-ene carbonitrile was obtained as brownish solid (1.1 g, 40 %) without further purification.

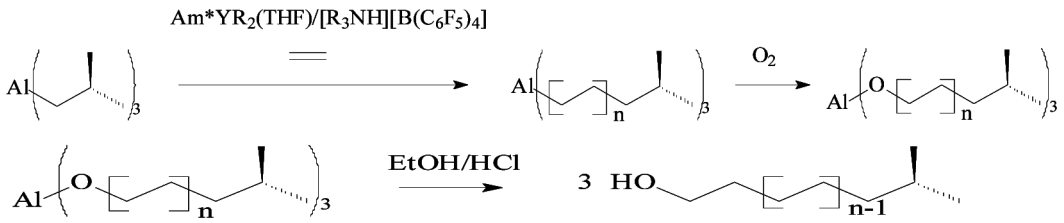

FIGURE 2. Polymerization to form long chain alcohol

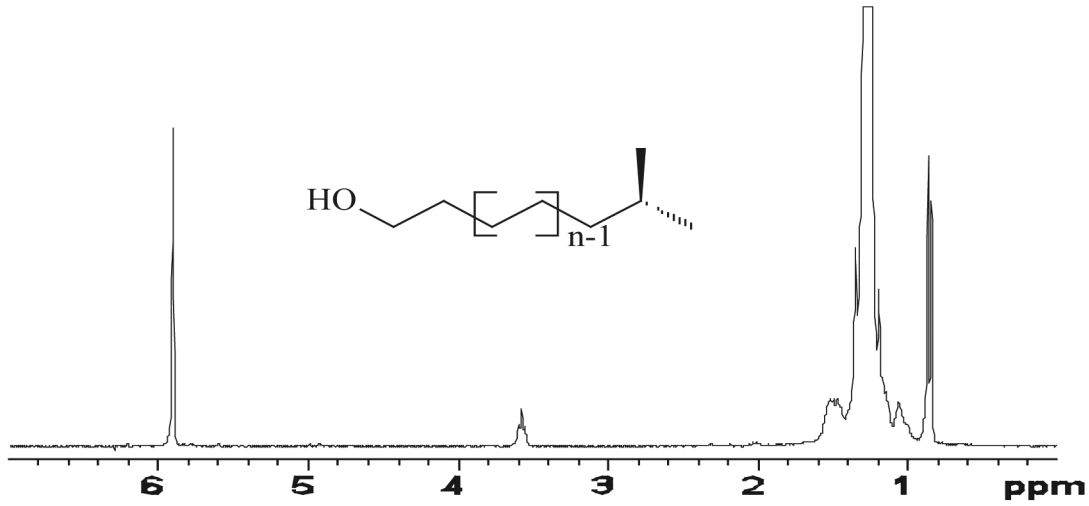

FIGURE 3. ^{1}H NMR spectrum ($C_2D_2Cl_4$, 120°C) of long chain alcohol after subsequently oxidative acidic workup

^{1}H-NMR ($CDCl_3$, 300 MHz, rt) δ (ppm) = 4.58 (s_{br}, 2H, NH_2), 2.50 (t, J = 6.9 Hz, 2H, CH_2), 2.43 (t, J = 7.7 Hz, 2H, CH_2), 1.89 (qi, J = 7.6 Hz, 2H, CH_2). Formula $C_6H_8N_2$, m/z =108 (M^+).

PYRIDINE DERIVATIVE SYNTHESIS

Very-long-chain β-keto esters (1.3 g) were suspended in anhydrous toluene, 2-aminocyclopent-1-ene carbonitrile (0.413 g, 5 eq) and tin (IV) chloride (0.9 mL, 10 eq) was added. The reaction mixture was refluxed under nitrogen for 20 h. The resulting mixture was cooled to room temperature. The resulting suspension was filtered and the residue was washed with methanol (5 × 20 mL). The product was dried in a vacuum oven to give pyridine derivative coupled to the long chain (1.325 g). ^{1}H-NMR ($C_2D_2Cl_4$, 300 MHz, 120°C) δ (ppm) = 0.65 (s_{br}, 2H, NH_2), 4.37 (t, J = 6.7 Hz , 2H, –COO–CH_2), 3.36 (t, J = 7.6 Hz, 2H, CH_2), 2.95 (s, 3H, CH_3), 2.74 (t, J = 7.3 Hz, 2H, CH_2), 2.26 (qi, J = 7.4 Hz, 2H, CH_2), 0.87 (d, J = 6.6 Hz, 6H, $2CH_3$).

CLEAVAGE OF PYRIDINE DERIVATIVE FROM THE LONG CHAIN

Tin-mediated pyridine synthesis product (0.2 g) was suspended in 40 mL of isopropanol. Sodium isopropoxide solution (1.1 mL) was added and then refluxed (T=110°C) for 24 h. The resulting mixture was cooled to room temperature. The resuting suspension was then filtered and the residue was washed with methanol (5 × 20 mL). The solid obtained was dried in a vacuum oven to give the long chain alcohol. The filtrate was evaporated and ethyl acetate was added. The ethyl acetate phase was washed with water, brine (3 × 20 mL) and dried over magnesium sulphate and evaporated to give the 4-aminopyridine derivative product (57 mg). ^{1}H-NMR ($C_2D_2Cl_4$, 300 MHz, 120°C) δ (ppm) = 3.59 (t, J = 6.0 Hz, 2H, –O–CH_2), 1.28 (s_{br}, long chain CH_2) 0.88 (d, J = 6.3 Hz, 6H, $2CH_3$). ^{1}H-NMR ($CDCl_3$, 300 MHz) δ (ppm) = 5.80 (s_{br}, 2H, NH_2), 5.26 (h, J = 6.2 Hz, 1H, CH), 2.97 (t, J = 7.8 Hz, 2H, CH_2), 2.68 (t, J = 7.7 Hz, 2H, CH_2), 2.67 (s, 3H, CH_3), 2.14 (qi, J = 7.7 Hz, 2H, CH_2), 1.37 (d, J = 6.3 Hz, 6H, $2CH_3$).

RESULTS AND DISCUSSION

A 4-aminopyridine derivative can be synthesized from a β-keto ester and a cyano enamine (Veronese et al. 1995). Thus, preparation of the β-keto ester of C-100 and the cyano enamine is first needed.

PREPARATION OF C-100 B-KETO ESTER

Transesterification is an equilibrium reaction, acid or base is usually utilized as a catalyst to promote the reaction. Boric acid has been shown to catalyze various transesterification of ethyl acetoacetate with a variety of

primary and secondary alcohols in good to excellent yields (Kondaiah et al. 2007). Boric acid promotes the enolization of the β-keto ester which is followed by ring closure to form a cyclic intermediate. The cyclic intermediate is then cleaved by the alcohol to give a new expected β-keto ester. This condition was carried out to C-100 alcohol to form the β-keto ester of C-100 (Figure 4). The structure of C-100 β-keto ester was confirmed by ^{1}H-NMR ($C_2D_2Cl_4$, 300 MHz) as can be seen in Figure 5.

PREPARATION OF CYANO ENAMINE

2-Aminocyclopent-1-ene carbonitrile (the cyano enamine) was prepared from adiponitrile/1,4-dicyano butane using a one step Thorpe-Ziegler cyclization initiated by sodium hydride (Figure 6). Thorpe-Ziegler condensation is the intramolecular base-catalyzed cyclization of dinitriles to afford enaminonitriles. This condensation reaction is a powerful method of assembling 5 to 33- membered rings (Ryndina et al. 2002). The structure of the cyano enamine was confirmed by ^{1}H-NMR (Figure 7) and ESI-MS (M^+ = 108)

After the β-keto ester of C-100 and 2-aminocyclopent-1-ene carbonitrile were successfully synthesized, synthesis of a pyridine derivative was performed on the long chain in the presence of $SnCl_4$ in refluxing toluene (Figure 8). The structure of which was confirmed by ^{1}H-NMR (Figure 9).

$SnCl_4$ mediates this reaction because it has the ability to coordinate with the β-keto ester and –CN functional group. $SnCl_4$ promotes the enolization of the β-keto ester and promotes the electrophilic character of –CN as well, thus improving the electrophilic addition of the cyano enamine to the β-keto ester.

The last step is final cleavage of product from the solid support. The first attempt was to cleave the product from the solid support using sodium methoxide in refluxing methanol, but no product was detected. In this case the long chain probably did not dissolve in refluxing methanol. Thereafter, the product was successfully cleaved using sodium isopropoxide in refluxing isopropanol although the long chain still did not dissolve (Figure 10). Sodium isopropoxide used in this reaction

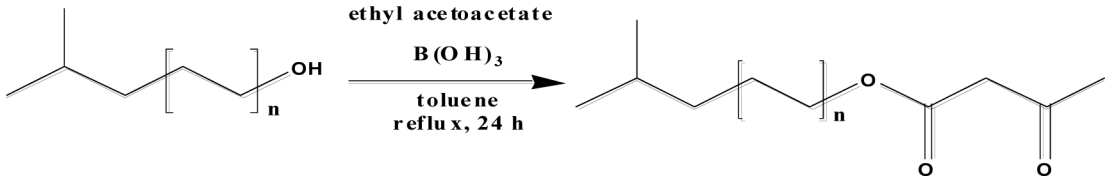

FIGURE 4. Transesterification of C-100 alcohol

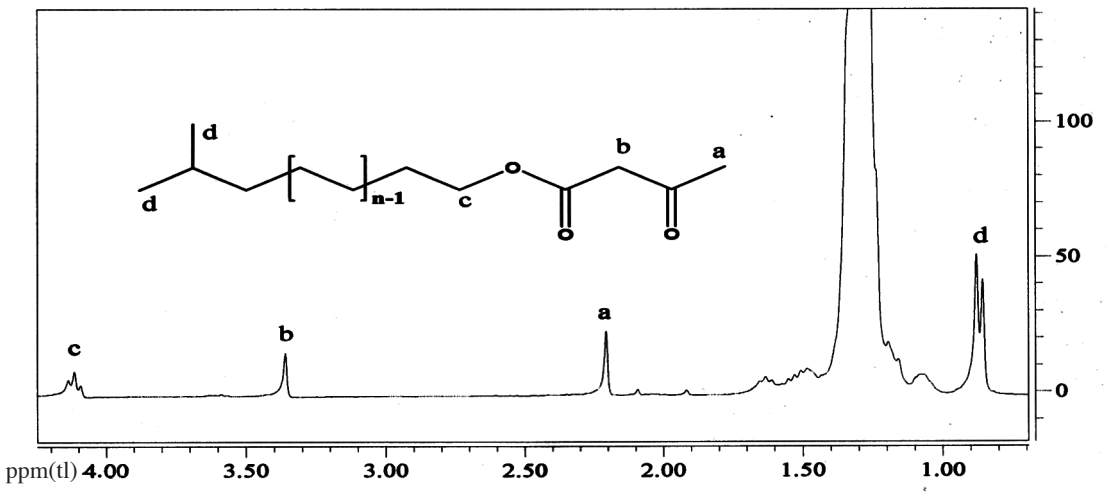

FIGURE 5. ^{1}H-NMR spectrum of very-long chain β-keto ester

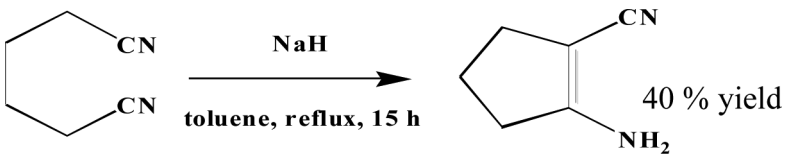

FIGURE 6. Thorpe-Ziegler condensation of adiponitrile

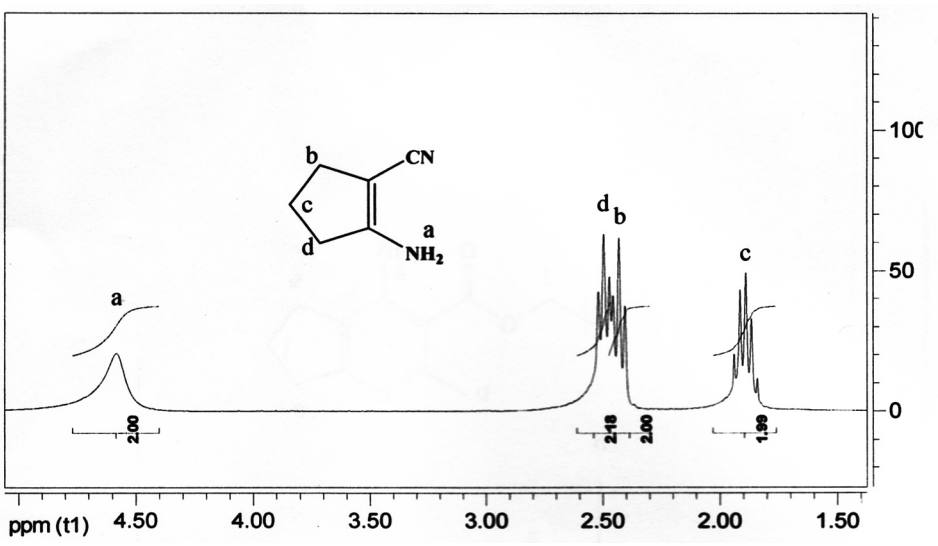

FIGURE 7. ^{1}H-NMR of 2-aminocyclopent-1-ene carbonitrile

$SnCl_4$-mediated Pyridine Derivative Synthesis

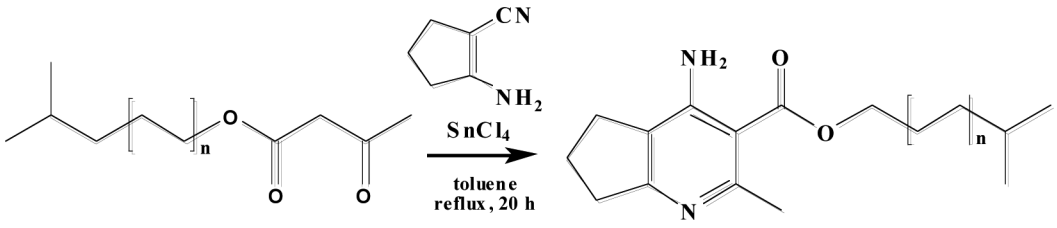

FIGURE 8. $SnCl_4$-mediated Pyridine Derivative Synthesis

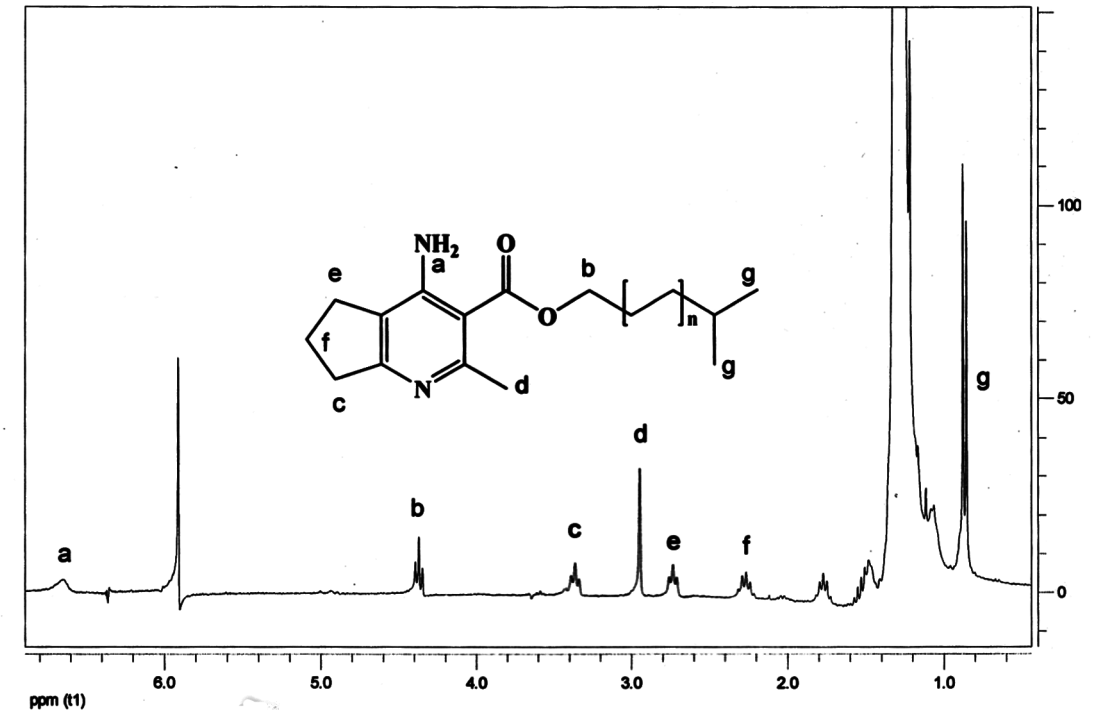

FIGURE 9. ^{1}H-NMR spectrum of very-long chain β-keto ester

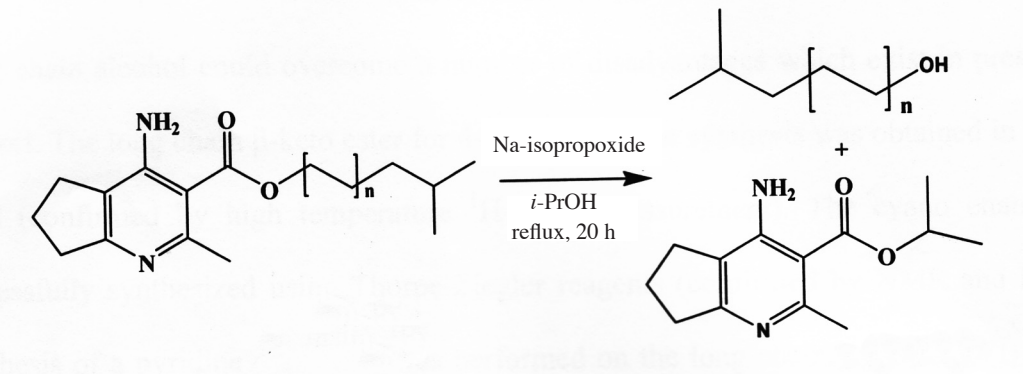

FIGURE 10. Cleavage of product from support

was made by reacting sodium in isopropanol. Instead of isopropoxide, triethyl amine in refluxing isopropanol was used to try cleaving the product, but it did not give the right product. The boric acid protocol was also used in the cleavage process, but not all product was cleaved from the solid support during a 20 h reaction (from ^{1}H-NMR, there is still evidence of product coupled to the long chain).

After cleavage, the 4-aminopyridine derivative was obtained and long chain alcohol can be recovered as is indicated in Figure 11. Thus, the long chain alcohol can be reused for other reactions.

THE MELTING POINT OF THE LONG CHAINS

From melting point measurement using melting point apparatus:

1. Melting point of long chain alcohol =125°C
2. Melting point of long chain β-keto ester =123.8°C
3. Melting point of pyridine coupled to the long chain = 123.5°C

From the results, we can conclude that the melting points of these long chains are only affected by the long methylene chain so that their melting points in average are the same.

CONCLUSIONS

Long chain alcohol could overcome a number of disadvantages which exist in present solid support. The long chain β-keto ester for 4-amino pyridine synthesis was obtained in excellent yield (confirmed by high temperature ^{1}H-NMR measurement). The cyano enamine was successfully synthesized using Thorpe-Ziegler reagents (confirmed by NMR and ESI-MS). Synthesis of a pyridine derivative was performed on the long chain using tin (VI) chloride. The product was successfully cleaved from the support using sodium isopropoxide. Thus, synthesis of a pyridine derivative can be performed effectively on the long chain alcohol.

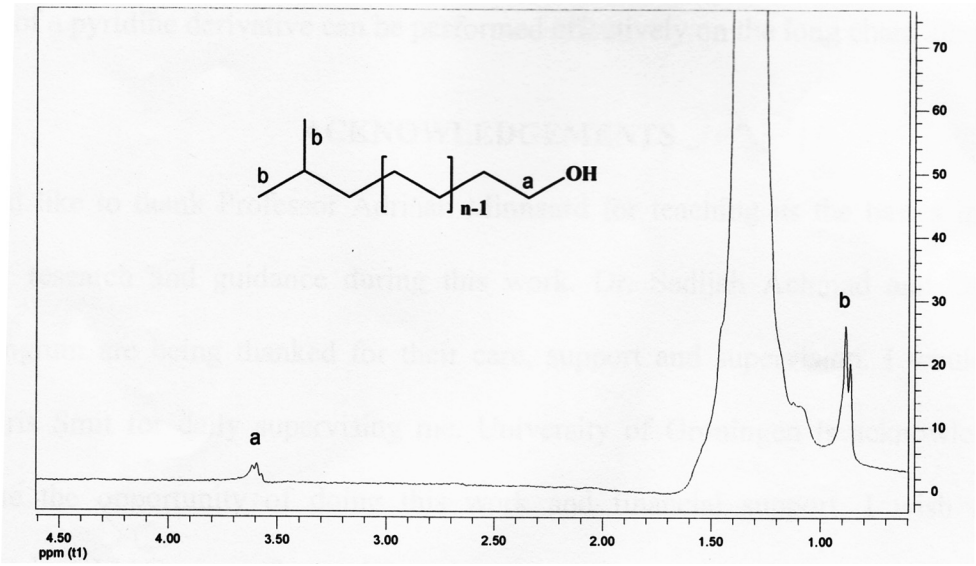

FIGURE 11. ^{1}H-NMR spectrum of cleavage product

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REFERENCES

Bleczinski, C.F. & Richert, C. 2000. Solid-phase synthesis of cyclic peptide-DNA hybrids. *Org. Lett*. 2(12): 1697-1700.

Dallinger, D., Stadler, A. & Kappe, C.O. 2004. Solid- and solution-phase synthesis of bioactive dihydropyrimidines. *Pure Appl. Chem*. 76(5): 1017-1024.

Garcı´a, O., Nicola´s, E. & Albericio, F. 2003. Solid-phase synthesis: a linker for side-chain anchoring of arginine. *Tetrahedron Letters* 44: 5319-5321.

Gordon, K. & Balasubramanian, S. 1999. Solid phase synthesis – designer linkers for combinatorial chemistry: a review. *J Chem Technol Biotechnol*. 74: 835-851.

Izumi, M. 2006. Solid-phase organic synthesis of heterocyclic compounds. *J. Pestic. Sci*. 31(1): 1-5.

Kondaiah, G.C., Reddy, M.L.A., Babu, K S., Gurav, V.M., Huge, K.G., Bandichhor, R., Reddy, Bhattacharyaa, A. & Anand R.V. 2007. Boric acid: An efficient environmentally benign catalyst for transesterification of ethyl acetoacetate. *Tetrahedron Letters* 49: 106-109.

Lejeune, V., Martinez, J. & Cavelier, F. 2003. Towards a selective Boc deprotection on acid cleavable Wang resin. *Tetrahedron Letters* 44: 4757-4759.

Makino, S., Nakanishi, E. & Tsuji, T. 2003. Efficient solid-phase synthesis of 1,2,3-benzotriazin-4-ones with synphase™ lanterns. *J. Braz. Chem. Soc*. 14(3): 452-455.

Merrifield, R.B. 1963. Solid Phase Peptide Synthesis I: The Synthesis of a tetrapeptide. *J. Am. Chem. Soc*. 85: 2149-2154.

Ryndina, S.A., Kadushkin, A.V., Solov´eva, E.V. & Granika, V.G. 2002. Application of the Thorpe-Ziegler reaction for the synthesis of functionalized thiophenes, thienopyrimidines, and thienotriazines. *Russian Chemical Bulletin, International Edition* 51(5): 854-859.

Veronese, A.C., Callegari, R. & Morelli, C.F. 1995. Tin (IV) chloride-promoted synthesis of 4-aminopyridines and 4-aminoquinolines. *Tetrahedron* 51(45): 12277-12284.

Vitre, C., Freebairn, K., Anson, M. & Bradley, M. 2003. Recycling solid supports – A head-to-tail linker. *Molecular Diversity* 6: 27-31.

Wang, S.S. 1973. p-Alkoxybenzyl alcohol resin and p-alkoxybenzyloxycarbonylhidrazide resin for solid phase synthesis of protected peptide fragments. *J. Am. Chem. Soc*. 95(4): 1328-1333

Yang, J. 2007. Fullerene-derivatized Amino acids: synthesis, characterization and solid phase synthesis. *Chem. Eur. J*. 13: 2530-2545.

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