An Improved Synthesis of Pyrazolines from Aryl Azides and Acrylic Esters[1]

J. S. Yadav,* B. V. Subba Reddy, V. Geetha

Indian Institute of Chemical Technology, Hyderabad-500 007, India
Fax +91(40)7170512; E-mail: yadav@iict.ap.nic.in

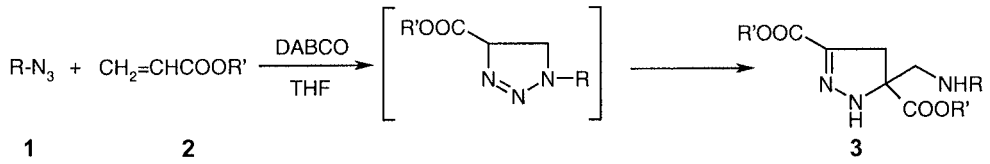
Received 4 January 2002

Abstract: Substituted pyrazoline derivatives are synthesized in high yields through the cycloaddition reactions of azides with acrylates under Baylis–Hillman reaction conditions. Improved yields and enhanced rates are obtained using DABCO as the base.

Key words: azides, Baylis–Hillman reaction, cycloaddition reactions, pyrazolines

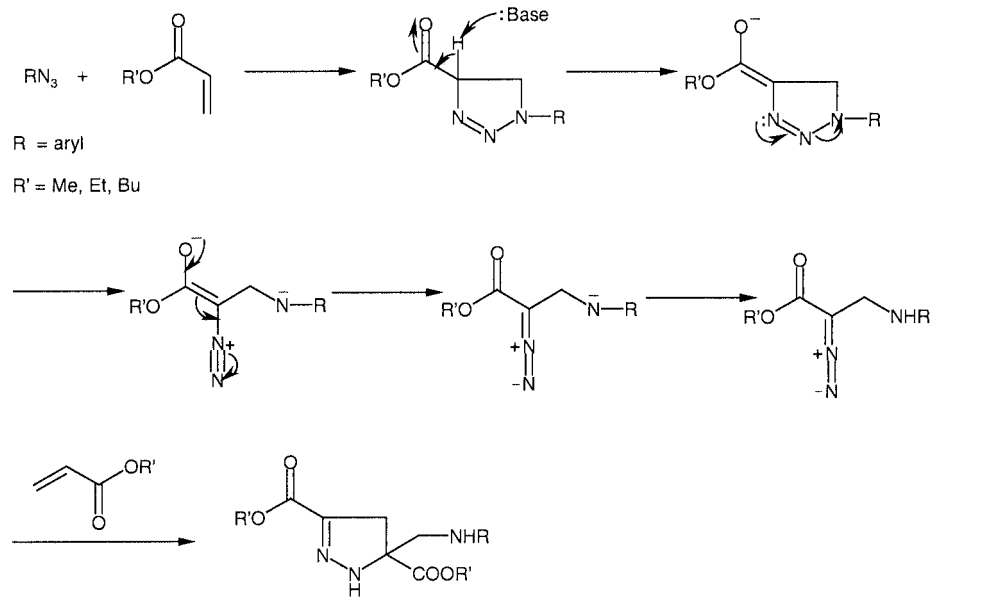
1,2,3-Triazole and 1,2-pyrazole derivatives are known to exhibit a wide range of biological activities such as plant growth regulators,[2] fungicides[3] and herbicides.[4] The most common method for the preparation of 1,2,3-triazoles is the 1,3-dipolar cycloaddition reaction of azides with substituted acetylenes.[5–7] The analogous reaction of azides with electron-deficient olefins leads to the formation of 1,4-disubstituted Δ^2-triazolines. Triazolines with electron withdrawing substituents in the 4-position are known to isomerize to the open-chain diazocompounds which on addition of a second molecule of olefin resulted in the formation of 3,5-disubstituted Δ^2-pyrazolines.[8] However, this isomerisation involves longer reaction times (days to months), low to moderate yields, low regioselectivity and also the formation of a mixture of products[9] comprising of: triazolines, aziridines and enamines along with the desired pyrazolines. Therefore, there is a need to develop a practical and efficient protocol for this transformation.

In this communication, we wish to report a facile synthesis of pyrazolines from azides and acrylates under Baylis–Hillman conditions (Scheme 1).



1 **2** **3**

Scheme 1



Scheme 2

Synlett 2002, No. 3, 04 03 2002. Article Identifier:
1437-2096,E;2002,0,03,0513,0515,ftx,en;D21701ST.pdf.

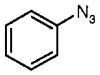
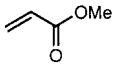
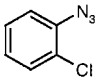
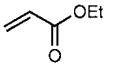
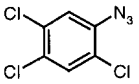
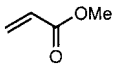
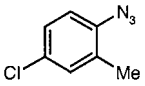
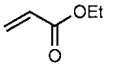
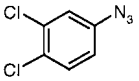
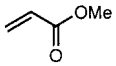
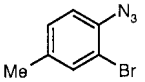
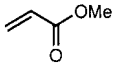
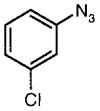
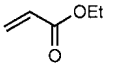
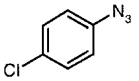
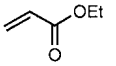
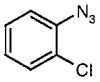
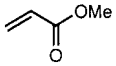
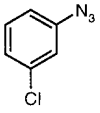
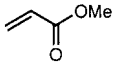
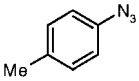
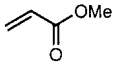
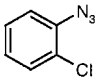
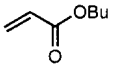
ISSN 0936-5214

The reaction of phenyl azide with methyl acrylate in the presence of 10 mol% DABCO in refluxing THF afforded the corresponding 5-phenyl aminomethyl-3,5-dicarbethoxy-Δ^2-pyrazoline in 87% yield. Similarly, the treatment of several substituted phenyl azides with methyl or ethyl acrylate in the presence of DABCO gave the corresponding pyrazolines in high yields (75–90%). The conversions are clean and complete in short reaction time (3–7 h). The reactions proceeded smoothly in the presence of catalytic amount of DABCO in refluxing THF to give the products in excellent yields. However, at room temperature the conversions required longer reaction times (8–14 h) to obtain comparable yields than those obtained under thermal conditions. Further, the reactions are very slow (3–7 days) at room temperature in the absence of catalyst and gave a mixture containing triazolines, open chain diazo compounds, aziridines and enamines along with the desired pyrazolines. The best results were obtained when THF was used as solvent. The reaction may proceed through the formation of triazole as intermediate that isomerizes to diazoester followed by the cycloaddition of the olefin resulting in the formation of pyrazolines (Scheme 2).

Among various bases like DBU, DBN and Et_3N used for this reaction, DABCO was found to be more effective with respect to yield and reaction rate. Several examples illustrating this novel and efficient protocol for the synthesis of pyrazolines are listed in the Table.

In summary, we have demonstrated an improved protocol for the synthesis of 3,5-disubstituted pyrazolines involving 1,3-dipolar cycloaddition of aryl azides with acrylic esters followed by rearrangement and subsequent cycloaddition using a catalytic amount of DABCO in THF under reflux conditions. Improved yields, enhanced reaction rates, cleaner reaction products, milder reaction conditions, greater regioselectivity, simple experimental and work-up procedures are the main advantages of this procedure over existing ones.

Table One-Pot Synthesis of Pyrazolines from Aryl Azides and Acrylic Esters[a]

Entry	Azide **1**	Acrylate **2**	Reaction time (h)	Yield[b] (%)
a			4.5	87
b			6.0	90
c			7.0	78
d			5.0	89
e			3.5	90
f			6.0	81
g			4.0	87
h			5.5	80
i			6.0	89
j			7.0	86
k			3.0	90
l			5.0	75

[a] All products were characterized by ^{1}H NMR, IR and mass spectra.
[b] Isolated and unoptimized yields.

General procedure for the synthesis of pyrazolines:
A mixture of azide (5 mmol) ethyl or methyl acrylate (15 mmol) and DABCO (10 mol% w/w of azide) in THF (15 mL) was stirred under reflux for an appropriate time (Table). After completion of the reaction as indicated by TLC, the reaction mixture was diluted with water (10 mL) and extracted with ethyl acetate (2 × 15 mL). The combined organic layers were dried (Na_2SO_4), concentrated in vacuo and purified by column chromatography on silica gel (Merck, 100–200 mesh, ethyl acetate–hexane, 2:8) to afford the pure 3,5-disubstituted pyrazoline.

Spectral data of compounds: **3b**: Viscous liquid, ^{1}H NMR ($CDCl_3$) δ: 1.50 (t, 3 H, *J* = 6.8 Hz), 1.80 (t, 3 H, *J* = 7.0 Hz), 3.10 (d, 1 H, *J* = 16.8 Hz), 3.45 (d, 1 H, *J* = 16.8 Hz), 3.60 (d, 2 H, 2.2 Hz), 4.20 (q, 2 H, *J* = 7.0 Hz), 4.30 (q, 2 H, *J* = 7.0 Hz), 4.65 (br s, NH), 6.70 (t, 1 H, *J* = 7.5 Hz), 6.75 (d, 1 H, *J* = 7.5 Hz), 7.10 (t, 1 H, *J* = 7.5 Hz), 7.30 (t, 1 H, *J* = 7.5 Hz). ^{13}C NMR ($CDCl_3$ proton decoupled) δ: 13.7, 13.9, 37.4, 48.6, 61.1, 62.3, 73.0, 111.5, 118.0, 119.4, 127.9, 129.0, 143.0, 152.6, 161.5, 173.3. FABMS: 353 (M^+), 308, 227, 167, 153, 140, 119, 109, 95, 81, 69. **3c**: Viscous liquid, ^{1}H NMR ($CDCl_3$) δ: 3.10 (d, 1 H, *J* = 16.7 Hz), 3.40 (d, 1 H, *J* = 16.7 Hz), 3.60 (d, 2 H, *J* = 2.2 Hz), 3.75 (s, 3 H), 3.80 (s, 3 H), 4.65 (br s, NH), 6.75 (s, 1 H, *J* = 7.3 Hz), 7.0 (br s, NH), 7.30 (s, 1 H, *J* = 7.3 Hz). ^{13}C NMR ($CDCl_3$ proton decoupled) δ: 171.3, 162.8, 152.3, 142.9, 129.1, 127.8, 122.7, 120.3, 112.4, 73.2, 53.2, 52.2, 49.0, 38.8. FABMS: 395, 363, 208, 186, 153, 139, 101, 67, 59. **3e**: Viscous liquid, ^{1}H NMR ($CDCl_3$) δ: 3.10 (d, 1 H, *J* = 16.7 Hz), 3.45 (d, 1 H, *J* = 16.7 Hz), 3.65 (d, 2 H, *J* = 2.2 Hz), 3.80 (s, 3 H), 3.85 (s, 3 H), 4.70 (br s, NH), 7.10 (t, 1 H, *J* = 7.3 Hz), 7.30 (d, 1 H, *J* = 7.3 Hz). ^{13}C NMR ($CDCl_3$ proton decoupled) δ: 172.4, 161.6, 152.0, 142.7, 128.9, 127.5, 122.5, 120.1, 112.1, 73.0, 53.0, 51.3, 48.8, 38.6 FABMS: 338 (M^+), 326, 154, 140, 133, 121, 109, 95, 81, 69. **3f**: Viscous liquid ^{1}H NMR ($CDCl_3$) δ: 2.25 (s, 3 H), 3.10 (d, 1 H, *J* = 16.8 Hz), 3.40 (d, 1 H, *J* = 16.8 Hz), 3.50 (d, 2 H, *J* = 2.3 Hz), 3.80 (s, 3 H), 3.85 (s, 3 H), 6.55 (d, 2 H, *J* = 7.5 Hz), 6.90 (br s, NH), 7.0 (d, 1 H, *J* = 7.5 Hz). ^{13}C NMR ($CDCl_3$ proton decoupled) δ: 173.5,

162.0, 151.8, 143.1, 132.6, 128.4, 127.8, 119.4, 111.0, 73.3, 53.5, 52.8, 49.7, 38.5, 20.8. **3j**: Viscous liquid, ^{1}H NMR ($CDCl_3$) δ: 3.10 (d, 1 H, *J* = 16.7 Hz), 3.35 (d, 1 H, *J* = 16.7 Hz), 3.45 (d, 2 H, *J* = 2.2 Hz), 3.70 (s, 3 H), 3.75 (s, 3 H), 4.10 (br s, NH), 3.45 (d, 2 H, *J* = 7.3 Hz), 6.55 (d, 1 H, *J* = 7.3 Hz), 6.60 (d, 1 H, *J* = 7.3 Hz), 7.0 (t, 1 H, *J* = 7.3 Hz). ^{13}C NMR ($CDCl_3$ proton decoupled) δ: 172.8, 161.7, 152.5, 142.9, 130.2, 129.0, 127.8, 120.5, 112.2, 73.1, 53.3, 52.5, 49.4, 38.7. FABMS: 261, 153, 127, 121, 66, 43. **3l**: Viscous liquid, ^{1}H NMR ($CDCl_3$) δ: 0.9 (t, 3 H, *J* = 6.8 Hz), 0.95 (t, 3 H, *J* = 6.8 Hz), 1.30–1.45 (m, 4 H), 1.60–1.75 (m, 4 H), 3.05 (d, 1 H, *J* = 16.5 Hz), 3.45 (d, 1 H, *J* = 16.5 Hz), 3.60 (d, 2 H, *J* = 2.3 Hz), 4.15 (q, 2 H, *J* = 6.8 Hz), 4.25 (q, 2 H, *J* = 6.8 Hz), 4.65 (br s, NH), 6.70 (t, 1 H, *J* = 7.4 Hz), 6.80 (t, 1 H, *J* = 7.4 Hz), 6.90 (br s, NH), 7.10 (t, 1 H, *J* = 7.4 Hz), 7.25 (d, 1 H, *J* = 7.4 Hz). ^{13}C NMR ($CDCl_3$ proton decoupled) δ: 13.1, 13.2, 18.6, 18.7, 29.9, 30.1, 38.3, 48.4, 64.7, 65.8, 72.9, 111.3, 117.8, 119.3, 127.3, 128.8, 142.2, 152.9, 161.5, 172.1.

Acknowledgement

BVS and VG thank CSIR, New Delhi for the award of fellowships.

References

(1) IICT Communication No. 4826.
(2) Holmwood, G.; Buechel, K. H.; Reinecke, P.; Brandes, W.; Haenssler, G. German patent 3510411, **1986**; *Chem. Abstr.* **1987**, 106, 14714e.
(3) Inke, S. A. Spanish patent 548092, **1986**; *Chem. Abstr.* **1987**, 106, 67321f.
(4) Luethy, C.; Zurflueh, R. European patent 202321, **1987**; *Chem. Abstr.* **1987**, 106, 138455r.
(5) (a) Patai, S. *The Chemistry of the Azide Group*; Interscience publishers: New York, **1971**, 331–383. (b) Gilchrist, T. L.; Gymer, G. E.; Katritzky, A. R.; Boulton, J. A. *Adv. Heterocycl. Chem.* **1974**, *16*, 33. (c) Borello, E.; Zecchina, A.; Gulielminotti, E. *J. Chem. Soc. B* **1969**, 307.
(6) Finely, K. T. In *The Chemistry of Heterocyclic Compounds*; Weissberger, A.; Talor, E. C., Eds.; John Wiley and Sons: New York NY, **1980**, 1–63.
(7) Abu-Orabi, S. T.; Atfah, M. A.; Jibril, I.; Mari, F. M.; A-Sheikh Ali, A. *J. Heterocycl. Chem.* **1989**, *26*, 1461.
(8) Huisgen, R.; Szeimies, G.; Mobius, L. *Chem. Ber.* **1966**, *99*, 475.
(9) Broeckx, W.; OverBergh, N.; Samyn, C.; Smets, G.; Labbe, G. *Tetrahedron* **1971**, *27*, 3534.