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A Novel Synthesis of (Z)-ethyl 3-amino-2-cyano-3-phenyl(or alkyl)acrylate and ethyl- 2-cyano-3-phenyl-3-propionylimino-propanoate

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ABSTRACT

Reaction between ethyl cyanoacetate and imidate, N-acetyl imidate and N-ethoxycarbonyl imidate in basic medium are student. The structure and geometrically configuration of (Z)-ethyl 3-amino-2-cyano-4-phenylbut-2-enoate **3c** was established by X-ray diffraction. The functionality in ethyl 2-cyano-3-(ethoxycarbonyl)-3-p-tolylacrylate **7b** was exploited to get the desired heterocycle.

Indexing terms/Keywords

Imidate; N-acetyl imidate; N-ethoxycarbonyl imidate; ethyl cyanoacetate; X-ray diffraction; H-bonds.

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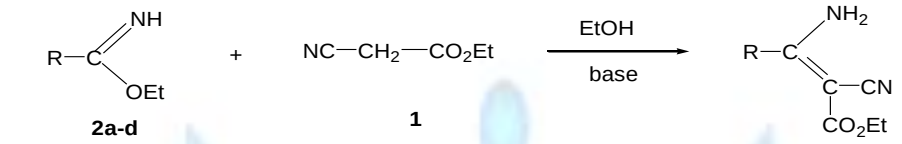
INTRODUCTION

It is well known that imidates are widely used as intermediates for a large number of heterocyclic compounds [1-9]. 4-(Imidazol-2-yl) pyridine is easily obtained by the reaction of imidate with aminoacetal [10]. Besides 3,5-diaryl-1,2,4-triazoles were synthesized via reaction between imidate and ammonium carbonate[11]. Also pyrazolo[3,4-d]pyrimidine are obtained by action of ammoniac in imidate [12]. Substitution of the ethoxy group of the imidate by a nucleophilic results in the synthesis of a large number of products (2,2-dicyano-1-arylvinylcarbamate, N1-tosylamidrazone, pyrimidine derivatives…) [13-15]. In connection with our previous work [13] we describe herein the condensation of ethyl cyanoacetate with ethyl alkyl (or aryl)imidate, ethyl N-acetyl alkyl (or aryl)imidate and ethyl N-ethoxycarbonyl alkyl (or aryl)imidate.

RESULTS AND DISCUSSIONS

Ethyl cyanoacetate **1** reacts with ethyl alkyl (or aryl)imidate **2a-d** in the presence of sodium or triethylamine in ethanol to obtain products **3a-d** (scheme 1).



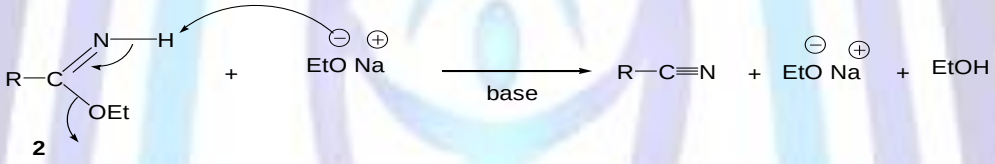
2a-d **1** **3a-d**

R= Ph; p-MeC_6H_4;Ph-CH_2-. iPr

base: EtO Na ; $(Et)_3N$

Scheme 1

The nature of the base affects the yield of the reaction (table 1). Using Na/EtOH as an inorganic base resulted in very poor yields products. This result can be explained by deprotonation of imidate to nitrile (scheme 2).



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Scheme 2

Table 1: Chemical structure of target compounds **3a-d**.

Compound	R	sodium ethoxide		Triethylamine	
		reaction time	Rdt (%)	reaction time	Rdt (%)
3a	Ph	24h	5%	6h	50%
3b	p-MeC_6H_4	24h	5%	6h	52%
3c	Ph-CH_2	24h	10%	4h	85%
3d	i*Pr*	24h	26%	4h	82%

The structures of compounds **3a-d** were confirmed by spectral data: ^{1}HNMR, ^{13}CNMR, IR and X-ray analysis for compound **3c**. In particular by the presence in the IR spectra of the typical absorption bands (at 3200-3400 and around 2210 cm^{-1}) due to the presence of amino and cyano groups. Ethyl 3-amino-2-cyano-4-phenylbut-2-enoate **3c** can exist in one of the two isomeric forms (Z or E). In order to know which specific configuration is formed, an X-ray crystallographic study of the compound **3c** was carried out (Figure 1). This study, showed only the formation of the compound **3c (Z)** and not **3c (E)**.

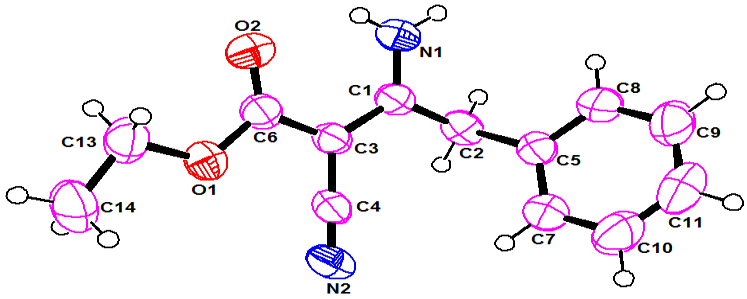

Figure 1: Asymmetric unit of the compound **3c**

X-ray data diffraction of the compound **3c:** $C_{13}H_{14}N_2O_2$, M = 230.26 g.mol^{-1}, monoclinic, space group $P2_1/c$, a = 10.4942 (5) Å, b = 14.2674 (8) Å, c = 8.3931 (5) Å, β = 96.457 (3)° , V = 1248.7 (1) Å^3 and Z = 4. 1867 reflections with I>2σ(I) were used for the refinement of the crystal structure. The final discrepancy factors R_1 and wR_2 were found to be 0.049 and 0.131. The crystal structure of this compound is stable by weak intermolecular (N1—H1B···N2^{i}) and intramolecular (N1—H1B···O2) hydrogen bonds (Figure 2).

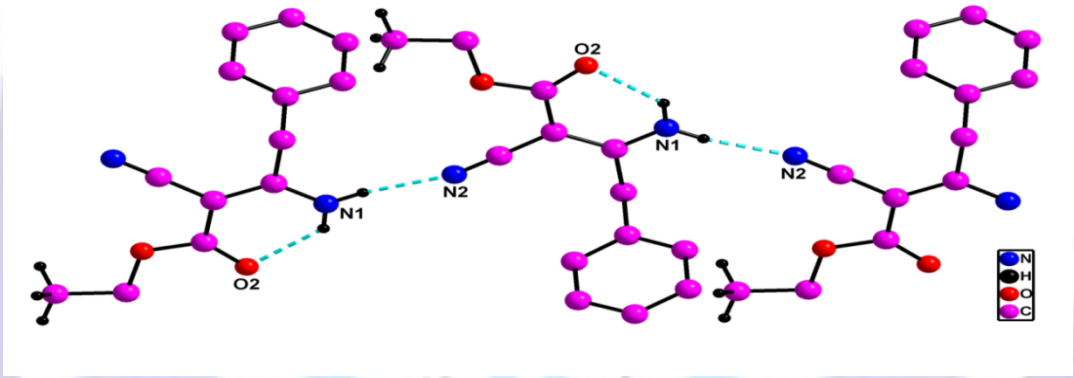

Figure 2: Inter and intramolecular H-bonds (showed with dashed lines) in the structure of compound **3c**.

Table 2: Bond length (Å) and angles (°) in the hydrogen bonding scheme of the compound **3c**.

D—H···A	D—H	H···A	D···A	D—H···A
N1—H1B···N2^{i}	0.86	2.07 (2)	2.928 (1)	172.2 (2)
N1—H1B···O2	0.86	2.05 (4)	2.701 (3)	131.8 (3)

Symmetry codes: (i) 2-*x*, *y*-1/2, -*z*+1/2

Moreover, the active methylene moiety of ethyl cyanoacetate **1**, in reaction with ethyl N-acetyl alkyl (or aryl)imidate **4a-d** , yielded the non-isolable intermediate **5a-d**, which reacted in situ with sodium ethoxide solution to produce compounds **3a-d** (scheme 3).

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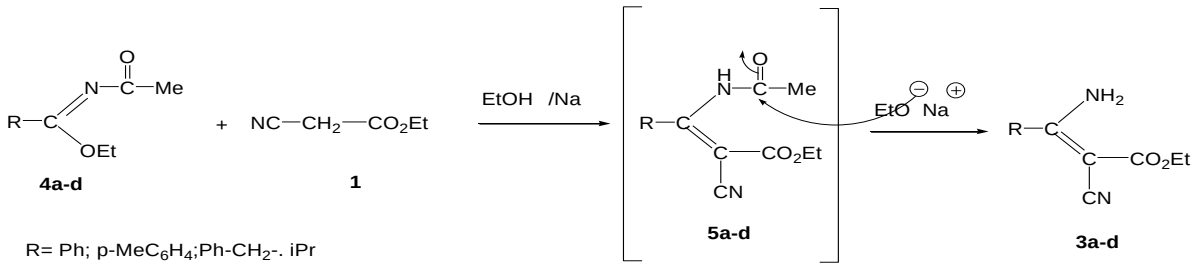
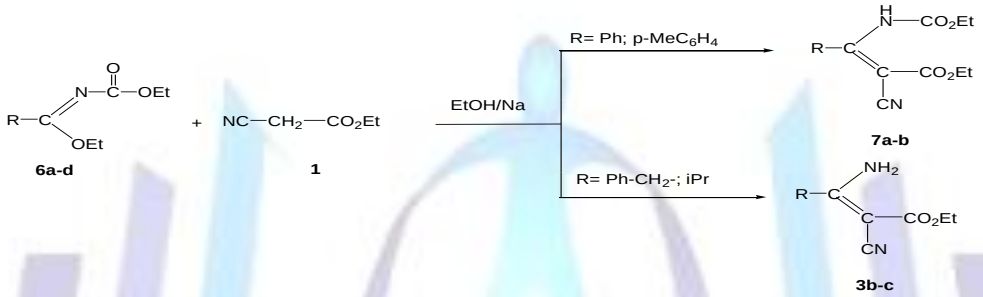


Scheme 3

Furthermore, the reactivity of ethyl cyanoacetate **1** towards ethyl N-ethoxycarbonyl arylimidate **6a-b** was also investigated as an alternative route to obtain ethyl 2-cyano-3-(ethoxycarbonyl)-3-phenylacrylate **7a** and 2-ethyl 2-cyano-3-(ethoxycarbonyl)-3-p-tolylacrylate **7b** (scheme 4).

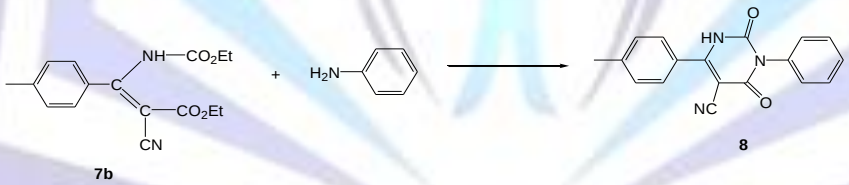


Scheme 4

In addition, the condensation of **1** with N-ethoxycarbonyl alkylimidate **6c-d** in ethanol in the presence of sodium produced compounds **3c-d** (scheme 4). This result is similar to the one, obtained previously when we condense **1** with N-acetyl alkyl (or aryl)imidate **4a-d**.

The IR spectra of compounds **7a** and **7b** showed bands for (NH), (CN), and (2C=O). The ^{1}HNMR spectrum of compounds **7a**-**b** revealed a singlet at δ 11.0 -11.30(s, 1H, NH), triplet at δ 1.20-1.30 (t, 3H, CH_3) and quadruplet at δ 4.0-4.10 (q, 2H, CH_2).

Compounds **7a-b** can be used for the synthesis of heterocyclic compounds for example we are condensed **7b** with aniline the result is the formation of 2,6-dioxo-1-phenyl-4-p-tolyl-1,2,3,6-tetrahydropyrimidine-5-carbonitrile **8** (scheme 5). Further work is in progress to obtain novel structures by using compounds **3a-d** and **7a-b**.



Scheme 5

CONCLUSION

To sum up, in this work we have tested the reactivity of imidate, N-acetyl imidate and N-ethoxycarbonyl imidate toward ethyl cyanoacetate. By means of X-ray analysis we have demonstrated that ethyl 3-amino-2-cyano-4-phenylbut-2-enoate exhibits geometrically configuration cis. Our synthetic products can be used as intermediates of heterocyclic compounds.

EXPERIMENTAL

Melting points are recorded in degrees Celsius on a Kofler apparatus. All reactions were followed by TLC (E. Merck Kieselgel 60 F-254), with UV detection at 254 nm. The IR spectra were recorded in the solid state as KBr discs on a Perkin-Elmer PARAGON 1000 FT-IR spectrometer. ^{1}H and ^{13}C NMR were determined in solution in DMSO-d_6 with an AC Bruker spectrometer at 300 MHz using TMS as an internal standard.

A suitable crystal was carefully selected under a polarizing microscope and mounted at the end of a thin glass fiber. The crystal structure determination was performed using a BRUKER SMART APEX CCD diffractometer which uses graphite monochromatized MoKα radiation (λ = 0.71073 Å). Unit cell parameters, optimized by least-squares refinement were calculated and refined using indexation of collected intensities. The structure was solved by direct method using SHELXS-97 [16] and refined by full-matrix least-squares procedures using the SHELXL-97 program [17].

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GENERAL EXPERIMENTAL PROCEDURE

General procedure for the preparation of 3a-d and 7a-b.

To a magnetically stirred solution of sodium (10^{-2} mol) in absolute ethanol (50 mL) and ethyl cyanoacetate (10^{-2} mol) we added the appropriate imidate the reaction mixture stirred for 24 h. The progress of the reaction was monitored by TLC (mobile phase, diethyl ether: hexane; 60/40;v/v). The solvent was removed in vacuo. The contents of the flask were neutralized by a saturated solution of NH_4Cl, and then extracted by diethyl ether. The organic layer was dried over anhydrous Na_2SO_4. The solvent was removed in vacuo. The precipitate formed was isolated by filtration and washed with diethyl ether to obtain the pure product.

General procedure for the preparation of 3a-d (method 2):

A mixture of tiethyamine (10^{-2} mol), ethyl cyanoacetate (10^{-2} mol) and appropriate imidate **2a-d** (10^{-2} mol) in absolute ethanol (50 mL) was heated under reflux for 4-6h. The solvent was removed under reduced pressure and the residue was neutralized by water, and then extracted by diethyl ether. The organic layer was dried over anhydrous Na_2SO_4. The solvent was removed in vacuo. The precipitate formed was isolated by filtration and washed with diethyl ether to obtain the pure product.

General procedure for the preparation of 8

To a magnetically stirred solution of ethyl 2-cyano-3-(ethoxycarbonyl)-3-p-tolylacrylate **7b** (1 mmol) in chlorobenzene (10 mL), aniline (1.2 mmol) were added and the reaction mixture stirred for 6 h at 110 °C. The progress of the reaction was monitored by TLC (mobile phase, diethyl ether: hexane; 50/50;v/v). The resulting mixture was allowed to cool at room temperature. The precipitate formed was isolated by filtration and washed with diethyl ether to obtain the pure product.

Spectral Data of New Compounds

(Z)-ethyl 3-amino-2-cyano-3-phenylacrylate : **3a** : Rdt=50% ; mp=120°C ; IR(KBr) : ν : 3194-3352(NH), 2214 (CN), 1672(C=O) cm^{-1}; ^{1}H-NMR: (DMSO-d6): δ=1.23(t, 3H, CH_3, $^3J_{HH}$ =6.9MHz), 4.19(q, 2H, CH_2, $^3J_{HH}$ =6.9MHz), 7.51-7.54(mu, 5H, H_{arom}), 8.9(s, 1H, NH), 9.2(s, 1H, NH); ^{13}C-NMR (DMSO-d6): δ = 14.8 (**C**H_3), 60.3(**C**H_2), 70.3(C2), 119.4 (CN), 167.9(C1), 171.1(C3),128.5-134.7(C_{arom}).

(Z)-ethyl 3-amino-2-cyano-3-p-tolylacrylate : **3b** : Rdt=52%; mp=115°C ; IR(KBr) : ν : 3221-3379 (NH), 2205 (CN), 1677(C=O) cm^{-1}; ^{1}H-NMR: (DMSO-d6): δ =1.32(t, 3H, CH_3, $^3J_{HH}$ =6.9MHz), 2.38(s, 3H, CH_3), 4.25(q, 2H, CH_2, $^3J_{HH}$ =6.9MHz), 5.99(s, 1H, NH), 7.23-7.46(mu, 4H, H_{arom}), 9.34(s, 1H, NH); ^{13}C-NMR (DMSO-d6): δ = 14.4 (**C**H_3), 21.5 (**C**H_3) 60.7(**C**H_2), 72.2(C2), 119.2 (CN), 168.3(C1), 170.3(C3),127.6-142.3(C_{arom}).

(Z)-ethyl 3-amino-2-cyano-4-phenylbut-2-enoate : **3c** : Rdt=85% ; mp=121°C ; IR(KBr) : ν : 3184-3342(NH), 2213 (CN), 1676 (C=O) cm^{-1}; ^{1}H-NMR: (DMSO-d6): δ =1.17(t, 3H, CH_3, $^3J_{HH}$ =7.2MHz), 3.74(s, 2H, CH_2), 4.1(q, 2H, CH_2, $^3J_{HH}$ =7.2MHz), 7.2-7.4(mu, 5H, H_{arom}), 8.9(s, 1H, NH), 9.1(s, 1H, NH); ^{13}C-NMR (DMSO-d6): δ = 14.7 (**C**H_3), 40.0 (**C**4), 60.0(**C**H_2), 70.0(C2), 119.0 (CN), 167.7(C1), 172.3(C3),128.5-134.8.3(C_{arom}).

(Z)-ethyl 3-amino-2-cyano-4-methylpent-2-enoate 3d **:** Rdt=82% ; mp=120°C ; IR(KBr) : ν :3213-3371(NH), 2201(CN), 1680 (C=O) cm^{-1}; ^{1}H-NMR: (DMSO-d6): δ =1.1(d, 6H, 2CH_3); 1.2(t, 3H, CH_3, $^3J_{HH}$ =7.2MHz); 3.07(mu, 1H, CH); 4.1(q, 2H, CH_2, $^3J_{HH}$ =7.2MHz); 7.3(s large, 2H, NH_2); ^{13}C-NMR (DMSO-d6): δ = 14.5(**C**H_3),14.6 (**C**5), 49.2 (**C**4), 60.5(**C**H_2), 60.7(C2), 118.4 (CN), 168.9(C1), 177.3(C3).

ethyl 2-cyano-3-(ethoxycarbonyl)-3-phenylacrylate **7a** : Rdt=55% ; mp=134°C ; IR(KBr) : ν : 3408 (NH), 2220 (CN), =1773 (C=O), 1650 (C=O) cm^{-1}; ^{1}H-NMR: (DMSO-d6): δ = 1.10(t, 3H, CH_3, $^3J_{HH}$ =6.9MHz); 1.26(t, 3H, CH_3, $^3J_{HH}$ =7.2MHz), 4.05(q, 2H, CH_2 , $^3J_{HH}$ =6.9MHz); 4.27(q, 2H, CH_2, $^3J_{HH}$ =7.2MHz), 7.44-7.61(mu, 5H, H_{arom}), 11.02(s, 1H, NH); ^{13}C-NMR (DMSO-d6): δ = 14.3(**C**H_3),14.4(**C**H_3), 62.2(**C**H_2), 62.9(**C**H_2), 85.8(C2), 116.6 (CN), 151.0 (C=O),165.2(C1), 165.4(C3), 128.6-132.8(C_{arom}).

ethyl 2-cyano-3-(ethoxycarbonyl)-3-p-tolylacrylate **7b** : Rdt=53% ; mp=136°C; IR(KBr) : ν : 3411(NH), 2223(CN), 1773(C=O), 1673 (C=O) cm^{-1}; ^{1}H-NMR: (DMSO-d6): δ = 1.20(t, 3H, CH_3, $^3J_{HH}$ =6.9MHz), 1.35(t, 3H, CH_3, $^3J_{HH}$ =7.2MHz), 2.41(s, 3H, CH_3), 4.10(q, 2H, CH_2, $^3J_{HH}$ =6.9MHz), 4.35(q, 2H, CH_2, $^3J_{HH}$ =7.2MHz), 7.27-7.35(mu, 4H, H_{arom}), 11.31(s, 1H, NH); ^{13}C-NMR (DMSO-d6): δ = 14.4(**C**H_3),14.5(**C**H_3), 30.1(**C**H_3), 62.6(**C**H_2), 63.2(**C**H_2), 85.2(C2), 116.4 (CN), 151.3 (C=O),166.7(C1), 167.0(C3), 128.2-141.9(C_{arom}).

2,6-dioxo-1-phenyl-4-p-tolyl-1,2,3,6-tetrahydropyrimidine-5-carbonitrile **8** : Rdt=23% ; mp>260°C; IR(KBr) : ν : 3422(NH), 2220(CN), 1665(C=O) cm^{-1}; ^{1}H-NMR: (DMSO-d6): δ = 2.41(s, 3H, CH_3), 7.30-7.65(mu, 9H, H_{arom}); ^{13}C-NMR (DMSO-d6): δ = 21.6(**C**H_3), 85.2(C5), 115.9 (CN), 143.2 (C2),150.6(C6), 161.7(C4), 127.5-135.1(C_{arom}).

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REFERENCES

[1] M. A. Schmidt, X. Qian, Tetrahedron Lettres, **54** (2013) 5721-5726.

[2] N. Mangarao, G. M. Basha, T. Ramu, R. Srinuvasarao, S. Prasanthi, V. Siddaiah, Tetrahedron Letters, **55** (2014) *177-179*.

[3] Y. Zhang, P. W. K. Woo, J. Hartman, N. Colbry, Y. Huang, C. C. Huang, Tetrahedron Letters, **46**(2005) 2087-2091.

[4] A. Chaker, E. Najahi, F. Nepveu, F. Chabchoub , Arabian Journal of Chemistry (2013) in press.

[5] F. Debatin, A. Thomas, A. Kelling, N. Hedin, Z. Bacsik, I. Senkovska, S. Kaskel, M. Junginger,H. müller, U. Schilde, C. jäger, A. Friedrich, H. J. Holdt, Angew. Chem.**122** (2010)1280 –1284.

[6] Y. Matsushima, J.Kino, Eur. J. Org. Chem.**10 (**2009) 1619–1624.

[7] G. A. Dutra, M. J. Finkes, J. A. Sikorski,Heteroatom Chemistry, **3** (1992)279-291.

[8] R. K. Bowman, J. S. Johnson,J. Org. Chem. **69** (2004) 8537-8540.

[9] J. D. Williams, S. T. Nguyen, S. Gu, X. Ding, M. M. Butler, T. F. Tashjian, T. J. Opperman, R. G. Panchal, S. Bavar, N. P. Peet, D. T. Moir, T. L. Bowlin, Bioorganic & Medicinal Chemistry, **21** (2013) 7790–7806.

[10] M. E. Voss, C. M. Beer, S. A. Mitchell, P. A. Blomgren, P. E. Zhichkin, Tetrahedron, **64** (2008) 645-651.

[11] K. Sudheendran, D. Schmidt, W. Frey, J. Conrad, U. Beifuss, Tetrahedron, **70** (2014) 1635-1645.

[12] A. Karoui, F. Allouche, M. Deghrigue, A. Agrebi, A. Bouraoui , F. Chabchoub, Med Chem Res. **23** (2014) 1591–1598.

[13] M. Boukthir, F. Zribi, M. Belhouchet, F. Chabchoub, Journal of Advances in Chemistry, **7**(2014)1434-1439.

[14] M. Kossentini, F. Chabchoub, Y. Le Bigot, M. Salem, J.Soc.Chim.Tun. **4**(2001)1233-1237.

[15] J. Krechel, M. A. Pérez, F. J. Cuadrado, J. L. Soto, Synthesis, **5**(1988)122-124.

[16] Sheldrick, G.M. SHELXS-*97* Program for the Solution of Crystal Structures, University of Göttingen, Germany, 1997.

[17] Sheldrick, G.M. SHELXL-97 Program for Crystal Structure Refinement, University of Göttingen, Germany, 1997