Michael Reactions of Arylidenesulfonylacetonitriles. A New Route to Polyfunctional Benzo[a]quinolizines

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Abstract: Arylidenesulfonylacetonitriles react in acetonitrile with 1-methylisoquinoline and isoquinolin-1-yl-acetonitrile in the presence of piperidine to give benzo[a]quinolizines 6,9 and 7,10, respectively. The structures of the products were established on the basis of elemental and spectral analyses and their chemical reactivity.

Keywords: Arylidenesulfonylacetonitriles, 1-methylisoquinoline, isoquinolin-1-yl-acetonitrile, benzo[a]quinolizines.

Introduction

High yielding syntheses of polyfunctional benzo[a]quinolizines are well documented [1-9]. As a continuation of our work on the use of isoquinoline and its derivatives for the synthesis of fused heterocyclic compounds [10,11], we now report a new and general one step route affording polyfunctional substituted benzo[a]quinolizines in good yield from readily available inexpensive starting materials, which competes favorably with the methods previously reported for the preparation of the title compounds.
Results and Discussion

Treatment of 1-methylisoquinoline (1) [12] with arylidenesulfonylacetonitriles 3a-c [13] in boiling acetonitrile in the presence of an equimolar amount of piperidine leads, in each case, to the formation of only one product 6a-c, as indicated by TLC and \(^{1}\)H-NMR analyses (Scheme 1).

\[
\text{Scheme 1}
\]

\[\begin{align*}
\text{CH}_3\text{O} & \quad \text{CH}_3 \quad \text{N} \\
\text{CH}_3\text{O} & \quad \text{CH}_3 \\
\text{1} & \quad \text{ArCH}=\text{C} & \quad \text{CN} & \quad \text{acetonitrile/piperidine (1 mol)} & \quad \Delta \\
\text{3a} & \quad \text{Ar} = \text{C}_6\text{H}_5 \\
\text{3b} & \quad \text{Ar} = 4-\text{ClC}_6\text{H}_4 \\
\text{3c} & \quad \text{Ar} = 4-\text{NO}_2\text{C}_6\text{H}_4
\end{align*}\]
The structures of the products 6a-c were established on the basis of their elemental analyses and spectral data (IR, \(^1\)H-NMR, MS). For example, the IR spectrum of compound 6a shows a stretching frequency at 3350 cm\(^{-1}\) (NH) in addition to characteristic bands at 1315 and 1155 cm\(^{-1}\) (asymmetric and symmetric stretching vibrations of a SO\(_2\) group). Its \(^1\)H-NMR spectrum reveals a singlet at \(\delta = 6.9\) assignable to the C-1 proton and a singlet at \(\delta = 8.8\), which disappears upon deuterium exchange, assignable to the NH proton, in addition to the typical signals of the isoquinoline moiety. The formation of 6 may be explained by cyclization of the initially formed Michael addition product 4 to the unisolated product 5. Subsequent autoxidation of the latter leads to the final product 6 (cf. Scheme 1). When the reaction of 1 with 3a-c was carried out in the presence of excess piperidine (2 moles) then the products 7a-c were formed directly. The structures of the products 7 were also inferred from their elemental analyses and spectral data. For example, the IR spectra show a characteristic peak near 3320 cm\(^{-1}\) due to a NH group. The mass spectra of the products also show a molecular ion peak of high intensity, and the \(^1\)H-NMR and chemical reactivity also support the proposed structures of the products. In light of the previous results, it may be suggested that the unisolated products 5 afford the end products 7 via loss of benzenesulfinic acid (Scheme 1). Similarly, isoquinolin-1-yl-acetonitrile (2) \([14]\) reacts with 3a,b to give 9a,b (cf. Scheme 2). The structures of the latter products were confirmed by elemental analysis and spectroscopic data. Upon treatment of p-nitrobenzylidene phenylsulfonylacetonitrile 3c in this fashion a product 10c was formed directly due to elimination of benzenesulfinic acid from the intermediate 8 (Scheme 2). The structure of the product 10c was confirmed by its independent synthesis via reaction of 2 with 11 (Scheme 3).
The structures of 10b,c were also confirmed by their chemical reactions as described in Scheme 4. For example, acylation of 10b,c with acetic anhydride or benzoylation with benzoyl chloride in pyridine affords the corresponding N-acetylimino or N-benzoylimino compounds 12b,c and 13b,c, respectively. Nitrosation of 10c with sodium nitrite in acetic acid gives the corresponding N-nitroso compound 14c. Thermolysis of 14c in xylene gives the carbonyl compound 15c. The structure of 15c was confirmed by its alternative synthesis by hydrolysis of 10c with dilute hydrochloric acid. Also, hydrolysis of 10b with dilute hydrochloric acid leads to the formation of 15b. Their elemental analyses and spectral data (cf. Table 1 and 2) confirmed the structures of 12, 13, 14 and 15.
Experimental

General

All melting points were determined on an Electrothermal melting point apparatus and are uncorrected. IR spectra were recorded (KBr discs) on a Shimadzu FT-IR 8201 PC spectrophotometer. $^1$H NMR spectra were recorded in CDCl$_3$ and (CD$_3$)$_2$SO solutions on a Varian Gemini 200 MHz spectrometer and chemical shifts are expressed in $\delta$ units using TMS as internal reference. Mass spectra were recorded on a Shimadzu GCMS-QP1000 EX mass spectrometer, operating at 70 eV. Elemental analyses were carried out at the Microanalytical Center of the University of Cairo, Giza, Egypt. The analytical and spectral data of the compounds prepared is summarized in Tables 1 and 2.

Synthesis of 2-aryl-6,7-dihydro-9,10-dimethoxy-4-imino-2-phenylsulphonyl-benzo[a]quinolizines 6 and 9.

Piperidine (0.5 mL, 0.005 mol) was added at room temperature to a solution of arylidene-sulfonylacetonitriles 3 (0.005 mol) and 1-methylisoquinoline (1) (1.02 g, 0.005 mol) or isoquinolin-1-yl-acetonitrile (2) (1.15 g, 0.005 mol) in acetonitrile (40 mL). The reaction mixture was refluxed for 8 h. The solvent was evaporated under reduced pressure and the residue was triturated with methanol (10 mL) whereupon it solidified. The crude product was collected and crystallized from DMF.

Synthesis of 2-aryl-6,7-dihydro-9,10-dimethoxy-4-iminobenzo[a]-quinolizines 7 and 10

These compounds were prepared by the same procedure described for the synthesis of compounds 6 and 9 using (1mL, 0.01 mol) of piperidine. The precipitated compounds were crystallized from DMF.

Nitrosation of 10c.

Cold sodium nitrite solution (0.7 g in 10 mL water) was added dropwise to a stirred solution of 10c (2.01 g, 0.005 mol) in acetic acid (30 mL). The mixture was left in an ice bath for 4 h., then the reddish solid that precipitated was collected. Crystallization of the crude product from DMF gave the corresponding N-nitroso derivative 14c.

Thermolysis of 14c.

The N-nitroso compound 14c (2.16 g, 0.005 mol) was refluxed in xylene (20 mL) until its red color disappeared (ca. 20 min). The reaction mixture was then cooled, the crude product was collected, washed with water and crystallized from DMF.
Acylations of 10b,c.

A solution of 10b,c (0.005 mol) in acetic anhydride (25 mL) was refluxed for 1 h. The solvent was removed under reduced pressure and the residue was triturated with water. The solid formed was collected, washed with water and crystallized from ethanol to give N-acetylimino derivatives 12b,c.

Treatment of 10b,c (0.005 mol) with benzoyl chloride (0.58 mL, 0.005 mol) in pyridine (30 mL) at reflux for 30 min. and workup of the reaction mixture in usual way gave the corresponding N-benzoylimino derivatives 13b,c.

Hydrolysis of 10b,c.

A suspension of 10b,c (2.01g, 0.005 mol) in 10% hydrochloric acid (20 mL) was refluxed for 30 min. The reaction mixture was cooled and the solid that precipitated out was collected and crystallized from DMF to give 15b,c.

Table 1. Analytical data of the synthesized compounds

| Compd. no. | Color       | Yield % | m.p. °C | Solvent | Mol. formula | % Analysis | Calcd. (Found) |
|------------|-------------|---------|---------|---------|--------------|------------|----------------|
| 6a         | yellow      | 80      | 225-226 | DMF     | C27H24N2O4S | 68.64      | (68.72) (5.02) |
| 6b         | dark yellow | 82      | 264-266 | DMF     | C27H21N2O4SCl | 63.96      | 4.54 (5.53)   |
| 6c         | orange      | 78      | 276-277 | DMF     | C27H21N4O4S | 62.67      | 4.45 (8.12)   |
| 9a         | dark yellow | 84      | 258-259 | DMF     | C28H23N3O4S | 67.61      | 4.63 (8.45)   |
| 9b         | bright brown| 77      | 320-322 | DMF     | C28H23N3O4SCl | 63.22      | 4.14 (7.90)   |
| 7a         | yellow      | 81      | 329-331 | DMF     | C21H20N2O2  | 75.90      | 6.02 (8.43)   |
| 7b         | yellow      | 85      | 206-207 | DMF     | C21H15N2O4Cl | 68.76      | 5.18 (7.64)   |
| 7c         | yellow      | 88      | 214-215 | DMF     | C21H19N4O4  | 66.84      | 5.04 (11.14)  |
| 10a        | dark yellow | 86      | 214-216 | DMF     | C22H10N3O2  | 73.95      | 5.32 (11.76)  |
| 10b        | bright brown| 79      | 223-224 | DMF     | C22H18N3O4Cl | 67.43      | 4.60 (10.73)  |
| Compd. no. | IR (cm\(^{-1}\)) | \(^{1}H\) NMR (\(\delta\) ppm) | M' |
|-----------|-----------------|---------------------------------|----|
| 6a        | 3350 (NH)       | 2.6 (m, 2H); 3.8 (s, 3H); 3.9 (s, 3H); 4.1 (m, 2H); 6.9 (s, 1H); 7.0-7.7 (m, 10H); 7.8 (s, 1H); 7.9 (s, 1H); 8.8 (s, 1H) | 472 |
| 6b        | 3380 (NH)       | 3.0 (m, 2H); 3.8 (s, 6H); 4.1 (m, 2H); 7.0 (s, 1H); 7.2-7.6 (m, 10H); 7.9 (s, 2H). | 507 |
| 6c        | 3446 (NH)       | 3.1 (m, 2H); 3.8 (s, 6H); 4.1 (m, 2H); 6.9 (s, 1H); 7.1-8.5 (m, 12H). | 517 |
| 9a        | 2216 (CN), 3417 (NH) | 3.0 (m, 2H); 3.8 (s, 6H); 4.1 (m, 2H); 6.9 (s, 1H); 7.0-7.6 (m, 11H); 7.7 (s, 1H) | 497 |
| 9b        | 2219 (CN), 3415 (NH) | 2.8 (m, 2H); 3.8 (s, 3H); 3.9 (s, 3H); 4.1 (m, 2H); 7.2 (s, 1H); 7.3-7.7 (m, 10H); 7.9 (s, 1H) | 532 |
| 7a        | 3386 (NH)       | 2.9 (m, 2H); 3.3 (s, 3H); 3.4 (s, 3H); 3.8 (m, 2H); 6.7 (s, 1H); 6.8 (s, 1H); 6.9 (s, 1H); 7.1 (s, 1H) | 432 |
| 7b        | 3252 (NH)       | 2.9 (m, 2H); 3.8 (s, 3H); 3.9 (s, 3H); 4.1 (m, 2H); 6.3 (s, 1H); 6.4 (s, 1H); 6.7 (s, 1H); 7.1-7.7 (m, 6H) | 367 |
| 7c        | 3323 (NH)       | 2.9 (m, 2H); 3.8 (s, 3H); 3.9 (s, 3H); 4.2 (m, 2H); 6.4 (s, 1H); 6.5 (s, 1H); 6.7 (s, 1H); 6.9 (s, 1H); 7.1-7.6 (m, 5H) | 377 |
| 10a       | 2221 (CN), 3316 (NH) | 2.9 (m, 2H); 3.8 (s, 3H); 3.9 (s, 3H); 4.0 (m, 2H); 6.3 (s, 1H); 6.4 (s, 1H); 6.7 (s, 1H); 7.2-7.6 (m, 5H) | 357 |
| Compound | 13C-NMR | References |
|----------|---------|------------|
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| 12b      | 1656(CO), 2217 (CN) | 5. Kametani, T.; Surgenor, S.; Fukumoto, K. Heterocycles 1980, 14, 303. |
|          | 2.8 (m, 2H); 3.7 (s, 3H); 3.9 (s, 6H); 4.0 (m, 2H); 6.7 (s, 1H); 7.3-8.2 (m, 11H) | 6. Meredith, R.F.K.; Ritcher, A.C.; Walker, T.; Whiting, K.D.E. J. Chem. Soc. 1963, 2672. |
| 12c      | 1658(CO), 2210(CN) | 7. Kappe, T.; Linnau, Y. Monatshfte Chem. 1963, 100, 1726. |
|          | 2.0 (s, 3H); 2.9 (m, 2H); 3.9 (s, 6H); 4.0 (m, 2H); 6.5 (s, 1H); 6.8 (s, 1H); 7.4-7.6 (m, 4H); 7.9 (s, 1H) | 8. Akiba, K.; Nakatani, M.; Wada, M.; Yamamoto, Y. J. Org. Chem. 1985, 50, 63. |
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|          | 3.0 (m, 2H); 3.9 (s, 6H); 4.6 (m, 2H); 6.8 (s, 1H); 7.3 (s, 1H); 7.4-8.2 (m, 10H) | |
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