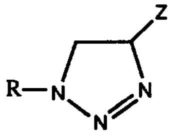
Tetrahedron Letters, Vol. 34, No. 25, pp. 4051-4054, 1993
Printed in Great Britain

0040-4039/93 $6.00 + .00
Pergamon Press Ltd

ONE POT MULTIPLE-STEPS REACTIONS OF ALLYL AZIDE AND ALKENES CARRYING ELECTRON-WITHDRAWING GROUPS

Chia-Hsi Yang* and Huang-Jang Shen,
Department of Chemistry, Chung-Yuan Christian University,
Chung-Li, Taiwan, R.O.C.

The reaction of acrylate or acrylonitrile with alkyl or phenyl azide was studied by L'abbe et. al..[1] Therein, product (**2a**) from Michael addition of Δ^2-1,2,3-triazoline **1** to acrylate, or products (**5a, 5b** and **5c**) involving isomerization of triazoline to diazoacetate followed by intermolecular [3+2] cycloaddition of diazoacetate and another molecule of acrylate or acrylonitrile (**1→3→4→5**) were obtained.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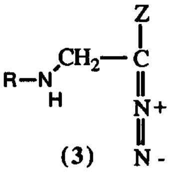
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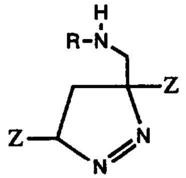
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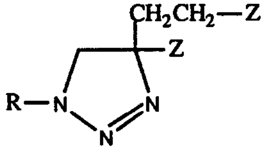
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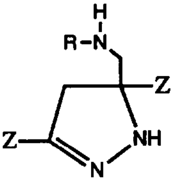
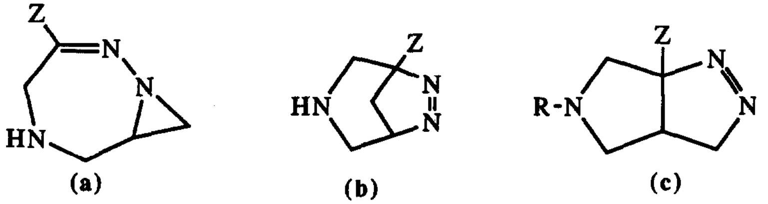

(5)

2a.	Z = CN	R = Bu
2b.	Z = CN	R= $(CH_2)_2CH{=}CH_2$
2c.	Z = COOMe	R= $(CH_2)_2CH{=}CH_2$

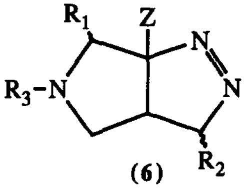
5a.	Z = CN	R= Ph
5b.	Z = COOEt	R= Bu
5c.	Z = $CONH_2$	R= Bu
5d.	Z = COOMe	R= $(CH_2)_2CH{=}CH_2$
5e.	Z = CN	R= $-CH_2CH{=}CH_2$
5f.	Z = COOMe	R= $(CH_2)_3CH{=}CH_2$

In this report, the reaction of alkenes carrying electron-withdrawing groups with allyl azide, instead of alkyl or phenyl azide, was studied, and a different pathway was observed. Thus, when methyl acrylate was added to allyl azide dropwisely over 4 hours at 20 °C and kept stirring for 24 hours, a neat reaction was observed and only one adduct resulting from one molecule of allyl azide and two molecules of methyl acrylate was obtained. However, there is no olefinic double bond in this adduct, which indicates that somehow the double bond of the allyl group participated in the reaction. Knowing that triazoline might isomerize to diazoacetate, it is conceivable there are three possible ways that the double bond might be involved in the reaction: (a). 1,1-cycloaddition of diazo group to double bond to give a bicyclo-[5.1.0] compound. [2] (b). 1,3-dipolar cycloaddition of diazo group to double bond to give a bicyclo-[3.2.1] compound .[3] (c). 1,3-dipolar cycloaddition of diazo group to double bond to give a bicyclo-[3.3.0] compound . [4] (Scheme 1)

Scheme 1. Expected products from pathway (a), (b) and (c) .



^{1}H- , ^{13}C- , ^{15}N- nmr and 2-D COSY nmr spectra are consistent with the structure of **6a** . [5] In the presence of acid, **6a** could be isomerized to **7a** ($R_1 = R_2 = H$, $R_3 = CH_2CH_2COOME$, Z = COOMe). In addition, **8** was obtained by pyrolysis of **6a** at 120 ^{0}C.[6] These results also support the assignment of the structure of **6a** . This product suggests that this is a multiple-steps reaction . Firstly, Δ^2-triazoline **1a** (R = CH_2=CH-CH_2) is formed by intermolecular [3+2] cycloaddition of methyl acrylate and allyl azide . Triazoline **1a** is then isomerized to diazoacetate **3a** (R = CH_2=CH-CH_2) which undergoes an intramolecular [3+2] dipolar cycloaddition with the double bond in the allyl group to give the bicyclo [3.3.0] compound **6** ($R_1 = R_2 = R_3$ =H, Z = COOR). Finally , Michael addition of the bicyclo compound to methyl acrylate gives compound **7a** .



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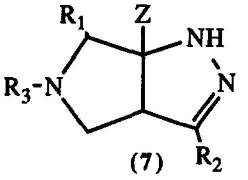

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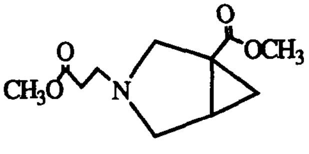

(8)

	R_1	R_2	R_3	Z	Yield %
6a	H	H	CH_2CH_2COOMe	COOMe	84.3
6b	H	H	CH_2CH_2COMe	COMe	76.5
6c	H	H	H	CN	91.0
6d	H	H	$CH_2CH_2CONH_2$	$CONH_2$	65.7
7e	Me	H	H	COOEt	10
6f	H	Me	CH_2CH_2COOMe	COOMe	50.5
7g	H	Ph	H	COOMe	82.0

The isolated yield of **6a** is as high as 84 % , which is equivalent to an average yield of 96 % for each step of this four-step reaction . Similar results were obtained when methyl vinyl ketone , acrylonitrile and acrylamide reacted with allyl azide , **6b** , **6c** and **6d** were obtained in good to high yields . The same reaction pathway was adopted when acrylates with methyl substituent at β-position (R1) and allyl azide with methyl or phenyl substituents (R2) were used in the reaction. Thus this one pot reaction provides a convenient method to prepare

2,3,7-triaza-bicyclo-[3.3.0]-oct-2-ene. Multiple components annulation to form several bonds in one pot is a rapid and efficient means for transforming simple molecules into complex, nonpolymeric compounds.[7,8] And useful compounds have been synthesized by applying this strategy.[9,10] Many reactions, such as, Aldol condensation, Wittig reaction, Michael addition were employed for this purpose. Different from those studied previuosly, in our case, intermolecular and intramolecular dipolar cycloaddition are invoked.

The reaction is sensitive to temperature. For example, only **6c** was obtained when acrylonitrile reacted with allyl azide at 20 °C; however, both **6c** and **7c** ($R_1 = R_2 = R_3 = H$, Z=CN) were produced when the reaction was carried out at 45 °C. A similar phenomenon was observed when the reaction of ethyl crotonate and allyl azide was studied. Therein, in crude product, a compound with ^1H nmr spectrum consistent with structure **6e** ($R_1 = CH_3$, $R_2 = R_3 = H$, Z = COOEt) is observed, however, its tautomer **7e** was obtained as we tried to purify it by column chromatography. In two cases intermediates with nmr spectra consistent to triazoline structures (**1f** : R = $CH_2CH{=}CHCH_3$ and **1g** : R = $CH_2CH{=}CHPh$) could be observed in the crude products, the triazoline intermediates could then be transformed to the corresponding bicyclo-[3.3.0] products(**6f** and **7g**) in appropriate conditions.

The reaction is also very sensitive to the concentration of acrylate in reaction. If the reaction was carried out by directly mixing allyl azide and acrylate, the reaction gave not only bicyclo-[3.3.0] products but also other products; among them was a product from intermolecular 1,3-dipolar cycloaddition product (**4** or **5**). For instance, when the reaction of allyl azide and acrylonitrile was carried out in this way not only **6c**, but also adduct **5f**, was obtained.

Intramolecular 1,3-dipolar cycloadditions were studied and employed for the synthesis of heterocyclic compounds.[11,12,13,14] In our cases, intramolecular 1,3-dipolar cycloaddition of diazoacetate to alkene was also involved. However, different from previous studies, the diazo functional group is prepared in situ by isomerization of triazoline. In the intramolecular 1,3-dipolar cycloaddition step, the double bond involved is unactivated. Unactivated alkene usually does not undergo 1,3-dipolar cycloaddition in intermolecular cases.[15] In our case, only a very mild condition is required. This result is most likely the result of favorable entropy effect from intramolecular reaction. Similar effect was observed in the intramolecular 1,3-dipolar cycloaddition of nitrile ylide with alkenes.[16]

The homologs of allyl azide were then allowed to react with methyl acrylate and acrylonitrile to study the possibility of synthesizing other bicyclo-[n.3.0] compounds by the same pathway. In the cases of 3-butenyl azide and 4-pentenyl azide, no intramolecular [3+2] cycloaddition product was obtained, only products involving intermolecular dipolar cycloaddition (**2b**, **2c**, **5d** and **5e**). Thus, in this case, the intramolecular [3+2] cycloaddition is less competitive to the intermolecular process. There are two possible reasons for the difference. One possibility is that the geometry allows the parallel plane approach of π-orbitals[17] of acrylate and diazo group in the intramolecular process for the case of allyl azide but not for 3-butenyl and 4-pentenyl azide. Another possibility is the favorable entropy effect resulting from 5-membered ring transition state[18] in intramolecular reaction for allyl azide case, no longer applies to the cases of 3-butenyl azide and 4-pentenyl azide, where a much higher entropy change for 6- or 7-membered-ring transition state is expected.

In summary, allyl azide reacts with alkenes carrying Z substituents to give a high yield of 2,3,7-triaza-bicyclo-[3.3.0]-oct-2-ene or its isomer in moderate conditions.

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5. The compounds (**7a, 8a** and **9a**) exhibit satisfactory spectroscopic and/or exact mass data . Physical properties of compounds :

   6a : oil, IR υ_{max}: 1735, 1550 cm^{-1} ; Mass (M^+): 255, 227, 224, 194, 154, 94 ; HRMS: Calcd = 255.1215, Found = 255.1214.^1H-nmr (500 MHz,TMS) δ: 4.75 (dd, 1H J=18.5, 9.0 Hz); 4.45 (dd, 1H J=18.5, 3.5 Hz) ; 3.75 (s, 3H); 3.60 (s, 3H); 3.43 (d,1H J=10Hz); 2.73 (d, 1H J=10 Hz); 2.70-2.64 (m, 2H); 2.66 (t, 2H J=7.5Hz); 2.39 (t, 2H, J=7.5Hz); 2.40- 2.37 (m,1H) ^{15}N-NMR (CH_3NO_2): δ:109.25, 100.24, −333.47 ; ^{13}C-DEPT ($CDCl_3$): δ=172.2, 169.0,104.9, 85.9 (CH_2), 60.0 (CH_2), 58.7 (CH_2), 52.6 (CH_3), 51.3 (CH_3), 49.1 (CH_2), 37.8 (CH), 33.2(CH_2) .

   7a.^1H-nmr (200 MHz,TMS) δ: 6.62 (δ, 1H J=1.2Hz); 6.15 (broad, 1H); 3.80(s, 3H); 3.67(s, 3H); 3.13(d, 1H J=9.6Hz); 3.04(dd, 1H J=9.4 , 2.0 Hz); 2.95-2.55 (m, 3H); 2.80 (t, 2H J=7.0Hz); 2.55 (t, 2H J=7.0 Hz) ; ^{13}C-DEPT ($CDCl_3$): δ=172.9, 172.3, 144.2 (CH), 74.3 (CH_2), 65.1 (CH_2), 57.3 (CH_2), 56.6 (CH) 52.8 (CH_3), 51.5 (CH_3), 49.7 (CH_2), 33.2 (CH_2) .

   8 : Mass : M^+= 227, 196, 168, 154, 138, 81 ; HRMS: Calcd = 227.1153, Found = 227.1164 ;^1H-nmr (200 MHz,TMS) δ: 3.67 (s,3H); 3.66 (s,3H); 3.10 (d,1H J=8.8 Hz); 2.98 (d, 1H J=8.6 Hz); 2.76 (t, 2H J=7.2Hz); 2.69 (d, 1H J=8.8Hz); 2.44 (t, 2H J=7.2Hz); 2.44-2.37 (m,1H); 1.96-1.87 (m, 1H);1.36-1.25 (m, 2H) ; ^{13}C-DEPT ($CDCl_3$): δ: 173.5, 172.6, 53.69(CH_2), 53.66(CH_2),51.5(CH_3),51.4(CH_3), 49.6(CH_2), 33.5(CH_2), 29.0, 27.2(CH), 16.2(CH_2) .
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(Received in Japan 18 February 1993)