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A novel pyridine-based three-component condensation reaction: synthesis of highly substituted quinolizines

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Abstract

Reaction of the zwitterions generated from pyridine or pyridine derivatives and dialkyl acetylenedicarboxylate with electron-deficient tetracyanoethylene lead to highly substituted quinolizines without using any catalyst or activation.

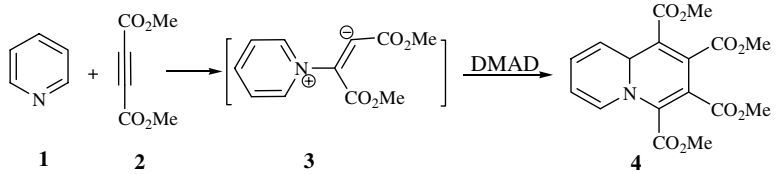
Keywords: Pyridine; Tetracyanoethylene; Zwitterions; Quinolizines

A large variety of nitrogen heterocycles are known to form zwitterionic species on addition of activated olefins or acetylenes. Pyridine deserves special mention owing to the variety of transformations that it mediates. The earliest work in the area was reported by Diels and Alder, and their study[1] and subsequently the structure elucidation of Acheson[2] showed that pyridine **1** reacts smoothly with dimethyl acetylenedicarboxylate (DMAD) **2** to form 4*H*-quinolizine **4** (Scheme 1).

Intermolecular trapping of the 1,4-dipole **3** with carbon dioxide,[3] hexachloroacetone,[4] phenyl isocyanide,[5] isocyanates,[6] benzoyl cyanide,[7] electrophilic styrenes[8] and various strong C–H acids[9] are also noteworthy. However, only an isolated example of the addition of a 1,4-zwitterionic intermediate to carbonyl groups has been described.[10]

Recently, Nair[11] and Shi[12] envisaged the possibility of intermolecular trapping of the 1,4-zwitterionic intermediate generated from pyridine and DMAD with arylaldehydes, N-sulfonated imines, *N*-tosyl imines and various arylmethylidene malononitriles. They found that the 1,4-zwitterionic intermediate, generated from pyridine **1** and DMAD **2**, adds to the C=X bond in **5** in a formal [2+2] manner (Scheme 2). On the other hand, they did not observe the expected multi-component reaction (MCR) product, instead the reaction afforded product **6** with pyridine playing the role of mediator for the formation of the carbon–carbon bond between C=X and DMAD.

Tetracyanoethylene (TCNE) is the simplest of the percyanoalkenes (cyanocarbons). Due to the presence of four strongly electron-withdrawing cyano groups the



Scheme 1.

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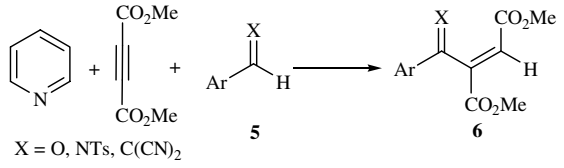


Scheme 2.

C=C double bond is highly electron-deficient and it is a strongly electrophilic reagent. TCNE undergoes two principal types of reaction, namely, addition to its double bond and replacement of the cyano group. TCNE has received extensive study and the chemistry of this compound has been reviewed several times.[13–15] However, a literature survey revealed that the reaction of pyridine and dialkyl acetylenedicarboxylate in the presence of TCNE has not been investigated.

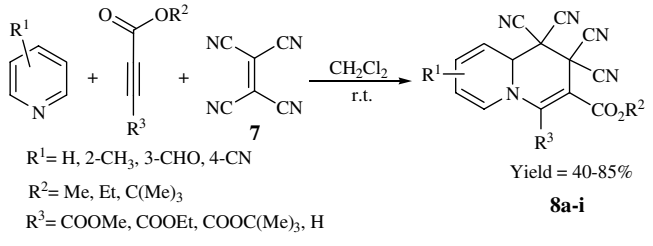
As a part of our current studies on MCRs involving zwitterionic species[16] and our interest in the chemistry of TCNE,[17] we have investigated trapping of the 1,4-dipole generated from the reaction of pyridine and dialkyl acetylenedicarboxylate with TCNE **7**.

We found that the three-component reaction of pyridine **1** and dialkyl acetylenedicarboxylate **2** in the presence of TCNE **7** occurred smoothly via a 1:1:1 addition reaction to produce fully substituted quinolizines **8** in relatively good yields in dichloromethane at room temperature (Scheme 3).

The structures of the products were deduced from their IR, ^{1}H NMR and ^{13}C NMR spectra. The ^{1}H NMR spectrum of **8a** consisted of a multiplet for the two methyl groups at $\delta = 1.40$–1.46 ppm and two quartets for the two OCH_2 groups of the carboxylate at $\delta = 4.41$ and 4.48 ppm. The ^{1}H decoupled ^{13}C NMR spectrum of **8a** showed 19 distinct resonances in agreement with the structure. The ^{1}H and ^{13}C NMR spectra of **8b–i** were similar to those of **8a** except for the R^1, R^2 and R^3 groups, which exhibited characteristic signals with appropriate chemical shifts. The mass spectra of these compounds displayed molecular ion peaks at the appropriate m/z values.

Finally, the structure of **8a** was confirmed unambiguously by single crystal X-ray analysis (Fig. 1).[18,19]

Although the mechanism of the reaction between the pyridine and dialkyl acetylenecarboxylate in the presence of tetracyanoethylene has not yet been established experimentally, a possible explanation is proposed in Scheme 4.



Scheme 3.

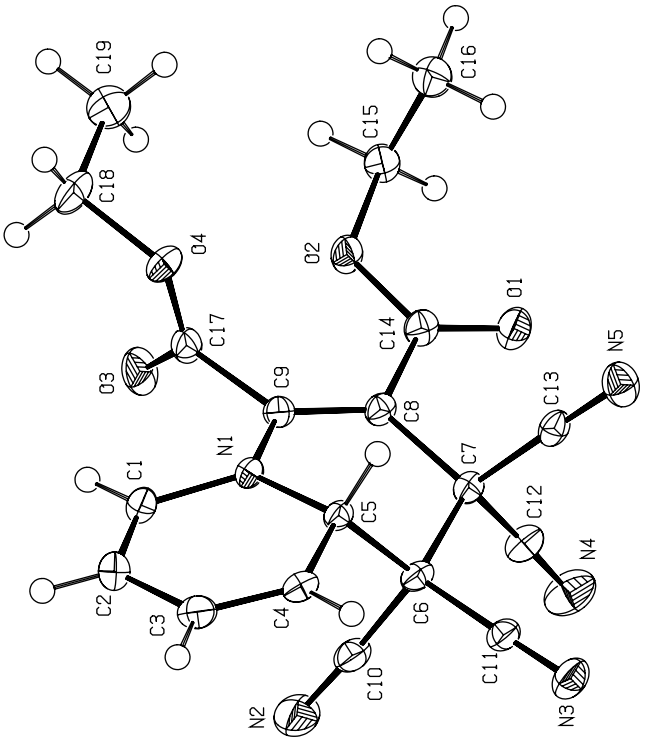
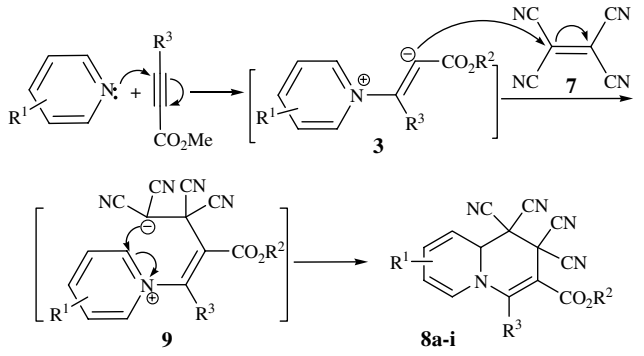


Fig. 1. ORTEP representation of **8a**.



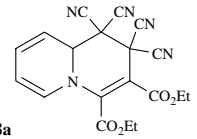
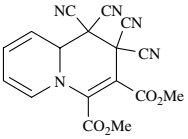
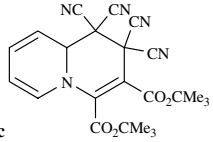
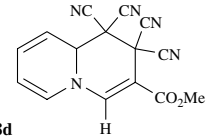
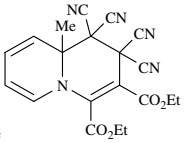
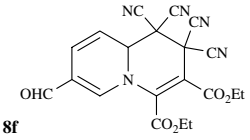
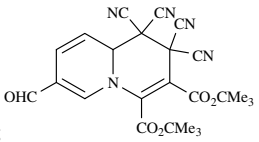
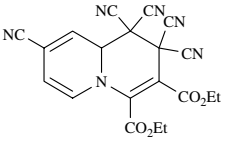
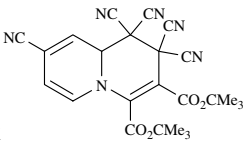
Scheme 4.

On the basis of the well established chemistry of pyridine,[10–12] it is reasonable to assume that zwitterionic intermediate **3** can add to the electrophilic C=C double bond of TCNE **7** resulting in the formation of **9**, which undergoes intramolecular cyclization to deliver quinolizine **8**.

To explore the scope and limitations of this reaction, we extended our studies to various dialkyl acetylenedicarboxylates in the presence of pyridine or pyridine derivatives. As indicated in Table 1, the reactions proceeded efficiently with both electron-withdrawing and electron-releasing pyridine derivatives; however, the reaction yields were increased considerably with electron-withdrawing pyridine derivatives without a catalyst at room temperature.

The low yields of **8a–e** can be explained by the greater nucleophilicity of pyridine and 2-methylpyridine relative to 4-cyanopyridine and 3-pyridinecarbaldehyde. As indicated in Scheme 4, products **8** are formed by initial attack of

Table 1
Synthesis of fully substituted quinolizines **8a**–**8i**

Entry	R^1	R^2	R^3	Product	Yield (%)/time
1	H	Et	CO_2Et	 **8a**	66/40 min
2	H	Me	CO_2Me	 **8b**	48, 70[a]/30 min
3	H	$C(Me)_3$	$CO_2C(Me)_3$	 **8c**	62/1 h
4	H	Me	H	 **8d**	40, 62[a]/70 min
5	2-Me	Et	CO_2Et	 **8e**	42, 65[a]/50 min
6	3-CHO	Et	CO_2Et	 **8f**	85/6 h
7	3-CHO	$C(Me)_3$	$CO_2C(Me)_3$	 **8g**	80/6 h
8	4-CN	Et	CO_2Et	 **8h**	72/6 h
9	4-CN	$C(Me)_3$	$CO_2C(Me)_3$	 **8i**	70/6 h

[a] Reaction yields with excess acetylenic ester (3 mmol).

pyridine or the pyridine derivative on the acetylenic esters. In contrast to 4-cyanopyridine and 3-pyridinecarbaldehyde, which attack selectively on the acetylenic esters, pyridine and 2-methylpyridine not only attack on the acetylenic ester but also react with TCNE leading to a by-product and a decrease in the desired product yield. The reactions of

pyridine and 2-methylpyridine were complete in very short times. To confirm the above suggestion, we carried out the reaction of pyridine (1 mmol) or 2-methylpyridine (1 mmol) and TCNE (1 mmol) with an excess amount of the acetylenic ester (3 mmol). The results showed that the reaction yields were considerably increased (Table 1, entries 2, 4 and 5).

In conclusion, we have reported an efficient, convergent and straightforward approach to novel highly substituted bicyclic pyridines containing a nitrogen ring-junction without using any catalyst. These compounds have been the subject of many studies from theoretical points of view, for the preparation of potentially biological analogues and for some industrial uses.[20]

Typical procedure for the preparation of 3,3,4,4-tetracyano-2H-quinolizine-1,2-diethyldicarboxylate (**8a**): To a magnetically stirred solution of tetracyanoethylene (0.128 g, 1.0 mmol) and diethylacetylenedicarboxylate (0.170 g, 1.0 mmol) in CH_2Cl_2 (15 mL) was added, dropwise, a mixture of pyridine (0.080 g, 1 mmol) in CH_2Cl_2 (2 mL) at −10 °C over 5 min. The mixture was allowed to warm to room temperature and was stirred for 6 h. After completion of the reaction, the solvent was removed under vacuum and the residue was crystallized from a CH_2Cl_2/*n*-hexane mixture 1:2 to yield **8a** as a cream solid (66%). Mp 136–138 °C. IR (KBr) (ν_{max}, cm^{-1}): 2209, 1750. ^1H NMR (300 MHz, $CDCl_3$): $\delta_H = 1.40–1.46$ (m, 6H, $2CH_3$), 4.41 (q, 2H, $^3J_{HH} = 6.90$ Hz, OCH_2), 4.48 (q, 2H, $^3J_{HH} = 7.00$ Hz, OCH_2), 5.24 (s, 1H, CH), 5.41 (t, 1H, $^3J_{HH} = 6.75$ Hz), 5.88 (d, 1H, $^3J_{HH} = 9.97$ Hz), 6.23 (d, 1H, $^3J_{HH} = 7.68$ Hz), 6.44 (t, 1H, $^3J_{HH} = 8.00$ Hz). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta_C = 13.74$, 13.89, 39.88, 44.52, 59.88, 63.27, 64.30, 92.92, 104.98, 107.48 (CN), 108.01 (CN), 109.83 (CN), 110.27 (CN), 112.76, 125.93, 127.74, 147.59, 160.60, 160.70. MS (EI, 70 eV), *m*/*z*, (%): 377 (M^+, 25), 304 (30), 205 (20), 176 (50), 133 (30), 105 (90), 79 (100).

Acknowledgement

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Supplementary data

Experimental procedures, mass, IR, ^1H NMR and ^{13}C NMR spectra for compounds **8a**–**i**. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.01.006.

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18. Crystal data analyses: Stoe IPDSII two-circle diffractometer, $Mo_{K\alpha}$ radiation ($\lambda = 0.71073$); $T = 120(2)$ K; graphite monochromator; numerical absorption correction. Structure solution by direct methods using SHELXS and refinement by full-matrix least-squares on F^2 using SHELXL of the X-STEP32 suite of programs;[19] all non-hydrogen atoms were refined anisotropically. Crystal data for **8a**: $C_{19}H_{15}N_5O_4$, $M = 377.36$ g mol^{-1}; crystal dimensions $0.27 \times 0.08 \times 0.05$ mm^3; monoclinic, space group $P2_1/n$; $a = 17.823(4)$, $b = 6.5534(13)$, $c = 17.823(4)$ Å, $\beta = 118.89(3)°$, $V = 1822.8$ (6) Å^3; $Z = 4$; $F(000) = 645$, $\rho_{calc} = 1.375$ g cm^{-3}; $2.61° < \theta < 27.94°$; section of the reciprocal lattice: $-23 \leqslant h \leqslant 23$, $-6 \leqslant k \leqslant 8$, $-18 \leqslant l \leqslant 23$; of 7384 measured reflections, 7384 were independent and 3868 with $I > 2\sigma(I)$; absorption coefficient 0.100 mm^{-1}; $R_1 = 0.0627$ for $I > 2\sigma(I)$ and $wR_2 = 0.1606$ (all data); largest peak (0.861 e Å^{-3}) and hole (−0.386 e Å^{-3}). (CCDC No. 649437).
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