Solvent-free Promoted One-pot Synthesis of 
H-quinolizine, pyrido[1,2-a]isoquinoline 
and pyrido[2,1-a] quinoline Derivatives

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Abstract
This work describes a fast, mild, convenient and simple method for preparing of nitrogen 
heterocyclic derivatives by MCR reaction under solvent-free condition.

Keywords: Solvent free reaction, Multi-component reactions, Acetylenic esters, H-quinolizine, 

Introduction
Quinolizines are of considerable interest due to their widespread occurrence in natural 
products, particularly in the field of alkaloids [1]. The importance of these nitrogen 
heterocyclic derivatives to the pharmaceutical industry has spurred a great amount of 
research, and numerous methods have been devised for their construction [2]. Although 
many routes to the basic ring systems are known, new general synthetic approaches are 
still highly desirable [2].
The possibility of performing chemical reactions in the absence of solvent has been 
receiving more attention now-a-days [3-8]. The examples reported [8,9], demonstrate 
that solvent-free reactions are generally faster giving higher selectivities and excellent 
yields. 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 [10] and subsequently the structure elucidation of Acheson [11-13].

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showed that pyridine reacts smoothly with dimethyl acetylenedicarboxylate (DMAD) to form indolizine-\(1\),\(4\),\(7\)-tricarboxylate and \(H\)-quinolizine in methanol as a solvent (Scheme 1) [\(^{11}\)].

![Scheme](image)

However, the above method suffers from drawbacks such as longer reaction time, the need for an unfriendly solvent, and moderate yield. Recently H. Valizadeh and et.al. have reported an addition reaction of Nitrogen-containing heterocyclic compounds with DMAD under neat condition \(^{22}\). Following, as part of our ongoing research program on the development of new protocols in heterocyclic synthesis \(^{32-62}\), herein, we applied this methodology to describe the synthesis of \(H\)-pyrido[1,2-a]isoquinoline, \(4\)-H-quinolizine, and \(aH\)-pyrido[1,2-a] quinoline derived from the reaction between diethyl acetylenedicarboxylate, di-\textit{tert}-butyl acetylenedicarboxylate and isoquinoline, pyridine, and quinoline under the same reaction conditions.

**Experimental**

**General**

Chemicals were purchased from Fluka and used without further purification. Melting points were measured on an Electrothermal \(\text{apparatus}\) apparatus. Elemental analyses for C, H, and N were performed using a Heraeus CHN-O-Rapid analyzer, and the results agreed favorably with the calculated values. Mass spectra were recorded on a Finnigan MAT \(\text{spectrometer}\) operating at an ionization potential of \(70\) eV. IR spectra were measured on a Shimadzu IR-\(\text{spectrometer}\), \(^1\)H and \(^{13}\)C NMR spectra were measured on a Bruker Avance DRX-\(\text{spectrometer}\) using CDCl\(_3\) as applied solvent and TMS as internal standard at \(\text{MHz}\) and \(\text{MHz}\), respectively.

**General procedure for the preparation of compound**

In a typical reaction, a mixture of isoquinoline (\(\text{g}\), \(\text{mmol}\)) and dimethyl acetylenedicarboxylate (\(\text{ml}\), \(\text{mmol}\)) under solvent free condition was stirred for \(\text{hour}\). The progress of reaction was...
monitored by TLC. The resulting precipitate was separated by filtration and recrystallized from diethyl ether (Et₂O) to afford the pure compounds.

**Tetraethyl H-pyrido[1,2,3-c]isoquinoline-tetracarboxylate (a)**

Yellow powder; yield: \*8.42 g (93.2%), mp 139-140°C. IR (KBr) (\(\nu_{\text{max}}/\text{cm}^{-1}\)):

\[
\begin{align*}
\text{H}\text{-NMR (}^{1}H\text{ MHz, CDCl}_3\text{): } & \delta = 1.44, 1.48, 1.52, 1.55, \text{ and } 1.58, \text{ (C-O), } 1.61, 1.47\text{ (C-C).} \\
\text{NMR (}^{1}H \text{ MHz, CDCl}_3\text{): } & \delta = 1.44, 1.48, 1.52, 1.55, \text{ and } 1.58, \text{ (C-O), } 1.61, 1.47\text{ (C-C).} \\
\text{C-C-Me}_2\text{ (C) } & \text{ by TLC.}
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\text{NMR (}^{1}H \text{ MHz, CDCl}_3\text{): } & \delta = 1.44, 1.48, 1.52, 1.55, \text{ and } 1.58, \text{ (C-O), } 1.61, 1.47\text{ (C-C).} \\
\text{C-C-Me}_2\text{ (C) } & \text{ by TLC.}
\end{align*}
\]

Yellow powder; yield: \*8.42 g (93.2%), mp 139-140°C. IR (KBr) (\(\nu_{\text{max}}/\text{cm}^{-1}\)):
**Tetra-tert-butyl H-pyrido[1,2-a]isoquinoline-tetracarboxylate (b)**

Yellow powder; yield: 94.4 g (80%), mp 170°C.

C 94.96 (C), 112.5 (CH), 122.8 (CH), 136.3 (C), 52.4, 56.7 (CH), 103.1 (CH), 197.3 (C), 198.3 (C), 204.5 (C).

IR (KBr) (ν max/cm⁻¹): 1735, 1711, and 1705.

Anal. Caled (C, H, N, O): C, 79.4; H, 7.9%; N, 7.1%.

For C, H, N, O (C, H, N, O): C, 78.4; H, 7.9%; N, 7.1%.

**H-NMR (57 MHz, CDCl₃):** δ = 4.31, 8.31, 0.41, and 1.41 (4 CH₃), 7.05, 7.1, 7.1, 7.2, and 7.2 (4 OCH₃), 6.9, 6.9 (s, CH), 7.3, 7.3 (dt, J = 7.6 Hz, J = 3.1 Hz, CH), 8.32 (s, C), 12.5, 12.5, 14.0, 14.0, and 14.1 (4 CH₃), 153.9, 153.9, 153.9, 153.9, 153.9 (C), 153.9, 153.9, 153.9, 153.9, 153.9 (C), 153.9, 153.9, 153.9, 153.9, 153.9 (C).

**C-H, J = 1.7 Hz, CH (5102))**

**H-NMR (57 MHz, CDCl₃):** δ = 4.31, 8.31, 0.41, and 1.41 (4 CH₃), 7.05, 7.1, 7.1, 7.2, and 7.2 (4 OCH₃), 6.9, 6.9 (s, CH), 7.3, 7.3 (dt, J = 7.6 Hz, J = 3.1 Hz, CH), 8.32 (s, C), 12.5, 12.5, 14.0, 14.0, and 14.1 (4 CH₃), 153.9, 153.9, 153.9, 153.9, 153.9 (C), 153.9, 153.9, 153.9, 153.9, 153.9 (C), 153.9, 153.9, 153.9, 153.9, 153.9 (C).

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Tetra-tert-butyl H-quinolizine- 
tetracarboxylate (b)

Yellow powder; yield: 1.01 g (93.8\%), mp 190-192°C.

IR (KBr) (\nu_{max} /cm\(^{-1}\)): 1743, 1712, and 1765 (C=O), 1360-1466 (C=C). \(^1H\)-NMR (DCl)\(^3\): \(\delta = 1.45, 1.41, 1.37\) and 1.30

\(\delta_{m}H, 6.8\) s, 1.7 CH\(_2\), 5.68 (1H, s, CH), 7.29, 3.6

\(\nu_{m}V, \gamma, \gamma, \gamma, \gamma\) (\(1H\), dt, \(J = 7.5\) Hz, 1.7 Hz, CH),

\(\nu_{m}V, \gamma, \gamma, \gamma, \gamma\) (\(1H\), m, CH), 8.58-8.54 (1H, dd,

\(\nu_{m}J = 9.1\) Hz, \(J = 1.7\) Hz, CH). \(^{13}C\)-NMR (\(\nu_{0}\)

MHz, DCl)\(^3\): \(\delta = 87.7, 77.9, 78.4\) and 78.3

(\(\xi\) CH), 97.8, 72.2, and 72.0 (\(\xi\) O-CHMe).

C=O). Anal.Calcd for C\(_7\)H\(_8\)NO\(_2\) (91.9, 5.2): C, 70.92; \(\nu, \gamma, \gamma\); N, 3.93; H,

\(\nu, \gamma, \gamma, \gamma\) (\(\xi\) O-CHMe).

Tetraethyl aH-pyridof \-a]quinolone- 
tetracarboxylate (b)

Yellow powder; yield: 1.04 g (93.7\%), mp 180-182°C.

IR (KBr) (\nu_{max} /cm\(^{-1}\)): 1741, 1744, and 1650 (C=O), 1360-1466 (C=C). \(^1H\)-NMR (DCl)\(^3\): \(\delta = 1.45, 1.41, 1.37\) and 1.30

\(\delta_{m}H, 6.8\) s, 1.7 CH\(_2\), 5.68 (1H, s, CH), 7.29, 3.6

\(\nu_{m}V, \gamma, \gamma, \gamma, \gamma\) (\(1H\), dt, \(J = 7.5\) Hz, 1.7 Hz, CH),

\(\nu_{m}V, \gamma, \gamma, \gamma, \gamma\) (\(1H\), m, CH), 8.58-8.54 (1H, dd,

\(\nu_{m}J = 9.1\) Hz, \(J = 1.7\) Hz, CH). \(^{13}C\)-NMR (\(\nu_{0}\)

MHz, DCl)\(^3\): \(\delta = 87.7, 77.9, 78.4\) and 78.3

(\(\xi\) CH), 97.8, 72.2, and 72.0 (\(\xi\) O-CHMe).

C=O). Anal.Calcd for C\(_7\)H\(_8\)NO\(_2\) (91.9, 5.2): C, 70.92; \(\nu, \gamma, \gamma\); N, 3.93; H,

\(\nu, \gamma, \gamma, \gamma\) (\(\xi\) O-CHMe).

Tetraethyl aH-pyridof \-a]quinolone- 
tetracarboxylate (a)

Yellow powder; yield: 1.04 g (93.7\%), mp 180-182°C.
$\delta={39.0, 71.1, 22.1, 53.1}\text{ (t, }^{\text{H}}, J=1.7\text{ Hz, CH$_3$), }\delta={04.1, 34.1, 5.1, 55.1}\text{ (s, CMe), }\delta={03.1}\text{ (CH), }\delta={19.0, 79.2}\text{ (CH), }\delta={121.9\text{ (C), }177.3\text{ (C), }130.4\text{ (CH), }162.1\text{ (C), }162.1\text{ (CH), }138.4\text{ (C), }131.9\text{ (C), }127.3\text{,}$
$^{12}$, $^{13}$, $^{14}$, and $^{15}$ (C=O). Anal. Calcd for

**C**$_2$**H**$_{12}$**NO**$_2$: C, 78.6; H, 5.7; N, 15.7.

Found: C, 78.1; H, 5.9; N, 15.6.

### Results and Discussion

The reaction of isoquinoline (I) and dialkyl acetylenedicarboxylate (II) in the absence of solvent at ambient temperature produces $^4$H-pyrido[γ,γ-a]isoquinoline (III) in an excellent yield (Scheme 2).

The reaction of isoquinoline (I) and dialkyl acetylenedicarboxylates (II) in the absence of solvent at ambient temperature produces functionalized $^1$H-pyrido[γ,γ-a]isoquinoline (III) in an excellent yield.

Isoquinoline undergoes a smooth reaction with dialkyl acetylenedicarboxylates (II) in the absence of solvent at ambient temperature to produce functionalized $^1$H-pyrido[γ,γ-a]isoquinoline (a-b) in an excellent yield.

The reaction was completed within an hour (monitored by TLC). The $^1$H and $^{13}$C NMR spectra of the crude products clearly indicated the formation of (III). The structures of compounds a-b were deduced from their elemental analyses and their IR, $^1$H and $^{13}$C NMR spectra. The mass spectra of these compounds displayed molecular ion peaks at the appropriate m/z values.

Although the mechanistic details of the reaction are not clearly known, a plausible rationalization may be advanced to explain the product formation. Presumably, the zwitterions [γ,γ] formed from isoquinoline and dialkyl acetylenedicarboxylate, adds to second acetylenic compound to furnish intermediate (IV). This intermediate undergoes cyclization and then $^1$-H-shift to furnish the fused structure (Scheme 3).

![Scheme 2](image-url)

![Scheme 3](image-url)
Scheme 3.

Reaction of pyridin and quinoline with dialkyl \( \text{CO}_2R \) + \( \text{CO}_2R \) \( \Rightarrow \) \( \text{CO}_2R \) + \( \text{CO}_2R \) under above conditions produce \( \text{H-quinolizine} \) and...


[23] I. Yavari, F. Nasiri, H. Djahaniani, Mol


