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A New and Efficient Procedure for Preparing 1,2,3-Triazoles

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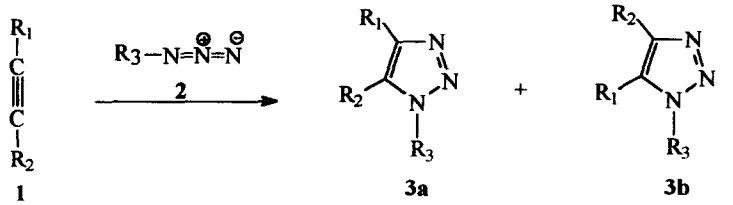
Abstract: 1,2,3-Triazoles are readily accessible in moderate to good yields by a diazo transfer reaction with β-amino-α,β-unsaturated ketones or esters and tosyl or mesyl azide reagent. In this methodology the nitrogen atoms N-2 and N-3 of the triazole ring are derived from diazo transfer reagent and nitrogen atom N-1 is derived from the appropriate enamine. © 1997 Published by Elsevier Science Ltd.

Substances containing a 1,2,3-triazole heterocycle ring are important targets in chemical synthesis because of their pronounced biological activities.[1-5] The most common method described in the literature for the preparation of 1,2,3-triazole ring is the 1,3-dipolar cycloaddition reaction[6-9] between substituted acetylenes **1** and an alkyl azide derivative **2** . This kind of methodology lacks regioselectivity. When asymmetrical acetylenes are used as dipolarophiles, the cycloaddition is expected to give a mixture of the two isomeric 1,2,3-triazoles **3a** and **3b**.[8] It is important to note that in this approach all the nitrogens of the 1,2,3-triazole ring are derived from the azide moiety. Other methods for preparing 1,2,3-triazoles from diazo compounds are also available.[10-13]

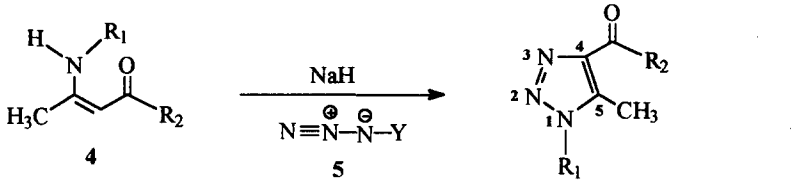


1 **3a** **3b**

DISCUSSION

In this communication, we report herein a versatile method for preparing 1,2,3-triazoles **6a-g** in good yields by reacting β-amino-α,β-unsaturated ketones or esters[14,15] **4** with a diazo transfer reagent such as tosyl[16] or mesyl azide[17] **5** . The advantages of this procedure are versatility of the substituents at positions 4 and 5, readily available reagents and the regiochemistry output. Only one of the possible isomers which is characterized by alkyl or aryl group at position 5 and acetyl or carboxylate group at 4-position is obtained.

The yields of the 1,2,3-triazoles **6a-g** were dependent on the structure of the β-amino-α-β-unsaturated ketones **6a-e** and esters **6f-g** and of the diazo transfer reagent **5** (Table 1). The reaction works very well with alkyl amines (**6a, 6c** and **6e**) but only moderate yields are obtained with aromatic amines (**6b** and **6d**). It is noticeable that β-amino-α-β-unsaturated ketones are more reactive than β-amino-α-β-unsaturated esters. Mesyl azide is a better diazo transfer reagent in this reaction than tosyl azide. This general procedure should allow rapid access to N-alkyl-substituted 1,2,3-triazoles such as **6a, 6c** and **6e-g** which are hard to prepare using other methods and it can be extended in the preparation of other 1,2,3-triazoles.



6a, R_1=Bn, R_2=CH_3
6b, R_1=Ph, R_2=CH_3
6c, R_1=n-Bu, R_2=CH_3
6d, R_1=*p*-MePh, R_2=CH_3
6e, R_1=n-decyl, R_2=CH_3
6f, R_1=Bn, R_2=OEt
6g, R_1=n-Bu, R_2=OEt

Typical Experimental Procedure: To a stirred mixture of sodium hydride (6.67 mmol, free of oil) in anhydrous acetonitrile (4 mL), under nitrogen at room temperature, was added a solution of β-Amino-α,β-unsaturated ketones or esters **4** (1.85 mmol in 4 mL of anhydrous acetonitrile). The stirring was continued for 0.5 h, followed by dropwise addition of mesyl azide (5 mmol in 1 mL of acetonitrile). Additional stirring was kept for 24 h and the reaction was quenched with sodium hydroxide solution (10%, w/w). The separated organic layer was dried over anhydrous magnesium sulfate, the solvent was removed under reduced pressure to give a residue which was extracted with methylene chloride (3 x 10 mL). After drying over anhydrous magnesium sulfate, the solvent was removed under reduced pressure to leave the crude 1,2,3-triazoles **6a-g**, which were purified by column chromatography on silicagel, eluting with 10% of

AcOEt in n-hexane (see Table 1). The structures of the 1,2,3-triazoles[18,19] were confirmed by ^{1}H NMR, ^{13}C NMR and MS .

Table 1: Synthesis of 1,2,3-triazoles **6a-g**.

	R_1	R_2	6 (TsN_3)[e]	6 (MsN_3)[e]
a	Bn[a]	CH_3	50	97
b	Ph[b]	CH_3	40	20
c	n-Bu	CH_3	40	79
d	p-MePh[c]	CH_3	10	37
e	n-Decyl	CH_3	30	87
f	Bn	OEt	23	72
g	n-Bu	OEt	2	83

a) Bn = benzyl; b) Ph = phenyl; c) p-MePh = p-methylphenyl; d) Ts = p-toluenesulfonate; e) Ms = methylsulfonate.

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19. ^{1}H NMR δ ($CDCl_3$, ppm). **6a**, 2.47 (s, $C_5\underline{CH_3}$), 2.70 (s,$\underline{CH_3}C$ =O), 5.52 (s, H_6), 7.15-7.21 (m, $H_{2'}$, $H_{6'}$), 7.31-7.38 (m, $H_{3'}$, $H_{4'}$, $H_{5'}$); **6f**, 1.42 (t, $OCH_2\underline{CH_3}$, J = 7.2 Hz), 2.46 (s,$C_5\underline{CH_3}$), 4.42 (q, $O\underline{CH_2}CH_3$, J = 7.2 Hz), 5.54 (s, H_6), 7.15-7.18 (m, $H_{2'}$, $H_{6'}$), 7.31-7.37 (m, $H_{3'}$, $H_{4'}$, $H_{5'}$). ^{13}C NMR δ ($CDCl_3$, ppm). **6a**, 8.9 ($C_5\underline{CH_3}$), 27.4 ($\underline{CH_3}C$=O), 51.4 (C_6), 127.0 ($C_{2'}$, $C_{6'}$), 128.4 or 128.9 ($C_{4'}$), 128.4 or 128.9 ($C_{3'}$, $C_{5'}$), 133.7 ($C_{1'}$), 136.6 (C_5), 143.7 (C_4), 194.1(C=O); **6f**, 8.8 ($C_5\underline{CH_3}$), 14.1 ($OCH_2\underline{CH_3}$), 51.7 (C_6), 60.8 ($O\underline{CH_2}CH_3$) , 127.0 ($C_{2'}$, $C_{6'}$), 128.3 or 128.9 ($C_{4'}$), 128.3 or 128.9 ($C_{3'}$, $C_{5'}$), 133.7 ($C_{1'}$), 136.8 (C_5), 138.1 (C_4), 161.5 (C=O). FAB-HRMS: **6a**, $(M+1)^+$ = 216.1137 (calcd = 216.1059); **6b**, $(M+1)^+$= 202.0980 (calcd = 202.0902); **6c**, $(M+1)^+$ = 182.1293 (calcd = 182.1215); **6d**, $(M+1)^+$ = 216.1137 (calcd = 216.1059); **6e**, $(M+1)^+$ = 266.2232 (calcd = 266.2154); **6f**, $(M+1)^+$ = 246.1243 (calcd = 246.1164) ; **6g**, $(M+1)^+$ = 212.1399 (calcd = 212.1321).

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