A New Synthesis of 1,2,4-Benzothiadiazines and a Selective Preparation of *o*-Aminobenzenesulphonamides

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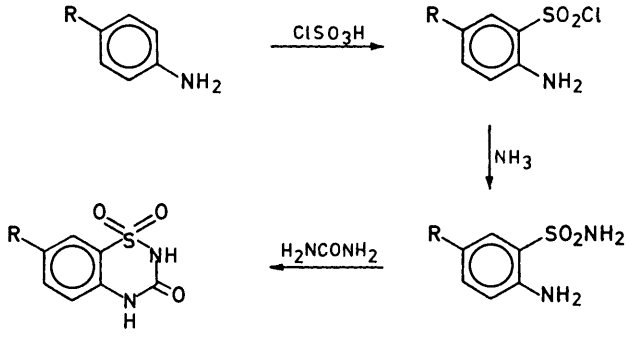
Reaction of a series of aniline derivatives with chlorosulphonyl isocyanate followed by cyclisation of the resulting chlorosulphonylureas with Lewis acids gives good yields of 2*H*-1.2.4-benzothiazidazin-3(4*H*)-one 1.1-dioxides. These, upon acid hydrolysis, yield the corresponding *o*-aminobenzenesulphonamides.

THE synthesis and chemistry of the 1,2,4-benzothiadiazine ring system has been extensively investigated, due primarily to the discovery of non-mercurial diuretic activity in this structure in the 1950's.[1] The subsequent discovery of the antihypertensive drug diazoxide [2] has served to maintain a high level of interest in the 1,2,4-benzothiadiazine structure in the pharmaceutical field.[3] By way of illustration, one of the most commonly used syntheses of this ring system is outlined below:



A number of syntheses of the ring system have been reported [4] but suffer from various disadvantages such as isomer formation, over-substitution, and length.

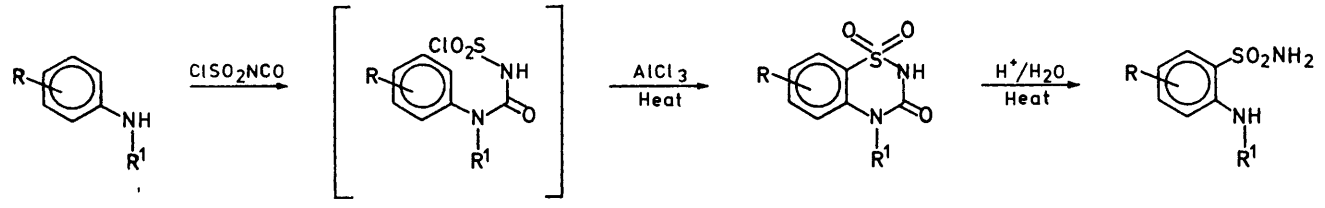
We describe here a new approach to the 1,2,4-benzothiadiazine ring system which overcomes some of the above problems, and which has also resulted in a novel and selective preparation of *o*-aminobenzenesulphonamides.

We have found that by condensing chlorosulphonyl isocyanate with an aromatic amine (1), followed by cyclisation of the intermediate chlorosulphonylurea under Friedel–Crafts conditions, good to excellent overall yields of the 1,2,4-benzothiadiazine ring system (2) are obtained. The reaction sequence is outlined in Scheme 1.

RESULTS

Chlorosulphonyl isocyanate has been reported to react with amines [5] to afford *N*-chlorosulphonylurea derivatives. We have not systematically isolated these intermediates, which are known to be rather unstable on handling and storing, but in the case of (1a), it has been isolated by simple filtration of the reaction mixture, and characterised and hydrolysed to the corresponding substituted phenylurea. The *N*-chlorosulphonylurea derivatives, as prepared *in situ*, underwent efficient cyclisation to the desired bicyclic compounds (2) using aluminium chloride or, somewhat less effectively, stannic chloride.

Table 1 contains the relevant data, including a comparison of the results obtained using nitromethane and nitroethane as solvents. Nitromethane was studied initially, with the reaction between the amine and chlorosulphonyl isocyanate being carried out at 0 °C. In order to obtain a significantly lower temperature, nitroethane was then used, the temperature being kept below −40 °C during the addition of the amine to chlorosulphonyl isocyanate. The reaction mixture was then allowed to warm to 0 °C, when aluminium chloride was added and the reaction heated as before. It can be seen that the reaction is not especially sensitive, but



(1)

	R	R^1
a	H	H
b	4-Me	H
c	2-Me	H
d	4-Cl	H
e	3-Br	H
f	4-OMe	H
g	H	CH_3
h	H	Ph

(2)

	R	R^1
a	H	H
b	7-Me	H
c	5-Me	H
d	7-Cl	H
e	6-Br	H
e′	8-Br	H
f	7-OMe	H
g	H	CH_3
h	H	Ph

(3)

	R	R^1
a	H	H
b	5-Me	H
c	3-Me	H
d	5-Cl	H
e	4-Br	H
e′	6-Br	H
f	5-OMe	H
g	H	Me
h	H	Ph

SCHEME 1

TABLE 1

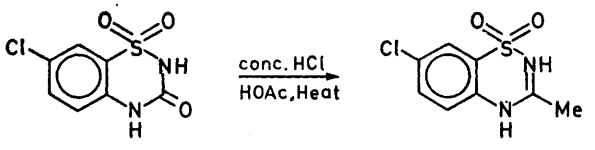
Synthesis of 2*H*-1,2,4-benzothiadiazin-3(4*H*)-one 1,1-dioxides (2)

Compound (2)	Yield (%) in $C_2H_5NO_2$ (in CH_3NO_2)	M.p. (°C) (lit. m.p.)	pK_a [a]	U.v. λ_{max}/nm (log ε) [b]	Elemental analysis for new compounds	C	H	N	S
a	85 (67)	300—302 (305) [c]	2.90	214 (4.08); 243 (4.01); 290 (3.26)					
b	92 (66)	316—318 (300) [f]	2.90	215 (4.16); 245 (4.08); 298 (3.24)					
c	87 (66)	297—300 (—)	2.70	215 (4.27); 242 (3.98); 290 (3.33)	Calcd:	45.30	3.80	13.20	15.10
					Found:	45.05	4.05	13.45	15.2
d	65 (69)	316—318 (314—315) [g]	2.69	215 (4.16); 251 (4.13); 304 (3.23)					
e [e]	50 (42)	318—321 (313—315) [h]	2.60	222 (4.50); sh245 (4.01); 295 (3.37)					
e′ [e]	16 (14)	290—300 (—)	2.37	220 (4.37); 249 (3.92); 298 (3.42)	Calcd: [j]	30.35	1.80	10.10	11.55
					Found: [k]	30.6	2.05	9.8	11.85
f	83 (61)	300 (—)	3.05	216 (4.13); 251 (4.12); 311 (3.36)	Calcd:	42.10	3.55	12.30	14.05
					Found:	41.95	3.65	12.25	14.15
g	74 (64)	246—248 (241—242) [i]	2.78	215 (4.16); 246 (4.03); 290 (3.30)					
h	89 (89)	235—237 (—)	2.55	216 (4.26); 245 (4.07); 291 (3.41)	Calcd:	56.95	3.70	10.20	11.70
					Found:	56.55	3.75	10.05	11.65
o-$ClC_6H_4CO_2H$ [d]			3.30						

[a] Taken from the titration curves in H_2O–MeOH (1 : 1). [b] Measured in EtOH on a Perkin-Elmer 202 spectrophotometer. [c] Separated by column chromatography. [d] Run for comparison purposes. Literature value 2.92 (G. Kortum, W. Vogel, and K. Andrussov, 'Dissociation constants of Organic Acids in Aqueous Solution,' Butterworths, London, 1961, No. 447). [e] D. V. Parke and R. T. Williams, *J. Chem. Soc.*, 1950, 1760. [f] J. R. Scott, *J. Chem. Soc.*, 1923, **123**, 3191. [g] L. Raffa, M. DiBella, and A. Monazni, *Farmaco* (*Pavia*), *Ed. Sci.*, 1960, **15**, 716. [h] D. F. Hayman, V. Petrow, and O. Stephenson, *J. Pharm. Pharmacol.*, 1962, **14**, 522. [i] L. Raffa, *Farmaco* (*Pavia*), *Ed. Sci.*, 1957, **12**, 495. [j] Br calculated 28.85. [k] Br found 29.05.

in most cases significantly improved yields can be obtained in nitroethane at the lower initial temperature, probably by decreasing the formation of by-products in the reaction between the amine and chlorosulphonyl isocyanate.

Hydrolysis of (2) afforded an easy and efficient two-step synthesis of the *o*-aminobenzenesulphonamides (3) (Scheme 1). Concentrated HCl was the system of choice since higher yields were generally obtained and the product can be isolated by evaporation of the reaction mixture. However, since in a number of cases (see Table 2) hydrolysis in HCl was extremely slow because of the insolubility of the starting material, we had recourse to hydrolysis in 50% aqueous H_2SO_4. In one attempt to use acetic acid as a co-solvent



(2d) diazoxide

in the hydrolysis of (2d), the major product isolated (*ca.* 35% yield) was diazoxide.[2] No attempt has been made to optimize this novel synthesis of this important benzothiadiazine ring system, but it may be a useful development from our synthesis of (2).

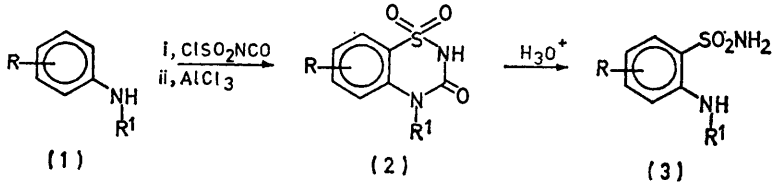
DISCUSSION

The sequence (1) ⟶ (2) ⟶ (3) has been found to constitute a new and unseful synthesis of the benzothiadiazine ring system and *o*-aminobenzenesulphonamides, both important structural types in medicinal chemistry.[3]

Many of the compounds described here in the series (2) and (3) are reported in the literature, and their properties corresponded well with those reported. The ^1H n.m.r. and mass spectra were all in excellent agreement with the expected structures and require little comment. In the case of new compounds, high resolution mass spectra confirmed the elementary composition found by combustion analysis.

It is to be noted that the one *meta*-substituted aniline studied (1e) gave rise to a mixture of benzothiadiazine isomers (2e) and (2e′), the major one resulting from cyclisation *para* to the bromine atom. The ^1H n.m.r. spectra easily identified the structure corresponding to each isomer.

In the series of *o*-aminobenzenesulphonamides, one of those reported in the literature was (3h) (see Scheme 1). However, there was a large discrepancy between the physical properties of our compound (m.p. 125—126 °C) and that described in the only report in the literature by Ghelardoni *et al.*[6] (m.p. 193—194 °C, for



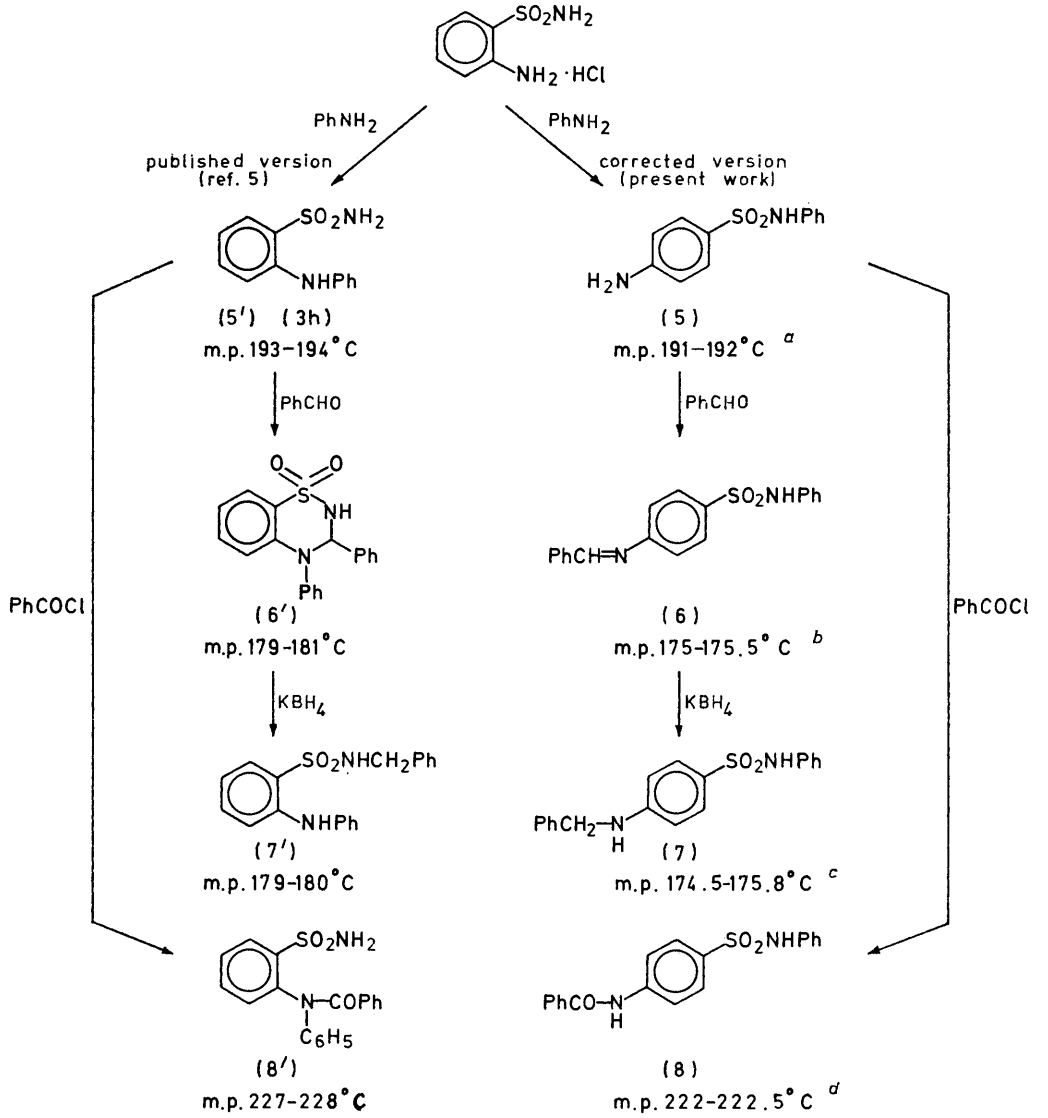
(1) (2) (3)

TABLE 2

Preparation of 2-aminobenzenesulphonamides (3)

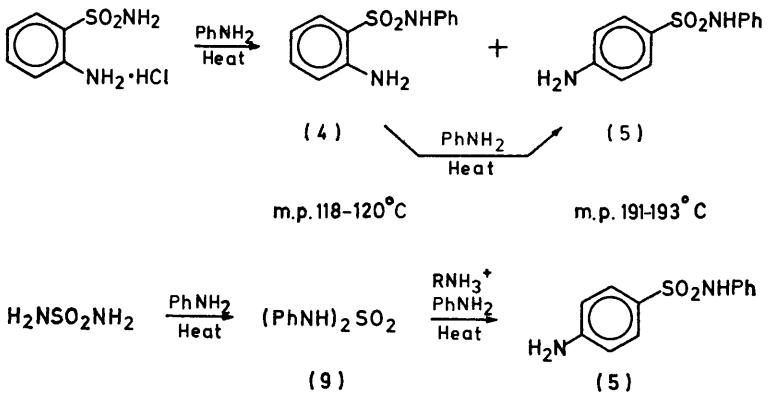
Compound (3)	Yield (%)	M.p. (°C) [a] (lit. m.p.)		Elemental analysis for new compounds C	H	N	S
a	90 [b]	152—153 (153—154.5) [d]					
b	96 [b]	118—120 (125) [e]					
c	73 [c]	113—115 (—)	Calcd: Found:	45.15 45.35	5.40 5.6	15.05 14.95	17.20 17.45
d	70 [c]	151—152 (152—153) [f]					
e	77 [c]	145—147 (146—148) [g]					
e′	48 [c]	152—154 (—)	Calcd: [k] Found: [l]	28.70 29.05	2.80 3.0	11.15 10.95	12.75 12.9
f	84 [b]	120—121 (125—130) [h]					
g	89 [b]	118—120 (116—116.5) [i]					
h	42 [c]	125—126 (—) [j]	Calcd: Found:	58.05 58.1	4.85 5.15	11.30 11.2	12.90 12.8

[a] M.p. of free base. [b] Hydrolysed in refluxing conc. HCl for 24 h; yields are of the HCl salts. [c] Hydrolysed in 50% aqueous H_2SO_4 at 130—140 °C for 1—5 h. [d] J. H. Short and U. Biermacher, *J. Amer. Chem. Soc.*, 1960, **82**, 1135. [e] B. A. Bierbaum, J. J. Traverso, and C. W. Whitehead, *J. Medicin. Chem.*, 1963, **6**, 272. [f] A. A. Rubin, F. E. Roth, M. M. Winbury, J. G. Topliss, M. H. Sherlock, N. Sperber, and J. Black, *Science*, 1961, **133**, 2067. [g] See footnote *h*, Table 1. [h] G. F. Holland, U.S.P. 3,251,837 1966. [i] L. Raffa, *Farmaco (Pavia), Ed. Sci.*, 1957, **12**, 483. [j] See text for discussion of reported structure. [k] Br calculated 31.80. [l] Br found 32.25.



SCHEME 2

[a] A. Mangini, *Boll. sci. facolta chim. ind., Bologna*, 1940, 127. [b] H. G. Kolloff and J. H. Hunter, *J. Amer. Chem. Soc.*, 1940, **62**, 158. [c] E. Miller, H. J. Rock, and M. L. Moore, *J. Amer. Chem. Soc.*, 1939, **61**, 1198. [d] H. G. Kolloff and J. H. Hunter, *J. Amer. Chem. Soc.*, 1940, **62**, 1647.



convenience referred to as compound Y). We repeated the synthesis as described by these authors and obtained two compounds, (4) and (5), in modest yields with no evidence for the formation of (3h). Structures (4) and (5) were prepared unambiguously by reaction of the corresponding *o*- and *p*-nitrobenzenesulphonyl chlorides with aniline followed by reduction with Pd/C–N_2H_4–EtOH, and were found to be identical with the compounds isolated. Compound (4), although similar to (3h) in m.p., was clearly distinguished from the latter by mixed melting point and comparison of spectral data.

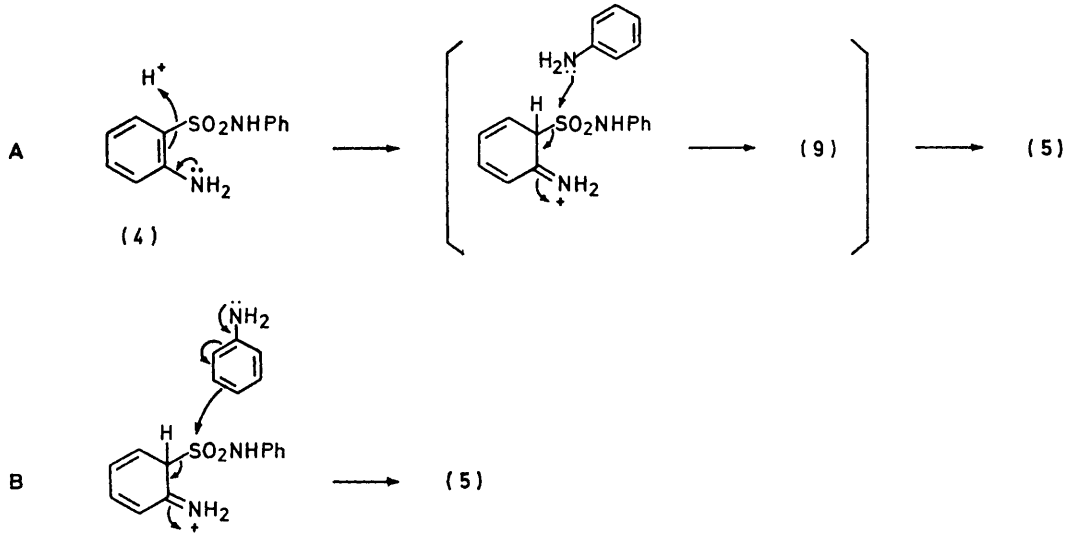
Compound Y to which Ghelardoni *et al.*[6] have assigned structure (3h) is in fact (5), with the result that the structural assignments for subsequent reactions of Y described by these authors are incorrect. In Scheme 2 are shown the structural assignments made by the previous workers along with the corrected structures.

The compounds (6), (7), and (8), derived from (5) as per Scheme 2, are isomeric with the structures assigned by Ghelardoni *et al.* and hence have analysed correctly in their hands. The melting points reported by these authors also correspond quite well with those of structures (6), (7), and (8) as reported in the literature.

Scott *et al.*[7] have shown that sulphamide reacts with an excess of aniline to yield 1,3-diphenylsulphamide (9) as the major product and that this compound, in the presence of ammonium salts and a large excess of aniline, reacts further to yield (5), as shown below.

The formation of (4), which we have observed, is readily explained by a reaction of this type. We have also shown that (4), under the conditions of the experiment, is transformed into (5). The formation of (5) can be rationalized by one of the two mechanisms shown in Scheme 3. In the transformation of (4) to (5) we have not been able to detect (9) as an intermediate (mechanism A); thus it is quite possible that (5) is obtained directly from protonated (4) as indicated in mechanism B. In either case, the overall reaction requires the novel cleavage of a carbon–sulphur bond.

In view of the extensive studies on the acidic properties of sulphonamide derivatives [8] and because of a lack of comprehensive data, the pK_a values and u.v. absorption data are also reported in Table 1. The structures (2), which can be viewed as cyclic acylsulphonamides, are about two pK_a units more acidic than their acyclic counterparts.[8a]



SCHEME 3

EXPERIMENTAL *

General Procedures for the Preparation of 2H-1,2,4-*Benzothiadiazine*-3(4H)-*one* 1,1-*Dioxides* (2).—*Method A*. A solution of (1) (0.03 mol) in nitromethane (5 ml) was added to a stirred, ice-cooled solution of chlorosulphonyl isocyanate (5 g, 0.037 mol) in nitromethane (45 ml) during 5 min (the chlorosulphonylurea intermediates crystallised out in most cases). Aluminium chloride (5 g, 0.038 mol) was added all at once, resulting in a clear solution. The reaction mixture was then refluxed for 30 min, cooled, and poured into ice–water. The precipitated solid was filtered, washed with water, and dried to yield essentially pure (2). Analytical samples were obtained by treatment with charcoal and recrystallisation from ethanol.

The isomers (2e) and (2e′) were separated by chromatography over silica gel using EtOAc–MeOH (3 : 1) containing 1% triethylamine. The major isomer (2e) eluted first followed by the minor isomer (2e′). The compounds were isolated as their triethylamine salts from the chromatography and were obtained by acidification of their aqueous solutions.

Method B. A solution of (1) (0.03 mol) in nitroethane (5 ml) was added to a stirred solution of chlorosulphonyl isocyanate (5 g, 0.037 mol) in nitroethane (45 ml) kept at < -40 °C during 5 min (the chlorosulphonylurea intermediates crystallised out in most cases). The reaction mixture was allowed to warm up to 0 °C, and aluminium chloride (5 g, 0.038 mol) was added all at once, resulting in a clear solution. The reaction mixture was then placed in a bath at 110 °C for 20 min, cooled, and poured into ice–water. The precipitated solid was filtered off, washed with water, and dried to yield essentially pure (2).

General Procedures for the Preparation of Substituted 2-*aminobenzenesulphonamides* (3).—*Method A*. A suspension of (2) (0.01 mol) in conc. HCl (100 ml) was refluxed for 24 h to give a clear solution. This was evaporated to dryness, treated with diethyl ether, and filtered to afford the crude hydrochloric salt. The free bases were obtained by treatment of an aqueous solution with dilute NH_4OH and filtration.

* Analytical data for all new compounds are given in Tables 1 and 2.

Method B. A suspension of (2) (500 mg) in H_2SO_4 (50%; 15 ml) was heated to 130—140 °C, until a solution resulted (1—3 h). After dilution with ice–water (250 ml) and neutralizing with NaOH (40%), the product crystallised. The crystals were filtered, washed with water and dried, yielding the pure product (3).

2-*Anilinobenzenesulphonamide* (3h). A suspension of (2h) (2.74 g, 0.01 mol) in H_2SO_4 (50%; 80 ml) was heated to 130—140 °C for 5 h when dissolution was complete. This solution was cooled, diluted with ice–water (*ca.* 200 ml), basified with NaOH (40%), re-acidified with HCl (1M), and extracted with ethyl acetate (2 × 100 ml). The organic layer was washed with water, dried over Na_2SO_4, filtered, and evaporated to dryness to yield crude material (1.4 g). Purification was carried out by chromatography on silica gel (2% MeOH–$CHCl_3$) to afford pure (3) (1.05 g. 42%).

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