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A New Approach to the Synthesis of Functionalized 1-Alkenyl-1*H*-1,2,3-Triazoles.

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Abstract: The Horner-Wadsworth-Emmons (HWE) olefination of 1-[(diethoxyphosphoryl)methyl]-4,5-bis(methoxycarbonyl)-1*H*-1,2,3-triazole and 1-[(diethoxyphosphoryl)methyl]-5-phenyl-1*H*-1,2,3-triazole by means of aldehydes was found to be a convenient method for the preparation of functionalized 1-alkenyl-1*H*-1,2,3-triazoles in moderate to good yields and low Z/E stereoselectivity.

1,2,3-Triazoles have attracted much attention in recent years due to their wide application in organic synthesis as well as their use in industry, agriculture and medicine.[1]

Although numerous synthetic methods for the preparation of 1-substituted-1*H*-1,2,3-triazoles[1] derivatives are known, access to 1-alkenyl-1*H*-1,2,3-triazoles is limited. So far alkenyltriazoles can be obtained by the following methods: (i) condensation of active methylene compounds with vinyl azides or their precursors, β-haloalkylazides in the presence of alkoxides,[2,3] (ii) 1,3-dipolar cycloaddition of vinyl azides and alkynes,[4-10] (iii) the regiospecific cycloaddition of vinyl azides to 2-oxoalkylidenetriphenylphosphorane,[11] (iv) alkylation of 1-vinyl and 1-propenylbenzotriazoles by means of alkyl halides in the presence of butyllithium,[12] (v) base catalysed isomerisation of 1-(alk-2-enyl)benzotriazoles,[12-15] (vi) dehydrochlorination of 1-chlorobenzotriazole - olefin adducts with potassium *t*-butoxide or 1,5-diazabicyclo[4,3,0]non-5-ene,[13,15,16] (vii) the Wittig or the Peterson olefinations of carbonyl compounds by means of (benzotriazol-1-ylmethyl)triphenylphosphonium chloride and 1-[1,1-bis(trimethylsilyl)alkyl]benzotriazoles respectively,[17] (viii) addition of 1*H*-benzotriazole to ethyl propiolate and methyl but-2-ynoate.[16]

Despite the E-stereospecificity of C=C double bond in derivatives of 1-alkenyl-1*H*-1,2,3-triazoles thus obtained, the first three synthetic approaches to these triazoles suffer from the same drawback - the vinyl azides or β-haloalkylazides used in those reactions are unstable[18] and therefore generally applied as crude materials. In addition the first method is applicable to simple azides only;[19] in the second method two regioisomeric triazoles are obtained in the most cases.[4] The methods (iv-viii) were applied to the synthesis of 1-alkenylbenzotriazoles so far.

From another point of view, the Horner-Wadsworth-Emmons (HWE) modification of the Wittig

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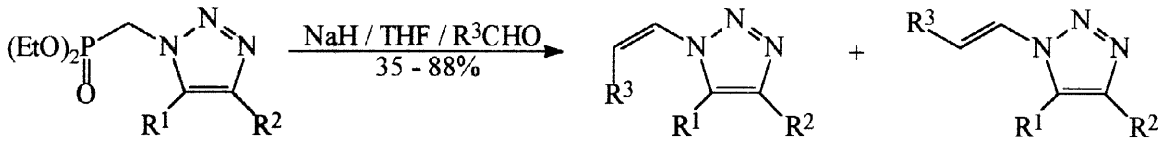
reaction is one of the most versatile tools for the construction of C=C double bonds.[20] Phosphonate anions are strongly nucleophilic and readily react with carbonyl compounds to form an olefin and a water soluble phosphate ester, usually in high yields.[20] In general this reaction preferentially leads to the more stable E-disubstituted olefin.[20] However, in the case of some contrived phosphonates, Z-olefins are formed with high stereoselectivity.[21]

In connection with our interest in the chemistry of organic compounds containing both phosphorus and nitrogen atoms we have recently become involved in the synthesis of 1-azidoalkylphosphonates,[22] as well as their application to the synthesis of diethyl 1-aminoalkylphosphonates[23,24] and derivatives of 1-[1-(diethoxyphosphoryl)alkyl]-1*H*-1,2,3-triazoles.[25]

In this context, we wish to report the results of the HWE olefinations of 1-[(diethoxyphosphoryl)methyl]-4,5-bis(methoxycarbonyl)-1*H*-1,2,3-triazole (**1a**) and 1-[(diethoxyphosphoryl)methyl]-5-phenyl-1*H*-1,2,3-triazole (**1b**) by means of aldehydes.

The starting triazole **1a** has been obtained by a facile 1,3-dipolar cycloaddition of diethyl azidomethylphosphonate[22] and dimethyl acetylenedicarboxylate, using a modification of the procedure given by Palacios et al.,[26] and the cycloaddition of the former compound and 2-phenyl-2-oxoethylidenetriphenylphosphorane, afforded triazole **1b**[25] in good yield.

The above mentioned olefination performed in tetrahydrofuran at room temperature, or under reflux, in the presence of sodium hydride as a base, afforded the expected triazoles **2** and **3**, in moderate to good yields (35-88%), after flash chromatography (Scheme 1).



1 **2** **3**

1a: $R^1 = R^2 = CO_2Me$
1b: $R^1 = Ph$, $R^2 = H$

2 and **3**: **a**: $R^1 = R^2 = CO_2Me$; $R^3 = i\text{-Pr}$
b: $R^1 = R^2 = CO_2Me$; $R^3 = t\text{-Bu}$
c: $R^1 = R^2 = CO_2Me$; $R^3 = Ph$
d: $R^1 = R^2 = CO_2Me$; $R^3 = 4\text{-Me-}C_6H_4$
e: $R^1 = R^2 = CO_2Me$; $R^3 = 2\text{-Me-}C_6H_4$
f: $R^1 = Ph$; $R^2 = H$; $R^3 = 4\text{-Me-}C_6H_4$

Scheme 1

The reaction conditions, yields, and Z/E ratios are given in Table 1.

All isolated triazoles exhibited analytical and spectral data in agreement with the assigned structures. The Z/E ratios of all products **2** and **3** were determined by integrating the olefinic protons signals (J_{cis}= 8.8-9.25 Hz and J_{trans}=14-14.5 Hz) in ^{1}H NMR spectra. The value of the vicinal coupling constants for E-isomer **3** are concordinate with literature data.[2] In general the olefinic protons of a Z-isomer **2** exhibit signals that are upfield to those of the corresponding E-isomer **3**.

Contrary to our expectation, the Z/E stereoselectivity of olefination was low and generally an almost equimolar mixture of both **2/3** was formed (see Table 1, entries 2, 3, 4). However in the olefination of **1a** by means of isobutyraldehyde and o-tolualdehyde (Table 1, entries 1, 5), and **1b** by means of p-tolualdehyde (Table 1, entry 6) the Z-selectivity was enhanced and was estimated to be in the range 76-78% and 59%, respectively.

Substitution of NaH by LDA increased the Z-selectivity for **2b/3b** to 71%, and for **2c/3c** to 77%. However, the Z-selectivity for **2a/3a** fell to 63% when LDA was used instead of NaH. Unfortunately the yield of the olefination dropped considerably when LDA was used as a base (see Table 1 footnotes for details).

Table 1. Triazoles **2/3** obtained.

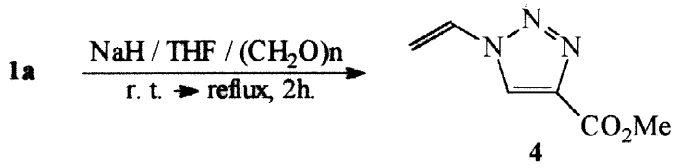
Entry	Product	Reaction conditions[a] Time (h), temp. (°C)	Yield[b] (%)	Z/E ratio[c]
1	**2a/3a**	3, r.t.[d]	50	78/22[c]
2	**2b/3b**	3, r.t.[d]	35	52/48[e]
3	**2c/3c**	3, r.t.[f]	71	53/47[c]
4	**2d/3d**	3, r.t.[f]	58	50/50
5	**2e/3e**	3, r.t.	68	76/24
6	**2f/3f**	3, r.t.[f]	88	59/41

[a] 1.2 mol equivalent of carbonyl compound was used. [b] Yields of Z/E mixture of pure triazoles **2/3**, based on **1**, isolated after flash chromatography. [c] Diastereomer ratio based on ^{1}H NMR spectra of the crude reaction mixture. [d] 1.05 mol equivalent of aldehyde was applied. [e] For LDA as a base at -78^0 to r.t., 2h; compd. (yield-%, Z/E): **2a/3a** (30, 63/37); **2b/3b** (18, 71/29); **2c/3c** (43, 77/23). [f] In addition the reaction mixture was refluxed 2h for completion.

The large amount of Z-isomer formed in these HWE olefinations was unexpected, however at this stage there are insufficient data to explain the observed stereoselectivity.

The Z/E mixture of triazoles **2/3** was separated by flash chromatography, to give pure (Z)-**2** and (E)-**3** isomers in moderate yields (15-46%). Attempted chromatographic separation of the **2a/3a** isomeric mixture was unsuccessful as the R_f values of **2a** and **3a** were very close.

Olefination of **1a** using paraformaldehyde was a special case of the HWE reaction (Scheme 2).



Scheme 2

Decarboxylation prior to hydrolysis took place under the reaction conditions, and 1-vinyl-4-methoxycarbonyl-1*H*-1,2,3-triazole **4** was obtained in 35% yield as the product instead of the expected 4,5-bis(methoxycarbonyl) derivative. Such decarboxylation, which sometimes occurs on heating the carboxylic derivatives of the triazole above its melting point has been previously described.[2] The structure of the triazole **4** was determined on the bases of ^{1}H and ^{13}C NMR spectra. In addition NOESY experiment showed non-bonding ^{1}H-^{1}H interaction between the proton located at position 5 on the triazole ring and the proton of vinyl moiety, which unequivocally confirms the assigned structure of **4**. The structure of **4** was also confirmed by mass spectrometry [the molecular ion peak at m/z 154 (MH^{+})], and elemental analysis as well.

In summary, the method described in this communication provides a simple access to functionalized 1-alkenyl-1*H*-1,2,3-triazoles from readily available starting materials and thus avoids the use of the unstable vinyl azides as substrates. Despite low Z/E stereoselectivity of the above mentioned synthesis, individual E- and Z-isomers can be, in general, easily isolated in pure state *via* chromatography.

Experimental.

NMR spectra were recorded on a Bruker DPX 250 instrument at 250.13 MHz for ^{1}H and 62.9 MHz for ^{13}C NMR, respectively using $CDCl_3$ as solvent unless otherwise specified. ^{31}P NMR spectra were recorded on a Bruker DPX 250 spectrometer at 101.3 MHz. Positive chemical shifts are downfield from ext. 85% H_3PO_4. Chemical shifts (δ) are indicated in ppm and coupling constants (J) in Hz. FAB/MS were recorded on a APO Electron (Ukraine) Modell MI 12001 E mass spectrometer equipped with a FAB ion source (thioglycerol matrix). IR spectra were measured on a Specord M 80 (Zeiss) instrument and are reported in wavennumbers (cm^{-1}). Flash chromatography was performed with glass column packed with Baker silica gel (30-60 μm). [Eluents: EtOAc/hexane (1:1) (A); EtOAc/hexane (1:2) (B)]. Melting points were determined in open capillaries and are uncorrected. All reagents were purchased from Fluka and used without further purification. The diethyl azidomethylphosphonate,[22] 2-phenyl-2-oxoethylidenetriphenylphosphorane,[27] and 1-[(diethoxyphosphoryl)methyl]-5-phenyl-1*H*-1,2,3-triazole[25] (**1b**) were prepared according to the literature procedures.

1-[(dicthoxyphosphoryl)methyl]-4,5-bis(methoxycarbonyl)-1*H*-1,2,3-triazole (1a) was obtained by a modification of the literature procedure[26] (time of the reaction was shortened 10 times, and pure triazole was obtained *via* crystallization instead of chromatography).

A mixture of dimethyl acetylenedicarboxylate (0.032 mol) and diethyl azidomethylphosphonate (0.03 mol) in toluene (20 mL) was heated under reflux for 3 h. Toluene was then evaporated under reduced pressure, and crude triazole was washed with the mixture of ether/hexane (1:1 v/v, 60 mL) to give analytically pure **1a** in 92% yield as a white-yellow needles; m.p. 82-84°C (lit.[26] m.p. 83-84°C); ^{1}H NMR ($CDCl_3$, TMS): δ = 1.29 (t, J=7.06, 6H, $2CH_3$), 3.98, 4.01 (2s, 6H, $2CH_3$), 4.05 (dq, J=7.06, J=8.38, 4H, $2CH_2$), 5.13 (d, J=13.23, 2H, CH_2); ^{31}P NMR ($CDCl_3$, H_3PO_4): δ = 15.56; IR (CCl_4): ν = 1739, 1734, 1540, 1466, 1255, 1050, 1022.

Preparation of 1-alkenyl-1*H*-1,2,3-triazoles (2a/3a-2f/3f). *General procedure.*

Triazole **1** (0.004 mol) was added in one portion under Argon to a stirred suspension of NaH (0.006 mol, 50% suspension in mineral oil) in anhydrous THF (20 mL) at 0°C. The resulting mixture was stirred for 15 min. at this temperature, and the solution of aldehyde (0.0042-0.0048 mol) in THF (5 mL) was added dropwise. The progress of the reaction was controlled *via* TLC. The resulting mixture was evaporated under reduced pressure, and the semicrystalline residue was extracted with ether (3x30 mL). Ether extracts were washed with water (3x5 mL) and dried over anhydrous Na_2SO_4. Solvent was evaporated, and the residue was subjected for flash chromatography to give pure triazoles **2** and **3**.

(*Z*/E)-1-(3-methylbut-1-enyl)-4,5-bis(methoxycarbonyl)-1*H*-1,2,3-triazole (2a/3a); (a Z/E=78/22 isomeric mixture; *data for E-isomer are given in italic*), yield: 50%, yellow viscous liquid; R_f =0.48 and *0.49* (A); ^{1}H NMR ($CDCl_3$, TMS): δ = 1.04, (d, J=6.60, 6H, $2CH_3$), *1.14* (*d, J=6.74, 6H, $2CH_3$,*), *2.45-2.62* (*m, 1H, CH*), 2.79 (ddsept., J=0.80, J=6.60, J=10.32, 1H, CH), *3.95, 3.98* (*2s, 6H, $2CH_3$*), 3.96, 3.97 (2s, 6H, $2CH_3$), 5.74 (dd, J_{cis}=8.76, J=10.32, 1H, CH^2), *6.69* (*dd, J=7.21, J_{trans}=14.04, 1H, CH^2*) 6.82 (dd, J=0.8, J_{cis}=8.76, 1H, CH^1), *7.16* (*dd, J=1.38, J_{trans}=14.04, 1H, CH^1*); IR (CCl_4): ν = 1736, 1632, 1556, 1288, 1224, 1064, 960; FAB/MS: m/z(%): 254(MH^+, 100); Anal. Calcd. for $C_{11}H_{15}N_3O_4$ (253.2): C: 52.17; H: 5.97; N: 16.59. Found: C: 52.00; H: 5.79; N: 16.41.

(Z)-1-(3,3-dimethylbut-1-enyl)-4,5-bis(methoxycarbonyl)-1*H*-1,2,3-triazole (2b); yield: 16%; viscous yellow oil; R_f =0.47 (A); ^{1}H NMR ($CDCl_3$, TMS): δ = 0.95 (s,9H, $3CH_3$), 3.98, 3.99 (2s, 6H, $2CH_3$), 5.94 (d, J_{cis}=9.20, 1H, CH^2), 6.62 (d, J_{cis}=9.2, 1H, CH^1); IR (CCl_4): ν = 1740, 1640, 1550, 1265, 1220, 1060; FAB/MS: m/z(%): 268(MH^+, 100); Anal. Calcd. for $C_{12}H_{17}N_3O_4$ (267.3): C: 53.92; H: 6.41; N: 15.72. Found: C: 53.81; H: 6.31; N: 15.60.

(E)-1-(3,3-dimethylbut-1-enyl)-4,5-bis(methoxycarbonyl)-1*H*-1,2,3-triazole (3b); yield: 15%; yellow oil, n_D^{20}=1.4883; R_f =0.52 (A); ^{1}H NMR ($CDCl_3$, TMS): δ = 1.18 (s,9H, $3CH_3$), 3.97, 4.01 (2s, 6H, $2CH_3$), 6.76 (d, J_{trans}=14.20, 1H, CH^2), 7.14 (d, J_{trans}=14.20, 1H, CH^1); IR (CCl_4): ν = 1735, 1624, 1552, 1284, 1208, 960; FAB/MS: m/z(%): 268(MH^+, 100); Anal. Calcd. for $C_{12}H_{17}N_3O_4$ (267.3): C: 53.92; H: 6.41; N: 15.72. Found: C: 53.82; H: 6.22; N: 15.59.

(*Z*)-1-(2-phenylethenyl)-4,5-bis(methoxycarbonyl)-1*H*-1,2,3-triazole (2c); yield: 35%; m.p. 88-91°C; R_f=0.20 (B); ^{1}H NMR ($CDCl_3$, TMS): δ = 3.82, 3.99 (2s, 6H, $2CH_3$), 6.68 (d, J_{cis}=9.00, 1H, CH^2), 7.07 (d,

J_{cis}=9.00, 1H, CH^1), 6.93-7.31 (m, $5H_{arom}$); IR (CCl_4): ν = 1740, 1735, 1620, 1556, 1280, 1100; FAB/MS: m/z(%): 288(MH^+, 100); Anal. Calcd. for $C_{14}H_{13}N_3O_4$ (287.3): C: 58.53; H: 4.56; N: 14.63. Found: C: 58.37; H: 4.40; N: 14.51.

(E)-1-(2-phenylethenyl)-4,5-bis(methoxycarbonyl)-1*H*-1,2,3-triazole (**3c**); yield: 23%; m.p. 76-78°C; R_f=0.28 (B); ^1H NMR ($CDCl_3$, TMS): δ = 4.00, 4.04 (2s, 6H, $2CH_3$), 7.34-7.54 (m, $5H_{arom}$) 7.68 (d, J_{trans}=14.32, 1H, CH^2), 7.93 (d, J_{trans}=14.32, 1H, CH^1); IR (CCl_4): ν = 1738, 1728, 1624, 1568, 1284, 1072, 960; FAB/MS: m/z(%): 288(MH^+, 100); Anal. Calcd. for $C_{14}H_{13}N_3O_4$ (287.3): C: 58.53; H: 4.56; N: 14.63 Found: C: 58.39; H: 4.41; N: 14.52.

(Z)-1-[2-(p-tolyl)ethenyl)]-4,5-bis(methoxycarbonyl)-1*H*-1,2,3-triazole (**2d**); yield: 33%; m.p. 55-57°C (dec.); R_f=0.21 (B); ^1H NMR ($CDCl_3$, TMS): δ = 2.29 (s, 3H, CH_3), 3.81, 3.98 (2s, 6H, $2CH_3$), 6.75-7.50 (m, $4H_{arom}$), 6.79 (d, J_{cis}=8.00, 1H, CH^2), 7.04 (d, J_{cis}=8.00, 1H, CH^1); IR (CCl_4): ν = 1736, 1620, 1542, 1268, 1230, 1066; FAB/MS: m/z(%): 302(MH^+, 100); Anal. Calcd. for $C_{15}H_{15}N_3O_4$ (301.3): C: 59.79; H: 5.02; N: 13.95 Found: C: 59.59; H: 4.89; N: 13.82.

(E)-1-[2-(p-tolyl)ethenyl)]-4,5-bis(methoxycarbonyl)-1*H*-1,2,3-triazole (**3d**); yield: 22%; m.p. 105-107°C (dec.); R_f=0.27 (B); ^1H NMR ($CDCl_3$, TMS): δ = 2.39 (s, 3H, CH_3), 3.99, 4.04 (2s, 6H, $2CH_3$), 7.18-7.4.5 (m, $4H_{arom}$), 7.65 (d, J_{trans}=14.51, 1H, CH^2), 7.88 (d, J_{trans}=14.51, 1H, CH^1); IR (CCl_4): ν = 1744, 1632, 1552, 1288, 1232, 1080, 968; FAB/MS: m/z(%): 302(MH^+, 100); Anal. Calcd. for $C_{15}H_{15}N_3O_4$ (301.3): C: 59.79; H: 5.02; N: 13.95. Found: C: 59.63; H: 4.92; N: 13.78.

(Z)-1-[2-(o-tolyl)ethenyl)]-4,5-bis(methoxycarbonyl)-1*H*-1,2,3-triazole (**2e**); yield: 46%; m.p. 120-122°C; R_f=0.24 (B); ^1H NMR ($CDCl_3$, TMS): δ = 2.28 (s, 3H, CH_3), 3.73, 3.92 (2s, 6H, $2CH_3$), 6.67-7.26 (m, $4H_{arom}$), 6.93 (d, J_{cis}=9.25, 1H, CH^2), 7.17 (d, J_{cis}=9.25, 1H, CH^1); IR (CCl_4): ν – 1739, 1620, 1559, 1226, 1144, 1062; FAB/MS: m/z(%): 302(MH^+, 100); Anal. Calcd. for $C_{15}H_{15}N_3O_4$ (301.3): C: 59.79; H: 5.02; N: 13.95. Found: C: 59.65; H: 4.95; N: 13.83.

(E)-1-[2-(o-tolyl)ethenyl)]-4,5-bis(methoxycarbonyl)-1*H*-1,2,3-triazole (**3e**); yield: 16%; m.p. 133-136°C (dec.); R_f=0.30 (B); ^1H NMR ($CDCl_3$, TMS): δ = 2.44 (s, 3H, CH_3), 3.99, 4.02 (2s, 6H, $2CH_3$), 7.19-7.55 (m, $4H_{arom}$), 7.76 (d, J_{trans}=14.26, 1H, CH^2), 7.88 (d, J_{trans}=14.26, 1H, CH^1); IR (CCl_4): ν = 1732, 1624, 1556, 1288, 1228, 1080, 988; FAB/MS: m/z(%): 302(MH^+, 100); Anal. Calcd. for $C_{15}H_{15}N_3O_4$ (301.3): C: 59.79; H: 5.02; N: 13.95. Found: C: 59.62; H: 4.91; N: 13.80.

(Z)-1-(2-phenylethenyl)-5-phenyl-1*H*-1,2,3-triazole (**2f**); yield: 46%; viscous oil; R_f=0.31 (B); ^1H NMR ($CDCl_3$, TMS): δ = 1.88 (s, 3H, CH_3), 6.50-7.35 (m, $9H_{arom}$), 6.73 (d, J_{cis}=8.75, 1H, CH^2), 7.14 (d, J_{cis}=8.75, 1H, CH^1), 7.62 (s, $1H_{triazole}$); IR (CCl_4): ν = 1635, 1550, 1260, 1235, 1110, 1005; FAB/MS: m/z(%): 262(MH^+, 100); Anal. Calcd. for $C_{17}H_{15}N_3$ (261.3): C: 78.13; H: 5.79; N: 16.08. Found: C: 78.00; H: 5.63; N: 15.95.

(E)-1-(2-phenylethenyl)-5-phenyl-1*H*-1,2,3-triazole (3f); yield: 25%; m.p. 89-92°C (dec.); R_f=0.39 (B); ^{1}H NMR ($CDCl_3$, TMS): δ = 2.41 (s, 3H, CH_3), 7.20-7.54 (m, $9H_{arom}$), 7.29 (d, J_{trans}=14.25, 1H, CH^2), 7.78 (d, J_{trans}=14.25, 1H, CH^1), 7.79 (s, $1H_{triazole}$); IR (CCl_4): ν = 1648, 1552, 1256, 1232, 1112, 1008, 944; FAB/MS: m/z(%): 262(MH^+, 100); Anal. Calcd. for $C_{17}H_{15}N_3$ (261.3): C: 78.13; H: 5.79; N: 16.08. Found: C: 77.97; H: 5.68; N: 15.98.

1-vinyl-4-methoxycarbonyl-1*H*-1,2,3-triazole (4); yield: 35%; m.p. 87-88°C; R_f=0.29 (A); ^{1}H NMR ($CDCl_3$, TMS): δ = 3.98 (s, 3H, CH_3), 5.32 (dd, J_{gem}=2.06, J_{cis}=8.82, 1H, CH^2), 5.84 (dd, J_{gem}=2.06, J_{trans}=15.83, 1H, CH^2), 7.36 (dd, J_{cis}=8.82, J_{trans}=15.83, 1H, CH^2), 8.33 (s, $1H_{triazole}$); ^{13}C NMR ($CDCl_3$): δ = 52.6 (s, CH_3), 107.7 (s, $CH_{2vin.}$), 125.1 (s, $CH_{5triazole}$), 130.0 (s, Ch_{vin}), 140.3 (s, $C_{4triazole}$),161.2 (s CO_2); IR (CCl_4): ν = 1728, 1644, 1524, 1192, 1032, 960; FAB/MS: m/z(%): 154(MH^+, 100); Anal. Calcd. for $C_6H_7N_3O_2$ (153.1): C: 47.06; H: 4.61; N: 27.44. Found: C: 46.97; H: 4.51; N: 27.32.

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