# Novel Synthesis of Indolizines

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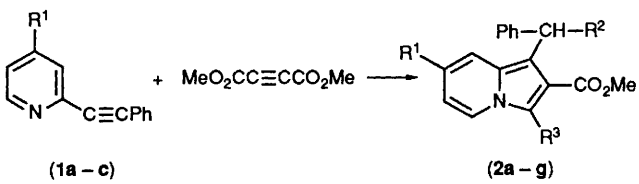
2-Phenylethnylpyridine reacted with dimethyl acetylenedicarboxylate (DMAD) in the presence of a proton source such as an alcohol to give indolizines having methoxycarbonyl groups at the 2- or 2,3-positions in high yields.

We previously reported the direct ethynylation of pyridines by the Reissert–Henze type reaction.[1] In order to use pyridines having an ethynyl group in the synthesis of bicyclic pyridines, we studied the reaction of acetylenylpyridines with dimethyl acetylenedicarboxylate (DMAD). Acheson and Bridson had tried this reaction, but they obtained only unidentified materials.[2] In contrast, we have now found that this reaction gave indolizine derivatives.

A benzene solution (10 ml) of 2-phenylethynylpyridine (**1a**) (1 mmol), MeOH (20 mmol), and DMAD (2 mmol) was stirred at room temperature for one day. The mixture was concentrated and chromatographed ($SiO_2$; hexane–AcOEt, 95 : 5) to give 1-(α-methoxybenzyl)-2-methoxycarbonylindolizine (**2a**) as a pale-yellow oil in 85% yield.

The structure of (**2a**) was determined from spectral and analytical data.† Measurement of $^1H$–$^1H$ 2D NMR nuclear Overhauser enhancements (NOEs) supported the structure; the correlations observed are shown in Figure 1. Since it is known that quinolizine derivatives may be obtained from pyridine and DMAD,[3] the quinolizine (**3**) is an alternative structure for the product. However, this possibility was easily excluded by observation of a doublet $sp^3$ carbon signal at δ 74.3 in the $^{13}C$ NMR spectrum.

Other dipolarophiles such as methyl acetylenemonocarboxylate, dimethyl maleate, and *N*-phenylmaleimide were not reactive under similar conditions. The present method was also applicable to substituted acetylenylpyridines. The acetylenylpyridines (**1b**) and (**1c**) gave the corresponding indolizine derivatives (**2e**) and (**2f**) in moderate yields.




(**1a – c**) (**2a – g**)

**Scheme 1.** *Conditions*: Additive, benzene, room temp., 1 day.

In the absence of an alcohol, the reaction of the pyridine (**1a**) with DMAD in benzene or tetrahydrofuran (THF) became more complicated. Thus, several alcohols were studied as a proton source, which seems to be essential for this reaction. With EtOH and $Pr^iOH$, the reaction proceeded similarly and formed the corresponding products (**2b**) and (**2c**), respectively. In the case of $Bu^tOH$, demethoxycarbonylation at the 3-position did not occur and (**2d**) was isolated. When MeOD was used instead of MeOH, the product (**4**) deuteriated at the benzyl position and the 3-position of the indolizine skeleton was obtained in 98% yield, showing that these two protons come from the alcohol. It is noteworthy that the reaction in the presence of dimethyl malonate instead of an alcohol resulted in carbon–carbon bond formation at the benzyl position and gave the indolizine (**2g**).

On heating the 2,3-bis(methoxycarbonyl) derivative (**2d**) in MeOH, substitution at the benzyl position occurred to give the analogue (**2h**). Generation of $MeO^-$ in the reaction of phenanthridine and DMAD in MeOH has been reported,[4] but further treatment of (**2h**) with MeONa (2 equiv.) caused no

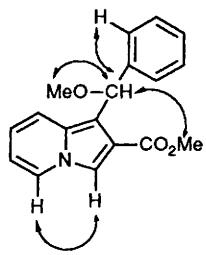


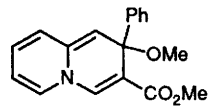

**Figure 1.** NOE correlations in (**2a**).

† All indolizine derivatives gave satisfactory spectral and analytical data.

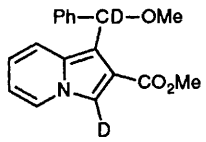
**Table 1.** Preparation of the indolizines (**2**) (Scheme 1).

| Pyridine | | | Indolizine | | | |
|---|---|---|---|---|---|---|
| | $R^1$ | Additive | | $R^2$ | $R^3$ | Yield (%)[a] |
| (**1a**) | H | MeOH | (**2a**) | MeO | H | 98 |
| | H | EtOH | (**2b**) | EtO | H | 80 |
| | H | $Pr^iOH$ | (**2c**) | $Pr^iO$ | H | 34 |
| | H | $Bu^tOH$ | (**2d**) | $Bu^tO$ | $CO_2Me$ | 77 |
| (**1b**) | Me | MeOH | (**2e**) | MeO | H | 64 |
| (**1c**) | Ac | MeOH | (**2f**) | MeO | H | 75 |
| (**1a**) | H | $(MeOCO)_2CH_2$ | (**2g**) | $(MeOCO)_2CH$ | $CO_2Me$ | 63 |

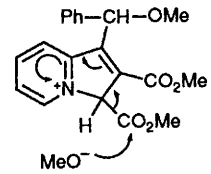
[a] By $^1H$ NMR spectroscopy; isolated yields were 5—15% lower than NMR yields in all cases.



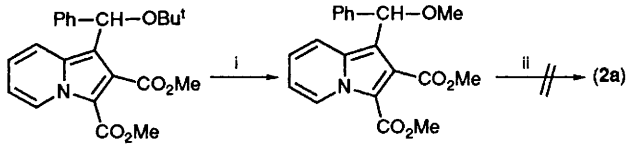

(**3**)




(**4**)




(**5**)




(**2d**) (**2h**)

**Scheme 2.** *Reagents and conditions*: i, MeOH, reflux, 5 h, 100%; ii, MeONa (2 equiv.), MeOH, reflux, 1 h.

change, such as demethoxycarbonylation at the 3-position leading to (**2a**) (Scheme 2). Thus, we assume that the intermediate (**5**) is a precursor of the demethoxycarbonylated indolizine (**2a**). Elimination of the methoxycarbonyl group was caused by attack of the counter anion of (**5**), $MeO^-$, on the methoxycarbonyl group, as shown by arrows on the structure. This mechanism is consistent with the detection of dimethyl carbonate. In the case of the sterically hindered alcohol, $Bu^tOH$, deprotonation at the 3-position seems to become predominant. The detailed reaction path is under investigation.

There are few preparative methods for indolizine derivatives[5] from acetylenylpyridines,[6] and the present reaction provides a useful synthetic route.

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