Asian Journal of Chemistry; Vol. 23, No. 8 (2011), 3763-3764

ASIAN JOURNAL OF CHEMISTRY

www.asianjournalofchemistry.co.in

NOTE

Facile and Efficient Synthesis of Ethyl 3-oxo-3-(pyridin-4-yl)-2-((pyridin-4-yl)methylene)propanoate

RAMAZAN ERENLER

Department of Chemistry, Faculty of Art and Science, Gaziosmanpasa University 60240 Tokat, Turkey

Corresponding author: Fax: +90 356 2521585; Tel: +90 356 2521616-3013; E-mail: rerenler@gop.edu.tr

(*Received*: 16 October 2010; *Accepted*: 30 April 2011) AJC-9897

The refluxing of ethyl isonicotinate with sodium ethoxide and ethyl acetate yielded the ethyl-3-oxo-3-(pyridin-4-yl)propanoate which was in equilibrium with enol form. The desired product, ethyl 3-oxo-3-(pyridin-4-yl)-2-((pyridin-4-yl)methylene)propanoate was synthesized by the treatment of ethyl-3-oxo-3-(pyridin-4-yl)propanoate and its enolic form with the isonicotinaldehyde under the reflux in neat condition.

Key Words: Pyridine derivatives, Ethyl-3-oxo-3-(pyridin-4-yl)-2-((pyridin-4-yl)methylene)propanoate.

Among the heterocyclic compounds, pyridine and its derivatives have been extensively investigated. They play an important role as structural units or key intermediates in naturally occurring alkaloids and have attracted the interest of synthetic and natural product chemists for their pharmacological, biological and medicinal properties[1-8].

β-Keto esters and β-diketones have been important intermediates in organic synthesis. Herein it was developed new and efficient method for synthesizing dipyridine ester **4** in high yield. When the phenyl group was used instead of pyridine, the reaction didn't run. So the nitrogen is crucial that activating the acidic proton in the solvent free reaction condition. This could be due to the strong electron withdrawing effect of the pyridyl group.

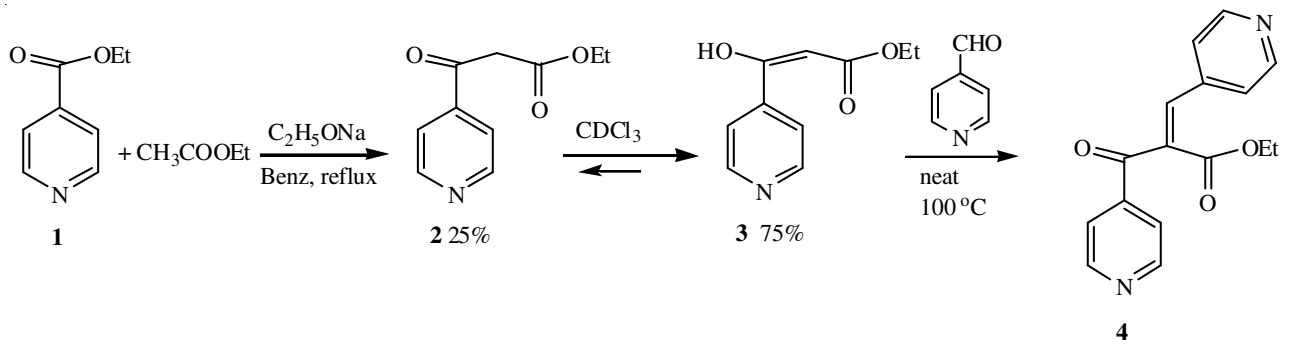
General procedures: Commercial reagents were purchased from standard chemical suppliers. Solvents were purified and dried by passing through activated aluminum oxide under argon pressure. Flash column chromatography was carried out on Silica Gel 60 (230-400 mesh, E. Merck). TLC was performed on pre-coated glass plates of Silica Gel 60 F_{254} (0.25 mm, E. Merck); detection was done by spraying with a solution of $Ce(NH_4)_2(NO_3)_6$, $(NH_4)_6Mo_7O_{24}$ and H_2SO_4 in water or ninhydrin and acetic acid solution in *n*-butanol and subsequent heating on a hot plate. Melting points were determined with a Büchi B-540 apparatus and are uncorrected. ^1H and ^{13}C NMR spectra were recorded with Bruker AMX 400 and 500 MHz instruments. Chemical shifts are in ppm from Me_4Si, generated from the $CDCl_3$. IR spectra were taken with a Perkin-Elmer Paragon 1000 FT-IR spectrometer. Elemental analyses were measured with a Perkin-Elmer 2400CHN instrument. Mass spectra were obtained with a FAB JMS-700 double focusing mass spectrometer (Jeol, Tokyo, Japan).

Treatment of ethyl isonicotinate (1) with ethyl acetate: To a solution of sodium ethoxide (2.02 g, 29.7 mmol) in benzene (10 mL) was added anhydrous ethyl acetate (3.49 g, 3.87 mL, 39.6 mmol). After refluxing 0.5 h, ethyl isonicotinate **1** (3.0 g, 19.8 mmol) was added to this solution. After 14 h of refluxing the benzene was removed under reduced pressure and the residual gum hydrolyzed with excess of dilute acetic acid. After adding an excess of potassium carbonate, the esther was extracted with ether, dried over $MgSO_4$, concentrated under reduced pressure, purified by column chromatography.

Ethyl-3-oxo-3-(pyridin-4-yl)propanoate (2): 2.89 g, 75 %. ^1H NMR (500 MHz, MeOD), δ = 1.16 (t, *J* = 7.1 Hz, *J* = 14.2 Hz, 3H), 4.11 (dd, *J* = 7.1 Hz, *J* = 14.2 Hz, 2H), 4.23 (s, 2H), 7.80 (d, *J* = 5.9 Hz, 2H), 8.82 (d, *J* = 5.9 Hz, 2H); ^{13}C NMR (125 MHz, MeOD), δ = 14.3, 46.0, 61.2, 121.7, 142.1, 151.3, 167.7, 194.3; Ms (FAB), m/z (%) = 194 $[M + H]^+$.

Ethyl-3-hydroxy-3-(pyridin-4-yl)acrylate (3): ^1H NMR (500 MHz, MeOD), δ = 1.27 (t, *J* = 7.1 Hz, *J* = 14.2 Hz, 3H), 3.28 (brs, 1H), 4.25 (dd, *J* = 7.1 Hz, *J* = 14.2 Hz, 2H), 6.13 (s, 1H), 7.78 (d, *J* = 5.8 Hz, 2H), 8.70 (d, *J* = 5.8 Hz, 2H)); ^{13}C NMR (125 MHz, MeOD), δ = 14.4, 61.1, 90.6, 120.1, 140.4, 150.9, 167.7, 172.5.

Ethyl-3-oxo-3-(pyridin-4-yl)-2-((pyridin-4-yl)methylene)-propanoate (4): Ethyl-3-oxo-3-(pyridine-4-yl)propanoate-ethyl-3-hydroxy-3-(pyridin-4-yl)acrylate mixture (0.5 g, 2.59 mmol) and isonicotinaldehyde (0.31 g, 0.27 mL, 2.85 mmol)



1 **2** 25% **3** 75% **4**

Scheme-I

were refluxed in solvent free condition for 4 h. The product purified by flash column chromatography (silica, hexane/EtOAc, 1/4). 0.60 g, 82 %. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.12 (t, *J* = 7.1 Hz, *J* = 14.2 Hz, 3H), 4.20 (dd, *J* = 7.1 Hz, *J* = 14.2 Hz, 2H), 7.10 (d, *J* = 5.9 Hz, 2H), 7.61 (t, *J* = 1.6 Hz, *J* = 5.9 Hz, 2H), 7.10 (d, *J* = 5.9 Hz, 2H), 7.61 (t, *J* = 1.6 Hz, *J* = 5.9 Hz, 2H), 7.87 (s, 1H), 8.48 (d, *J* = 5.2 Hz, 2H), 8.75 (t, *J* = 1.6 Hz, *J* = 5.9 Hz, 2H), ^{13}C NMR (100 MHz, $CDCl_3$) δ = 13.8, 62.2, 121.3, 123.1, 134.6, 139.5, 140.7, 141.3, 150.5, 151.2, 163.5, 193.6; IR (CH_2Cl_2, ν_{max}, cm^{-1}): 1225, 1410, 1594, 1712, 1727, 2472, 2981, 3343. UV/VIS (CH_2Cl_2) λ_{max} (ε) = 241 (10.070), 261 (9860); Ms (FAB), m/z (%) = 283 [M + H]$^+$; HRMS (FAB$^+$) calcd. (%) for $C_{16}H_{14}N_2O_3$: m/z 282.1004 [M + H]$^+$, found (%) m/z 282.1007.

Ethyl isonicotinate was treated with ethyl acetate in the presence of sodium ethoxide in benzene under reflux for 14 h to yield the corresponding products **2**, **3** as tautomeric mixtures[9]. It is detected by ^{1}H NMR spectroscopy that the enol form is more than that of the keto form in $CDCl_3$ (enol/keto: 3/2). The desired product **4** was synthesized by treating the tautomeric mixtures **2**, **3** with isonicotinaldehyde in solvent free condition under reflux for 4 h. The structure is confirmed by its ^{1}H/^{13}C NMR data. The signal observed at δ 1.12 as triplet and δ 4.20 as dublet of dublet belong to methyl and metylene of ester group, respectively. The characteristic olefinic proton shifts to the downfield (δ 7.87) as singlet due to the withdrawing effect of the pyridines and carbonyl groups and delocalization of the electrons causing the electron deficient of the proton. The ^{13}C signals of ester carbonyl and the pyridyl carbonyl detected at δ 163.5 and δ 193.5, respectively consistent with the proposed structure (**Scheme-I**).

REFERENCES

1. A.S. Girgis, N. Mishriky, A.M. Farag, W.I. Eraky and H. Farag, *Eur. J. Med. Chem*., **9**, 1818 (2008).
2. J.B. Veron, H. Allouchi, G.E. Gueiffier, R. Snoeck, G. Andrei, E.D. Clercq and A. Gueiffier, *Bioorg. Med. Chem*., **16**, 9536 (2008).
3. C.H. Li, L.X. Zhang, L.H. Cai, Y. Liu and P.Z. Hu, *Chin. J. Chem*., **26**, 1537 (2008).
4. V. Murugan, K.M. Geetha, M.S. Sandhyavali and S. Badami, *Asian J. Chem*., **20**, 5166 (2008).
5. U. Ursin, J. Steve and B. Stanovnik, *Tetrahedron*, **64**, 9937 (2008).
6. M.J. O'Neil, A. Smith, P.E. Heckelman, J.R. Obenchain, J.A.R. Gallipeau, M.A. D'Arecca and S. Budavari, The Merck Index, An Encyclopedia of Chemicals, Drugs and Biologicals, Merck Research Laboratories Division of Merck & Co., Whitehouse Station, NJ, USA, edn. 13, p. 391, 831, 894, 1164 (2001).
7. Z. Zhao, F.Z. Shenqing and G. Shuomingshu, 457,786 (Cl. A61K31/505) (2003); *Chem. Abstr*., **142**, 379358 (2005).
8. L.F. Lee, K.C. Glenn, D.T. Connolly, D.G. Corley, D.L. Flynn, A. Hamme, S.G. Hegde, M.A. Melton, R.J. Schilling, J.A. Sikorski, N.N. Wall and J.A. Zablocki, G.D. Searle & Co., USA, PCT Int. Appl. WO 99 41.237 (Cl. CO7D213/80) (1999); *Chem. Abstr*., **131**, 157711 (1999).
9. A.R. Katritzky, Z. Wang, M. Wang, C.R. Wilkerson, C.D. Hall and N.G. Akhmedov, *J. Org. Chem*., **69**, 6617 (2004).