NITROOLEFINS. I. A NEW AND CONVENIENT ACCESS TO INDOLIZINES AND PYRAZOLO[1,5-a]PYRIDINES USING 1-NITRO-2-(PHENYLTHIO)ETHYLENE

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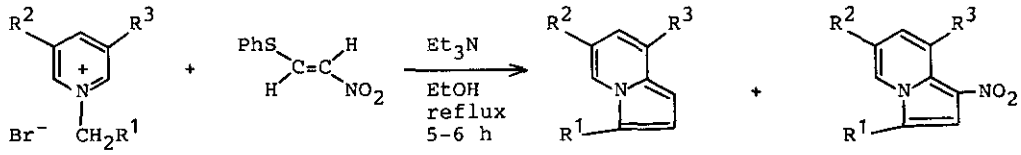
Abstract——1-Nitro-2-(phenylthio)ethylene (1) reacts with a variety of N-ylides and N-imines (pyridinium, isoquinolinium, quinolinium, phthalazinium N-ylides and N-imines) in the presence of triethylamine to give the corresponding fused pyrrole and pyrazole derivatives (indolizines, pyrrolo[2,1-a]isoquinoline, pyrrolo[2,1-a]phthalazine, pyrazolo[1,5-a]-pyridine, pyrazolo[5,1-a]quinoline, and pyrazolo[5,1-a]iso-quinoline) along with the corresponding 1-nitropyrrolopyri-dines and 1-nitropyrazolopyridines, respectively, in moderate yields.

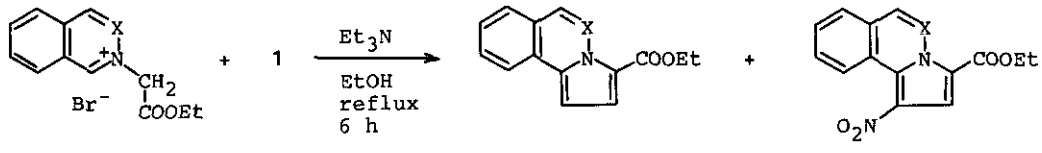
Nitroolefins are useful reagents not only for the synthesis of heterocycles but also for various synthetic transformations.[1-4] The presence of electron-donating groups on the vicinal olefinic carbon atom has made this nitroolefin moiety especially reactive and attractive for the synthesis of a wide variety of nitrogen- and sulfur-containing heterocyclic compounds. Among these polarized nitroolefins, ketene dithioacetals,[5] ethoxymethylene compounds,[6,7] and aminomethylene compounds[8,9] are widely used. Recently, 1-nitro-2-(phenylthio)ethylene (**1**)[3] was prepared conveniently by the reaction of acetoxynitroethane with thiophenol followed by treatment with sulfuryl chloride and triethylamine. To our knowledge, **1**, known as a precursor to sulfinyl or sulfonynitroethylenes, has been allowed to react only with pyrrole to give 1-nitro-2-pyrrolylethylene,[3] although the electrophilic reagent **1** may be a potential building block for the synthesis of heterocyclic compounds. Indeed we report herein that **1** is an efficient and unprecedented reagent for the synthesis of indolizine and pyrazolopyridine derivatives.

The reaction of 1-ethoxycarbonylmethylpyridinium bromide (**2a**) with **1** in the presence of triethylamine in ethanol gave the desired ethyl indolizine-3-carboxylate (**3a**) in 56.5% yield, along with ethyl 1-nitroindolizine-3-carboxylate (**4a**) in 38.8% yield. Similarly 1-ethoxycarbonylmethyl-3,5-dimethylpyridinium bromide (**2b**) reacted with **1** to give ethyl 6,8-dimethylindolizine-3-carboxylate (**3b**) in 55.8% yield. 3-Cyanoindolizine derivatives (**3c, d**)[10] were also obtained from the corresponding 1-cyanomethylpyridinium bromides (**2c, d**). 1-Nitro-6,8-dimethylindolizines (**4b, d**) could not be almost detected in the reaction mixture in the cases of **2b** and **2d**, although similar results were found in the reaction of 3,5-dimethylpyridinium N-ylides with nitroketene dithioacetal.[11] Furthermore reactions of **1** with **2e** and **2f** under the similar conditions of the synthesis of indolizines gave the corresponding cyclized products, ethyl pyrrolo[2,1-a]isoquinoline-3-carboxylate (**5a**), ethyl pyrrolo[2,1-a]phthalazine-3-carboxylate (**5b**), together with ethyl 1-nitro-substituted derivatives, **6a** and **6b**, respectively, in yields as indicated in Scheme 1.



2a-d **1** **3a-d** **4a-d**

entry	2:	R^1	R^2	R^3	3 mp(°C)	3 Yield(%)	4 mp(°C)	4 Yield(%)
1	**a:**	COOEt	H	H	oil	56.5	139	38.8
2	**b:**	COOEt	Me	Me	48	55.8	---	trace
3	**c:**	CN	H	H	48	73.3	231	17.6
4	**d:**	CN	Me	Me	108	54.7	---	----

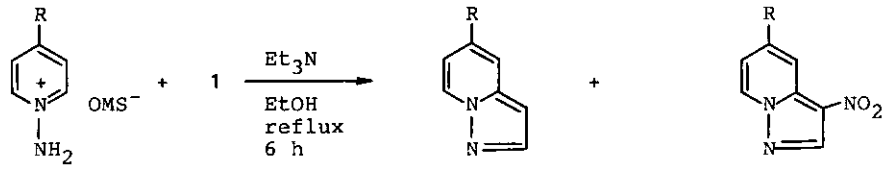


2e,f **5a,b** **6a,b**

entry	2:	X	5 mp(°C)	5 Yield(%)	6 mp(°C)	6 Yield(%)
1	**e:**	CH	94	51.0	167	34.9
2	**f:**	N	115	35.0	212	7.0

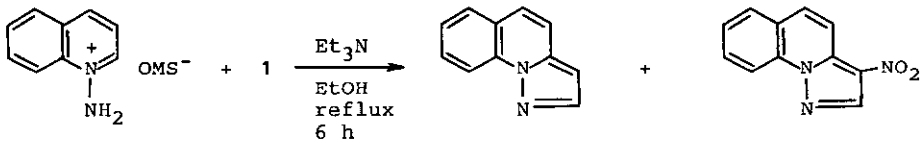
Scheme 1

This method using **1** can be readily applied to the synthesis of pyrazolo[5,1-a]pyridines. Thus we attempted to synthesize pyrazolopyridine derivatives which were known as very important and interesting intermediates for the synthesis of pharmacologically active compounds and dyes.[12] The reaction of 1-aminopyridinium mesitylenesulfonates (**9a, b**) with **1** in the presence of triethylamine gave the desired pyrazolo[5,1-a]pyridines (**10a**,[13] **b**[14]) and 1-nitropyrazolo[5,1-a]-pyridine derivatives (**11a**,[14] **b**) in yields as shown in Scheme 2. Pyrazolo[5,1-a]quinolines (**12**,[15] **13**) and pyrazolo[5,1-a]isoquinolines (**14, 15**) were also prepared from **9c** and **9d** in a manner similar to that described for the synthesis of pyrazolo[5,1-a]pyridines (**10, 11**).



9a,b **10a,b** **11a,b**

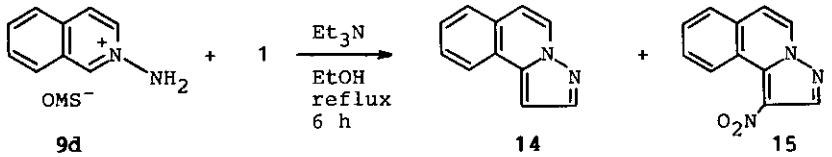
entry	9: R	10 mp(°C)	10 Yield(%)	11 mp(°C)	11 Yield(%)
1	**a**: H	oil	12.7	182	48.5
2	**b**: Me	oil	11.4	158	40.7



9c **12** **13**

oil
Yield 14.3%

mp 228°C
Yield 58.2%



9d **14** **15**

mp 62°C,
Yield 9.5%

mp 153°C
Yield 62.0%

Scheme 2

In conclusion, it has been proved that 2-nitro-1-(phenylthio)ethylene (1) is a very useful electrophilic reagent for the synthesis of indolizine and pyrazolopyridine derivatives. Related works are now under active progress.

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REFERENCES AND NOTES

1. S. Rajappa and M. D. Nair, Adv. Heterocyclic Chem., 1979, 25, 113.
2. a) Miyashita, T. Yanami, and A. Yoshikoshi, J. Am. Chem. Soc., 1976, **98**, 4879 ; b) M. Ochiai, M. Arimoto, and E. Fujita, Tetrahedron Lett., 1981, **22**, 1165.
3. N. Ono, A. Kamimura, and A. Kaji, J. Org. Chem., 1986, 51, 2139 and references therein.
4. M. Node, Yakugaku Zasshi, 1986, **106**, 1.
5. Y. Tominaga and Y. Matsuda, J. Heterocyclic Chem., 1985, **22**, 937.
6. O. S. Wolbeis, Synthesis, 1977, 136.
7. E. D. Cuesta and C. Avendano, J. Heterocyclic Chem., 1985, **22**, 337.
8. T. Severin, B. Bruck, and P. Adhikary, Chem. Ber., 1966, **99**, 3097.
9. D. Pocar, S. Mariorana, and P. Dalla Croce, Gazz. Chim. Ital., 1968, **98**, 949.
10. K. Matsumoto, T. Uchida, Y. Ikemi, T. Tanaka, M. Asahi, T. Kato, and H. Konishi, Bull. Chem. Soc. Jpn, 1987, **69**, 3645.
11. Y. Tominaga, Y. Shiroshita, T. Kurokawa, H. Gotou, Y. Matsuda, and A. Hosomi, J. Heterocyclic Chem., in press.
12. J. V. Greenhill, "Pyrazoles with Fused Six-membered Heterocyclic Rings" in Comprehensive Heterocyclic Chemistry" in Vol. 8, ed. by A. R. Katrizky and C. W. Rees, Pergamon Press, Oxford, 1984, p. 305.
13. V. Boekelheide and N. A. Federuk, J. Org. Chem., 1968, **33**, 2062.
14. B. M. Lynch and B. P. -L. Lem, J. Heterocyclic Chem., 1974, 11, 223.
15. R. Huisgen, R. Grashey, and R. Krischke, Justus Liebigs Ann. Chem., 1977, 506.
16. Satisfactory elemental analysis and spectral data were obtained for all new compounds.
17. Similar reaction mechanism for the formation of indolizines and 1-nitroindolizines is shown in Refer. **3**, **5**, and **11** and the following paper: Y. Tominaga, et. al., Yakugaku Zasshi, 1984, **104**, 440.

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