Cycloaddition Reactions of *N*-*p*-Toluenesulfonylimino Derivatives of Quinoline and Isoquinoline. A Route to Pyrazolo[1,5-*a*]quinolines and Pyrazolo[5,1-*a*]isoquinolines

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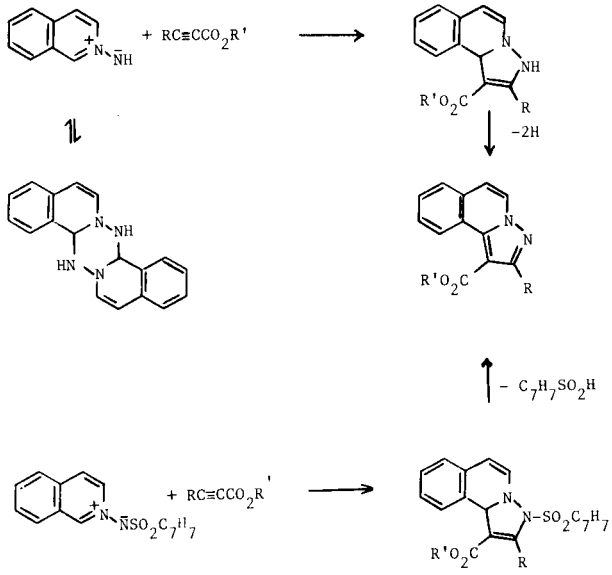
Received November 23, 1981

N-*p*-Toluenesulfonylimino ylides of quinoline and isoquinoline give cycloadducts with electrophilic acetylenes at 105°. The adducts are spontaneously aromatized under the conditions of their formation by elimination of *p*-toluenesulfinic acid to give pyrazolo[1,5-*a*]quinolines and pyrazolo[5,1-*a*]isoquinolines, respectively. The orientation of cycloaddition is the same as for *N*-amino ylides for acetylenic esters. The adducts from *p*-nitrophenylacetylene are formed by addition of the imino nitrogen to the unsubstituted acetylenic carbon. The orientation and unreactivity of phenylacetylene indicate that the cycloaddition is controlled by dipole HOMO-dipolarophile LUMO interactions.

J. Heterocyclic Chem., **19**, 573 (1982).

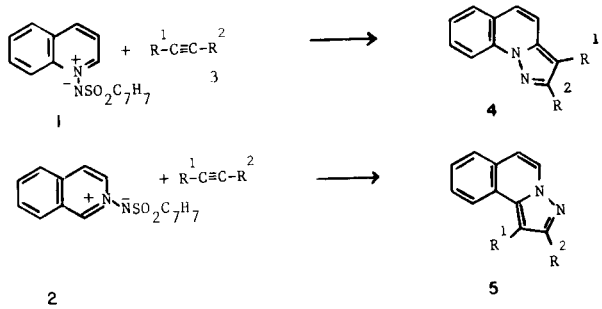
The cycloaddition reactions of the imino-derivatives of pyridine are well known (1). Although not as thoroughly studied, there are also examples of similar reactivity on the part of the *N*-imines of quinoline and isoquinoline (2,3,4). Upon considering the potential of this reaction for the preparation of some representative pyrazolo[1,5-*a*]-quinolines and pyrazolo[5,1-*a*]isoquinolines, we encountered the reports of Huisgen, Grashey and Krischke (3) and of Tamura, Mitei and Ikeda (4) in this area. Although Huisgen and coworkers reported fair yields of cycloaddition for *N*-iminoquinoline and *N*-iminoisoquinoline, the more detailed report of Tamura indicated only modest yields of around 10-15% for dimethyl acetylenedicarboxylate and about 30% for methyl propiolate. After brief study of the reaction, as described by Tamura, confirmed his experience, we felt it would be necessary to modify the system to achieve our particular synthetic objectives. Two properties of the system seemed likely to be contributing to the low yields. First, the imines themselves are unstable towards dimerization so that the cycloaddition must compete with the reversible dimerization for the reactive imine (5). Secondly, after the cycloaddition there must be a net oxidation to provide the desired aromatic system. Although the dihydro adducts have been observed in some cases (3), the usual conditions evidently involve a spontaneous aromatization, presumably mediated by oxygen or possibly by a disproportionation. It seemed that both of these problems might be alleviated by the use of an arenesulfonyl derivative of the *N*-imines. Such imine derivatives are stable in the monomeric form and the potential for elimination of the sulfonyl substituent as a sulfinic acid gave promise of a non-oxidative aromatization. Remaining at issue, however, was the level of reactivity of the *N*-sulfonylimines as 1,3-dipoles since no such reactions have been reported. In this paper we describe the reactivity of the *p*-toluenesulfonylimino derivatives of quinoline and isoquinoline toward some acetylenic dipolarophiles, and the determination of the structure of the cycloadducts.



Although other methods have been reported for the synthesis of *N*-sulfonylamino derivatives of quinoline and isoquinoline (6), the amination of the parent heterocycle, followed by sulfonylation, which has been routinely applied to pyridine (7), was chosen as the most direct route. Amination was carried out following the procedure of Tamura (8). Reaction of the *N*-amino mesitylenesulfonates with *p*-toluenesulfonyl chloride in methylene chloride in the presence of potassium carbonate gave the *N*-*p*-toluenesulfonyliminoquinolinium ylide (**1**, 80%) and *N*-*p*-toluenesulfonyliminoisoquinolinium ylide (**2**, 60%).

Each of these ylides was heated with the series of acetylenes **3a-f**. The reactions were usually carried out in toluene at 105° for 18 hours. Except for phenylacetylene,

which was unreactive with both ylides, cycloadducts having the composition expected for cycloaddition followed by aromatization by elimination of *p*-toluenesulfinic acid were isolated. The yields are given in Table I.



1

2

	R^1	R^2
a	CO_2CH_3	CO_2CH_3
b	CO_2CH_3	H
c	CO_2CH_3	CH_3
d	$CO_2C_2H_5$	phenyl
e	*p*-nitrophenyl	H
f	H	phenyl

Table I

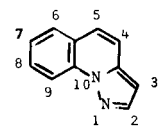
Yields of Cycloadducts from **1** and **2** (a)

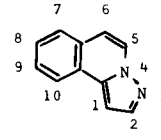
Acetylene	**4**	**5**
3a	54	46
3b	52	43
3c	45	40
3d	36	33
3e	33	35
3f	0	0

(a) Reactions carried out are described in the Experimental section except for **3a** in which case the reaction was run in chloroform at 68°.

The reaction had taken the expected course with dimethyl acetylenedicarboxylate, as established by comparison of spectral data and physical constants of adducts **4a** and **5a** with the data reported by Tamura, pertaining to these same compounds prepared from *N*-aminoquinolinium and *N*-aminoisoquinolinium salts. Because of a discrepancy in melting points, the product **4b** from the reaction of methyl propynoate (**3b**) with **1** and the product obtained by Tamura's method (4) were compared directly. We find mp 148-149° for the compound prepared by either of the methods. The yields were significantly higher for the reactions using *N*-tosylimino ylides than for the corresponding *N*-aminoheterocycle in each instance. These reactions represent the first examples of cycloadditions of *N*-sulfonylimino ylides, so far as we are aware.

The reaction was extended to the methyl- and phenyl-substituted esters **3c** and **3d**, with yields of 30-45% being observed. The assumption was made that the regiochemistry of the cycloaddition was parallel to that with methyl propynoate and the structures **4c**, **4d** and **5c**, **5d** were assigned to the respective cycloadducts. The assumption is supported in the case of **4c** and **5c** by the close correspondence between the nmr spectra of **4c** and **5c** with **4b** and **5b**, respectively. Although Huisgen and coworkers (3) reported the cycloaddition reactions of *N*-iminoquinolinium ylide and *N*-iminoisoquinolinium ylide and **3d**, no physical constants or spectral data were available for comparison. To secure the structures, adducts **4d** and **5d** were hydrolytically decarboxylated. Compound **4d** gave 2-phenylpyrazolo[1,5-*a*]quinoline which was identical with an authentic sample prepared by an independent method (9). Similarly **5d** gave a substance **5f** whose spectral properties are in accord with assigning the structure as 2-phenylpyrazolo[1,5-*a*]isoquinoline. Each of the esters **5a-d** showed a characteristic multiplet at very low field 9.5 ±0.3 ppm which is assigned to the C-10 proton which is in close proximity to the ester group. This signal is not present in the decarboxylation product, **5f** formed from **5d**.





The structure of the nitrophenylacetylene adducts **4e** and **5e** were determined by comparison with the decarboxylation products **4f** and **5f**. By the arguments previously presented, the decarboxylation products have the phenyl groups at positions 2 in both the pyrazolo[1,5-*a*]quinoline and pyrazolo[5,1-*a*]isoquinoline rings. If the *p*-nitrophenylacetylene adducts were also 2-aryl derivatives, a close correspondence between the proton nmr spectra would be expected. No such correspondence was found. Whereas **4f** shows a singlet attributable to the 3 proton at 6.80 ppm, there is no corresponding signal in **4e**. The singlet instead appears at 8.28 ppm which is much more consistent with assigning **4e** the structure 3-(*p*-nitrophenyl)pyrazolo[1,5-*a*]-quinoline. Similarly, the singlet for **5e** was at 7.95 ppm but for **5f** there is a singlet at 7.20 ppm. We conclude that the orientation of the cycloaddition for *p*-nitrophenylacetylene is regioselective in the sense that the sulfonylimino group is bound to the unsubstituted acetylene carbon to give **4e** and **5e**, respectively.

This sense of orientation and the unreactivity of phenylacetylene itself indicate the addition reaction is governed by the LUMO of the dipolarophile and the HOMO of the sulfonylimino ylides.

Table II

NMR Data for Cycloadducts and Derivatives (a)

4b	8.58 (d, J = 8 Hz, 1H), 8.40 (s, 1H), 8.05 (d, J = 9 Hz, 1H), 7.8-7.2 (m, 4H), 3.90 (s, 3H)
4c	8.50 (d, J = 9 Hz, 1H), 7.95 (d, J = 9 Hz, 1H), 7.2-7.8 (m, 4H), 3.85 (s, 3H), 3.67 (s)
4d	8.66 (d, J = 8 Hz, 1H), 8.12 (d, J = 9 Hz), 7.2-7.9 (m, 9H), 4.30 (q, 2H), 1.30 (t, 3H)
4e (b)	8.64 (d, J = 8 Hz, 1H), 8.34 (d, J = 9 Hz, 2H), 8.28 (s, 1H), 7.7-7.9 (m, 5H), 7.62 (d, J = 9 Hz, 1H), 7.53 (t, J = 7 Hz, 1H)
4f (b)	8.68 (d = 8 Hz, 1H), 8.06 (d, J = 8 Hz, 2H), 7.75 (d, J = 7 Hz, 1H), 7.68 (t, J = 8 Hz, 1H), 7.35-7.50 (m, 6H), 6.90 (s, 1H)
5b	9.95 (m, 1H), 8.43 (s, 1H), 8.24 (d, J = 7 Hz, 1H), 7.5-7.7 (m, 3H), 7.15 (d, J = 7 Hz, 1H), 3.92 (s, 3H)
5c	9.50 (m, 1H), 8.16 (d, J = 7 Hz, 1H), 7.3-7.7 (m, 3H), 7.05 (d, J = 7 Hz, 1H), 3.90 (s, 3H), 2.55 (s, 3H)
5d	9.25 (m, 1H), 8.25 (d, J = 7 Hz, 1H), 7.0-7.8 (m, 9H), 4.22 (q, 2H), 1.10 (t, 3H)
5e (b)	8.37 (d, J = 7 Hz, 2H), 8.30 (d, J = 7 Hz, 1H), 8.2 (d, J = 7 Hz, 1H), 7.95 (s, 1H), 7.76 (overlapping d, 3H), 7.55 (t, 1H), 7.4 (t, 1H), 7.09 (d, J = 7 Hz, 1H)
5f (b)	8.27 (d, J = 7 Hz, 1H), 8.14 (d, J = 8 Hz, 1H), 8.01 (d, J = 7 Hz, 2H), 7.72 (d, J = 7 Hz, 1H), 7.57 (m, 2H), 7.47 (t, J = 7 Hz, 2H), 7.38 (t, J = 7 Hz, 1H), 7.08 (s, 1H), 7.00 (d, J = 7 Hz, 1H)

(a) In deuteriochloroform spectra were recorded at 90 MHz unless otherwise noted. (b) Spectra recorded at 360 MHz.

EXPERIMENTAL

N-p-Toluenesulfonyliminoquinolinium Ylide **1** and *N-p*-Toluenesulfonyliminoisoquinolinium Ylide **2**.

A solution of the *N*-amino mesitylenesulfonate salt (0.50 g, 1.45 mmoles) of quinoline or isoquinoline (8) was added over 15 minutes to a mixture of *p*-toluenesulfonyl chloride (0.55 g, 2.9 mmoles) and potassium carbonate (0.40 g, 2.9 mmoles) in methylene chloride (5 ml). After stirring overnight, the mixture was shaken with water and the methylene chloride layer separated and further washed with water. After drying and evaporation, the solid residue was recrystallized from ethanol: **1** (80% yield, mp 217-219°, lit (10) 227-228°); **2** (60%; mp 222-223°, lit (6b) 226°).

General Procedure for Cycloadditions.

A solution of **1** or **2** (0.50 g) and an equimolar amount of the acetylene **3** was heated to 105° in toluene for a period of 18 hours. The toluene solution was decanted from an oily precipitate and evaporated to give an oil. The oil was purified by flash chromatography and recrystallized, usually from ethanol. Table III gives mp and analytical data.

2-Phenylpyrazolo[1,5-*a*]quinoline (**4f**) by Hydrolytic Decarboxylation of **4d**.

A solution of **4d** (50 mg) in 5 ml of 57% hydroiodic acid was heated to reflux for 3 hours. The solution was cooled to room temperature, carefully made alkaline with sodium bicarbonate and extracted with ether. The ether extract was dried and evaporated leaving a white solid which was recrystallized from ligroin to give needles, mp 85-86°(35 mg, 90%). This material was identical by direct spectroscopic and chromatographic comparison with an authentic sample prepared as described by Tamura (9).

2-Phenylpyrazolo[5,1-*a*]isoquinoline (**5f**) by Hydrolytic Decarboxylation of **5d**.

A solution of **5d** (100 mg) was refluxed for 3 hours in 57% hydroiodic acid (10 ml) and then diluted with water. The acidic solution was diluted and neutralized and the major product was extracted into chloroform and isolated as a brown solid (65 mg) after drying and evaporating the solvent. A pure sample was obtained by thin layer chromatography on silica gel and recrystallization from ligroin, mp 105° resolidifies and remelts 115-116°.

Acknowledgement.

This research was carried out under the auspices of the Walter Reed Army Institute of Research, Medical Research and Development Command, Contract DAMD 17-78-C-8016. This paper is designated Contribution No. 1635 to the Army Research Program on Antiparasitic Drugs.

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Table III

Analytical Data for Cycloadducts

Compound	Formula	Mp °C	Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
4c	$C_{14}H_{12}N_2O_2$	108-109	70.0	5.0	11.7	69.9	5.1	11.6
4d	$C_{20}H_{16}N_2O_2$	125-128	75.9	5.1	8.9	75.8	5.2	8.8
4e	$C_{17}H_{11}N_3O_2$	256-257	70.6	3.8	14.5	70.5	3.9	14.5
5c	$C_{14}H_{12}N_2O_2$	108-109	70.0	5.0	11.7	69.9	5.1	11.6
5d	$C_{20}H_{16}N_2O_2$	77-78	75.9	5.1	8.9	75.8	5.1	8.8
5e	$C_{17}H_{11}N_3O_2$	171-172	70.6	3.8	14.5	70.4	3.9	14.5
5f	$C_{17}H_{12}N_2$	114-115	83.6	5.0	11.5	83.4	5.0	11.5

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