This method appears to be a general, one-pot method for synthesis of 4-aminoquinazolines in high yields and is much less time consuming than previous methods.

Experimental Section

Melting points are uncorrected. Infrared spectra were recorded using a Perkin-Elmer Model 137 instrument; NMR spectra were obtained with Varian EM-360 and Jeolco MH-100 spectrometers. Mass spectra were taken with a Consolidated Electrodynamics Corp. Model 21-110B spectrometer system.

Preparation of 4-Aminoquinazolines. General Procedure. Ammonia was bubbled into a mixture of an isatoic anhydride (0.05 mol) in DMF (50 ml) at room temperature. The reaction was monitored by ir spectra of aliquots, and when complete conversion was indicated (~15–30 min) the mixture was degassed with N_2 to remove $(NH_4)_2CO_3$. $POCl_3$ (8.5 ml) was then added dropwise at 0–15 °C. The resulting mixture was heated for 30 min at 40–60 °C, then cooled to room temperature, and H_2O (15–20 ml) was added. A primary amine or ammonia was then added until the mixture was basic,[10] and the resulting solution was heated at 100 °C until TLC indicated conversion to the desired product. On cooling, the product crystallized and was isolated by filtration. In some cases addition of H_2O was necessary to cause crystallization.

The following compounds were prepared as described:[11] **4a**, R = H (47%, mp 268–269 °C[1]); **4a**, R = CH_3 (63%, mp 196–197 °C); **4a**, R = C_6H_5 (44%, mp 218–220 °C[2]); **4b**, R = H (79%, mp >310 °C[12]); **4b**, R = CH_3 (66%, mp 256–257 °C[13]); **4b**, R = C_6H_5 (51%, mp 229–230 °C).

Acknowledgments. We wish to thank Professor E. C. Taylor for helpful discussions.

Registry No.—**1a**, 118-48-9; **1b**, 4743-17-3; **4a** (R = H), 15018-66-3; **4a** (R = CH_3), 7154-47-4; **4a** (R = C_6H_5), 34923-95-0; **4b** (R = H), 19808-35-6; **4b** (R = CH_3), 32084-63-2; **4b** (R = C_6H_5), 59169-66-3; ammonia, 7664-41-7; methylamine, 74-89-5; phenylamine, 62-53-3.

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(10) Alternatively, only 2–3 equiv of amine may be added with enough 50% NaOH to make the mixture basic.
(11) No attempt was made to optimize yields, but we feel that yields >60% would be easily attainable in all cases. Yields are isolated yields based on **1a**, **1b**. Satisfactory ir, NMR, mass spectral, and elemental analyses were obtained for all compounds.
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An Unusual Addition–Fragmentation Reaction between Bisulfite and a Methallyl Ether

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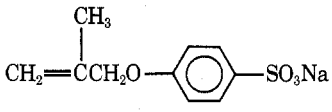
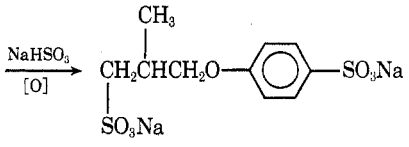
The formation of organic sulfonates by the addition of bisulfite to nonconjugated olefins appears to be a radical process accelerated by oxygen or other oxidizing agents.[1,2] Thus, isobutylene and sodium bisulfite give a good yield of sodium 2-methylpropanesulfonate.[1] While investigating radical reactions of polymerizable olefins, we have discovered a novel variant of the bisulfite–olefin reaction.

The reaction of sodium *p*-sulfophenyl methallyl ether (**1**) with a slight excess of sodium bisulfite gave the expected addition product, disodium *p*-sulfophenyl 2-methyl-3-sulfopropyl ether (**3**), in good yield when the aqueous reaction



1



3

medium was about 1 M in bisulfite. The structure of **3** was confirmed by elemental analysis and NMR spectrum. Analysis of mixtures of **1** and **3** was possible using high-pressure liquid chromatography (HPLC, see Experimental Section).

When **1** was combined with a dilute solution of bisulfite (ca. 10^{-3} M) only trace amounts of **3** were formed; after separation from unreacted **1** by column chromatography, the new products were identified as sodium phenolsulfonate (**6**) and sodium methallylsulfonate (**5**) by comparison of NMR spectra with spectra of the known compounds. The presence of **6** was fur-

Chart I

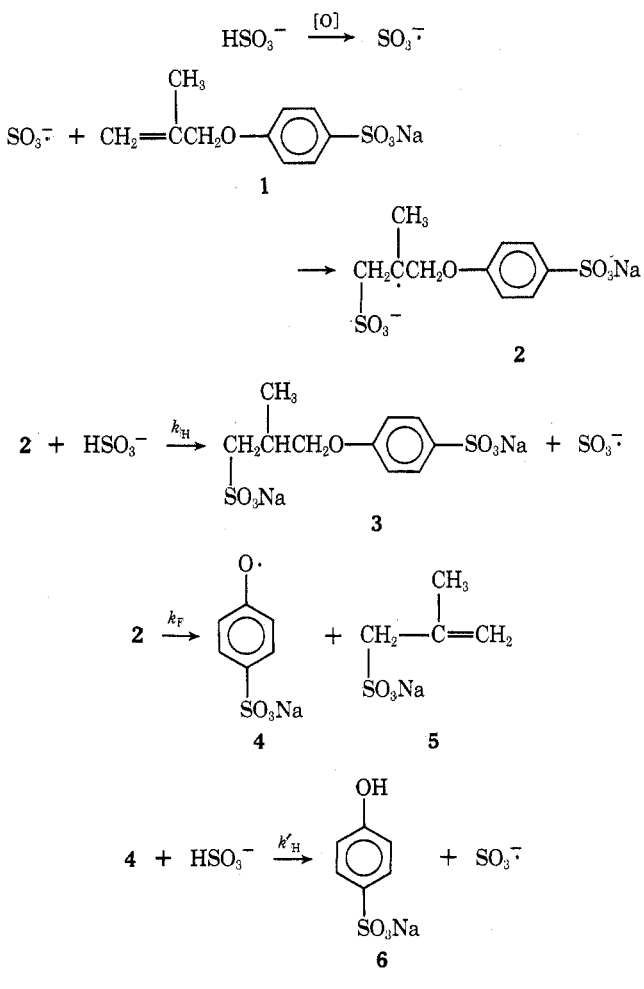


Table I. Reaction of Sodium *p*-Sulfophenyl Methallyl Ether (1) with Bisulfite [a]

$[1]_0$	$[HSO_3^-]_0$	[3]/[6]
0.008	0.024	0.15
0.008	0.040	0.44
0.008	0.080	1.6
0.008	0.100	2.6
0.004	0.100	2.4
0.004	0.090	2.1
0.004	0.080	1.8
0.004	0.060	1.3
0.002	0.070	1.5
0.002	0.060	1.4
0.002	0.050	1.0
0.002	0.030	0.30
0.008	0.004	<0.05
0.008	1.00	>25

[a] Reaction conditions 100 °C, 10 min; 0.01 equiv of potassium persulfate (based on sodium bisulfite) was also present in each run. Where excess bisulfite was employed conversion of 1 to products was quantitative.

ther indicated by a shift in ultraviolet absorption to longer wavelength in basic solution.

The course of the reaction of 1 with bisulfite was largely unaffected by temperature (25–100 °C) or pH (2–7). Addition of a small amount of persulfate greatly improved product yield but did not alter product identity. At bisulfite concentrations intermediate between 1 and 10^{-3} M a mixture of products **3**, **5**, and **6** was obtained. These observations suggest the mechanism shown in Chart I wherein a radical derived from bisulfite adds to 1 to give an intermediate (**2**) which may either form **3** by transfer of hydrogen from bisulfite (k_H) or fragment (k_F) to form, after hydrogen transfer, **5** and **6**. The overall reaction to give **5** and **6** is thus viewed as a rather unusual radical addition–fragmentation reaction. A direct determination of the rate of the fragmentation reaction is made difficult by the fact that the process is too rapid to follow using HPLC analysis for **3** and **6**. An estimate of the relative rates (k_H/k_F) can, however, be obtained from the product data given in Table I. With reference to Chart I, the formation rates of **3** and **6** are given by

$$\frac{d[3]}{dt} = k_H[2][HSO_3^-]$$

$$\frac{d[6]}{dt} = k'_H[4][HSO_3^-]$$

Applying the steady-state approximation[3] to the radical **4**,

$$k_F[2] = k'_H[4][HSO_3^-]$$

Hence,

$$\frac{d[6]}{dt} = k_F[2]$$

and

$$\frac{d[3]}{d[6]} = \frac{k_H}{k_F}[HSO_3^-]$$

Thus, the relationship

$$\frac{[3]}{[6]} = \frac{k_H}{k_F}[HSO_3^-]_t$$

predicts that a plot of bisulfite concentration vs. the molar ratio of **3** to **6** as a function of time will be linear with slope k_H/k_F. $(HSO_3^-)_t$ can be approximated by the initial bisulfite concentration provided that it is in sufficient excess over **1** as to undergo little concentration change during the reaction.[4]

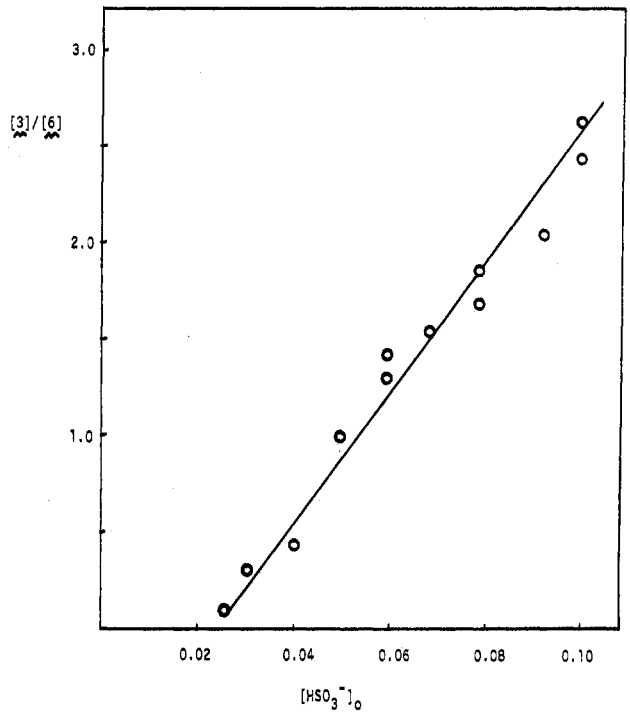


Figure 1. Initial bisulfite concentration vs. product ratio for the reaction of bisulfite with **1**.

Figure 1 shows this plot, from which a value of $k_H/k_F = 35$ is derived. The plot, which presumably should pass through the origin, is unreliable at low $(HSO_3^-)_0$ because of the difficulty in maintaining the excess of bisulfite required for the approximation of $(HSO_3^-)_t$ with $(HSO_3^-)_0$. Note, however (Table I), a value of [3]/[6] < 0.05 for $(HSO_3^-)_0 = 0.004$.

Radical transfer of hydrogen from bisulfite is, in general, a rapid process.[5] Hence the addition–fragmentation reaction is seen to be quite facile, probably because of the stability of the phenolic radical **4**.

The possibility that products **5** and **6** were formed from **3**

$$3 + SO_3\cdot^- \rightarrow 2 + HSO_3^-$$

$$2 \rightarrow \rightarrow 5 + 6$$

was ruled out by combining bisulfite with **3** under reaction conditions for formation of **5** and **6** from **1**. **3** was recovered unchanged.

Experimental Section

Reaction of Sodium *p*-Sulfophenyl Methallyl Ether (1) with Sodium Bisulfite in Concentrated Solution. A solution of 0.10 mol of **1** (prepared by the method of Masson[6] and recrystallized from aqueous ethanol), 0.12 mol of sodium bisulfite, and 0.001 mol of potassium persulfate in 200 ml of water adjusted to pH 3 with sulfuric acid was stirred at the boil for 30 min. Titration of an aliquot of the solution with iodine to a starch end point indicated that 80% of the bisulfite had reacted. The solution was evaporated to about one-tenth its original volume and the solid which separated was isolated by filtration, dried, and weighed (32.5 g). This represents a 92% yield of disodium *p*-sulfophenyl 2-methyl-3-sulfopropyl ether (**3**): NMR (D_2O) δ 1.58 (J = 7 Hz, methyl), 4.33 (J = 6 Hz, CH_2O), 3.26, 3.58 (J = 14 Hz, $CH_2SO_3^-$), 2.82 (CH), 7.41, 8.17 (aromatics, AA'BB' pattern).

Anal. Calcd for $C_{10}H_{12}O_7S_2Na_2$: C, 33.90; H, 3.41; S, 18.10; Na, 12.98. Found: C, 33.49; H, 3.70; S, 18.95; Na (by atomic absorption spectroscopy), 13.0.

Reaction of 1 with Sodium Bisulfite in Dilute Solution. A solution of 4 mmol of **1**, 2 mmol of sodium bisulfite, and 0.1 mmol of potassium persulfate in 500 ml of water adjusted to pH 3 with sulfuric acid was stirred at the boil for 30 min. Separation of the reaction products from unreacted **1** was accomplished by adsorption of the components on Amberlite XAD-2 resin (a nonionic, cross-linked polystyrene with a macroreticular structure, from Rohm & Haas Co.)

followed by elution with 2% LiCl/20% MeOH/78% H_2O. Under these conditions, **1** is retained on the column. Products (contaminated with LiCl) were isolated by evaporation of the column eluent to dryness. An NMR spectrum of these products was essentially identical with a spectrum of an equimolar mixture of sodium phenolsulfonate (**6**) and sodium methallylsulfonate (**5**) (δ 2.33, 4.07, 5.47, and 5.53 for **5**). An aqueous solution of the products showed the ultraviolet shift expected for **6** when the solution pH was raised (λ_{max} 231 nm at pH 6, 254 nm at pH 10).

Analysis of Reaction Products by High-Pressure Liquid Chromatography (HPLC). A Waters Associates ALC 202 liquid chromatograph equipped with a Model U6K injector and a Bondapak AX anion exchange column was used. With 0.05 M $NaClO_4$ in 90% H_2O/10% MeOH as the mobile phase components were eluted in the order **6**, **1**, **3**, and were detected using a Perkin-Elmer Model LC-55 variable wavelength detector set at 231 nm.

Acknowledgments. The author is grateful to E. W. Wilburn, W. W. Lanier, and H. A. Taylor for product separations and analyses using liquid chromatography, and to Claudette Deatherage for NMR analyses.

Registry No.—**1**, 1208-67-9; **3**, 59219-47-5; **5**, 1561-92-8; **6**, 825-90-1; sodium bisulfite, 7631-90-5.

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A Simple Synthesis of 2-Alkylcyclohexenones[1]

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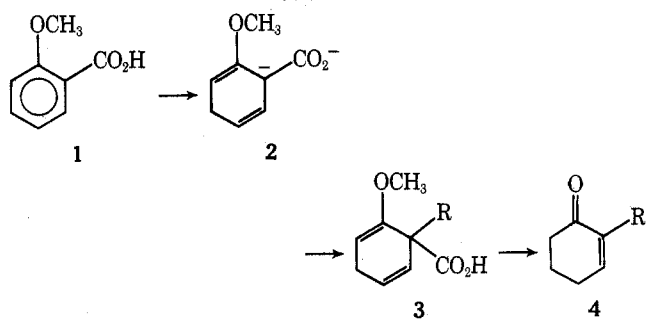
Cyclohexenones are versatile intermediates in organic synthesis. Among other applications, they are useful precursors to substituted cyclohexanones by conjugate addition,[2] enolate trapping,[3] and Diels–Alder addition,[4] as well as to alkynyl aldehydes.[5] While several procedures[6] have been employed for the preparation of 2-alkylcyclohexenones, by and large these procedures are lengthy or lead to isomeric mixtures of products.

The report[7] of the reductive alkylation of an *o*-methoxy substituted benzoic acid derivative led us to investigate this approach as a possible simple approach to 2-alkylcyclohexenones. Thus, addition of alkali metal to a suspension of the ammonium salt of **1** in liquid ammonia should give the dianion **2**, which could be alkylated. Evaporation of the ammonia followed by the hydrolysis of **3** with aqueous acid should then give the cyclohexenone **4**.

Scheme I



1 **2** **3** **4**

In fact, this one-pot procedure (see Experimental Section) works well, and is amenable to large-scale application. Thus, the enones listed (Table I) were prepared pure in gram quantity from the inexpensive acid **1**. Even given the modest yields achieved, this is currently the method of choice for preparing most 2-alkylcyclohexenones.

Experimental Section

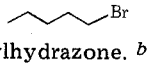
General. Melting points were taken on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Microanalysis was performed by Spang Microanalytical Laboratory, Ann Arbor, Mich. All chemicals were used as received, except for allyl chloride, which was distilled immediately prior to use. Tetrahydrofuran was stored over Linde 4A molecular sieve after opening. NMR spectra were recorded on a JEOLCO MH-100 spectrometer. Infrared spectra were recorded on a Perkin-Elmer 257 spectrophotometer.

The general procedure for reductive alkylation followed by hydrolysis is illustrated by the synthesis of 2-allylcyclohexenone.

2-Allylcyclohexenone. A 1-l. three-neck round-bottom flask was charged with 15.2 g (100 mmol) of *o*-methoxybenzoic acid and 100 ml of THF. The solution was stirred magnetically, and ammonia (400 ml) was distilled in to give a thick white suspension. The reaction mixture was then maintained at reflux under a nitrogen atmosphere. Lithium wire (washed sequentially with hexane, methanol and hexane) was added in 7-cm pieces until a blue solution was maintained.[9] The reaction vessel was cooled in a dry ice–acetone bath and 1,2-dibromoethane (2 ml) was added, followed by allyl chloride (12.0 ml, 120 mmol).

The reaction mixture was allowed to warm to room temperature under a stream of nitrogen. The resultant brown slurry was diluted with 100 ml of ethylene chloride, then acidified with 100 ml of concentrated aqueous HCl (*foams!*). Water (100 ml) and hydroquinone (200 mg) were added, and the two-phase mixture was refluxed for 30 min. The mixture was diluted with water (300 ml), the organic phase was separated, and the aqueous phase was extracted with one 50-ml portion of ethylene chloride. The combined organic phase was washed with 100 ml of aqueous sodium bicarbonate solution, dried over anhydrous sodium sulfate, and concentrated in vacuo. The residual oil was distilled through a 10-cm Vigreux column to yield 3.65 g (27%) of colorless oil: bp 67–68 °C (3.2 mm); NMR ($CDCl_3$) δ 1.98, m, 2 H; 2.36, m, 4 H; 2.88, bd, J = 6 Hz, 2 H; 4.92, bd, J = 12 Hz, 2 H; 5.5–6.0,

Table I. Preparation of 2-Substituted Cyclohexenones

Registry no.	Alkylating agent	Bp, °C (mm)	Yield, %	Lit. bp, °C (mm)	Mp of derivative, °C	Lit. mp, °C	Ref.
107-05-1		67–68 (3.2)	27	98–103 (15)	174[a]	171[a]	6a
107-08-4		65–66 (2.4)	30	95 (14)	172[a,b]	163–164[a]	8
75-30-9		56–58 (2.3)	26	150	168[c]	163–164[c]	6g
110-53-2		74 (0.5)	27	72–78 (0.5)	113[a]	112[a]	6b

[a] 2,4-Dinitrophenylhydrazone. [b] Anal. Calcd for $C_{15}H_{18}N_4O_4$: C, 56.58; H, 5.70; N, 17.61. Found: C, 56.88; H, 5.78; N, 17.53. [c] Semicarbazone.