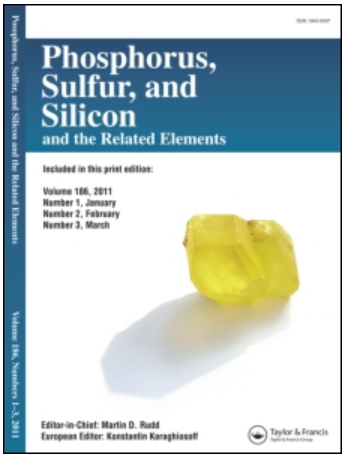

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NOVEL SYNTHESIS OF THIAZOLIDINES

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NOVEL SYNTHESIS OF THIAZOLIDINES

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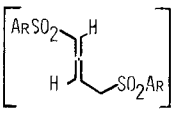
A novel synthesis of thiazolidine derivatives is described, based on nucleophilic additions across the triple bond of 1,4-diarylsulfonyl-2-butynes. The use of bidentate nucleophiles like *N,N'*-dialkylthioureas, under mild base catalysis, at ambient conditions affords good yields of the title compounds. A mechanism for the formation of the compounds is offered and supported by appropriate experiments.

Key words: Thioureas; dialkyl; thiazolidine-benzimidazolo; butynes, 1,4-(diarylsulfonyl); allenes-arylsulfonyl; benzimidazole-(2-mercapto).

Interest in the chemistry of thiazolidines stems from the presence of that ring skeleton among a great many medicinally valuable agents—notably penicillil derivatives. Over the past four decades, numerous syntheses have been devised for the ring system.[1,2,3] In recent publications[4,5] we have outlined the usefulness of arylsulfonyl allenes (**1**) in regiospecific and stereoselective nucleophilic additions.



1

We now wish to report a novel approach to the synthesis of thiazolidine derivatives utilizing the intermediacy of similar allenes. The methodology described hereunder is a novel mode of cyclization utilizing a bidentate nucloephile such as *N,N'*-dialkyl thiourea to add across the triple bond of 1,4-diarylsulfonyl-2-butynes. Scheme 1 depicts the different steps envisaged in the ring formation. The impressive feature of this ring formation is that it occurs very rapidly, at ambient temperatures, under mild base (NEt_3) catalysis and in good yields. Although the allene and the vinyl sulfide are only incipient intermediates in this reaction the validity of the vinyl sulfide is substantiated by the following observations. The reaction between the butyne 2a and the thiourea in a mixed solvent system containing water affords a mixture of two thiazolidines (**5a** and **6a**).

In earlier work[5] we have demonstrated the formation of a diene from the vinyl sulfide. A vinyl sulfide similar to **7** from the thiourea adduct **10** could analogously

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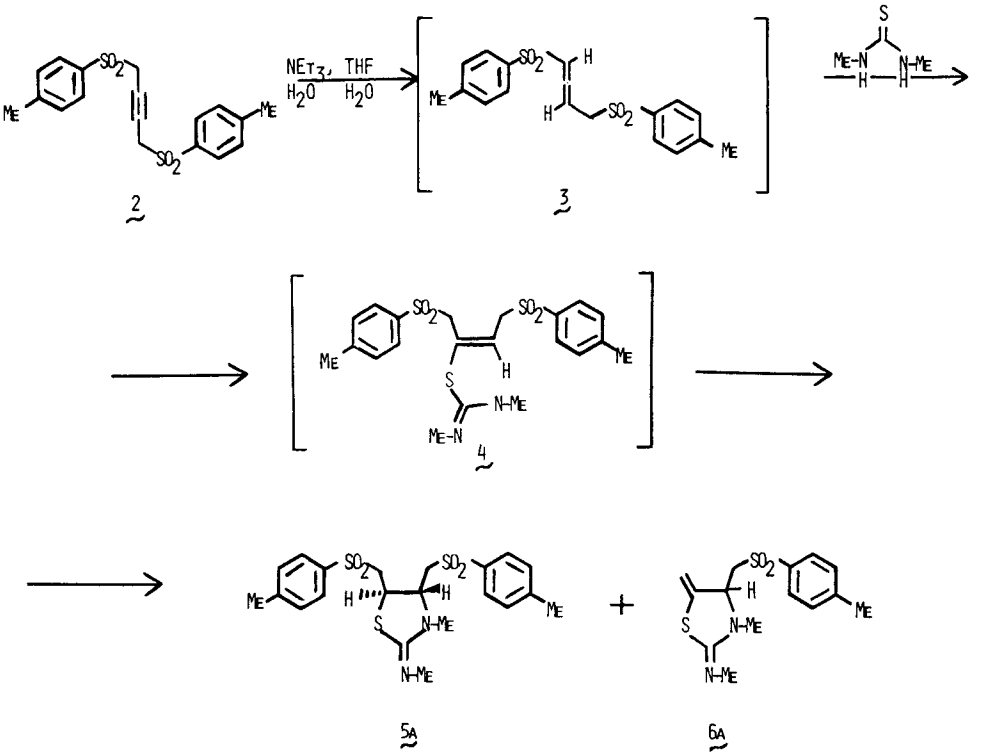
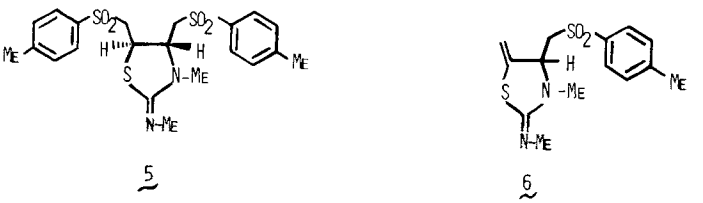
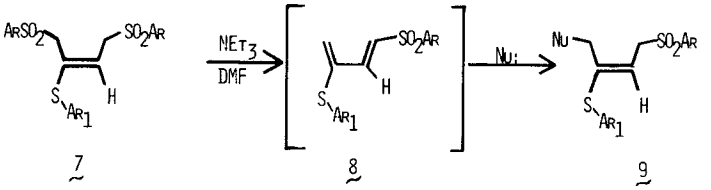


SCHEME 1

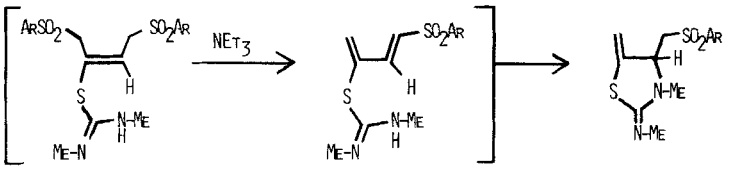


produce **11** to be followed by its intramolecular ring closure, by a 1,2-addition to the vinyl sulfone. To substantiate such a line of argument we have succeeded in obtaining the 5-exomethylene thiazolidine derivatives from a variety of 1,4-diarylsulfonyl-2-butynes. (See experimental.)

Even stronger support for these suggested intermediates comes from the following additional observations. The use of 2-mercaptobenzimidazole (in place of the *N,N'*-dimethylthiourea) helps to slow down the cyclization step beyond the

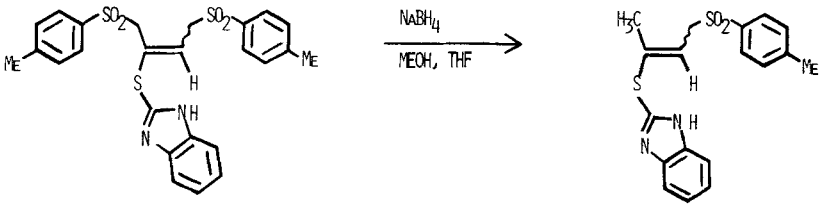


SCHEME 2



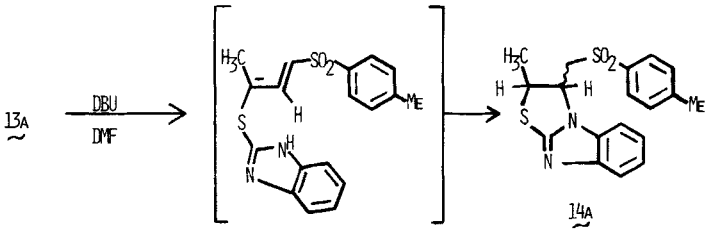
10 11 6

SCHEME 3



12A 13A

SCHEME 4

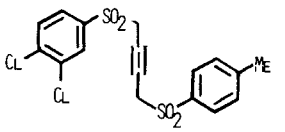


13A 14A

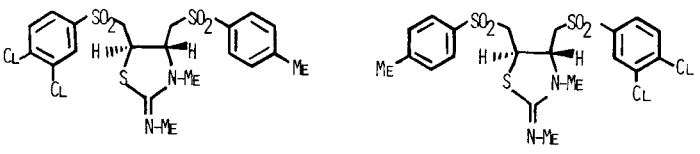
SCHEME 5

vinyl sulfide. Owing to the diminished nucleophilicity of the aniline nitrogen, we are thus able to isolate the vinyl sulfide **12a** as a stable compound. Reduction[6] of **12a** with excess $NaBH_4$ readily affords the butene **13a**. Butene **13a** on further treatment with DBU in DMF cleanly affords the benzimidazolothiazolidine **14a**. Thus the formation of the vinyl sulfide **10** and its cyclization to the thiazolidine **5a** are amply corroborated by two independent tracks.

Equally interesting and mechanistically supportive of the above postulates are the following observations. When an unsymmetrical disulfone such as **15** is treated with *N,N'*-dimethylthiourea, two modes of addition are possible forming **16** and **17**. In such an unsymmetrical butyne as shown above (**15**) one could



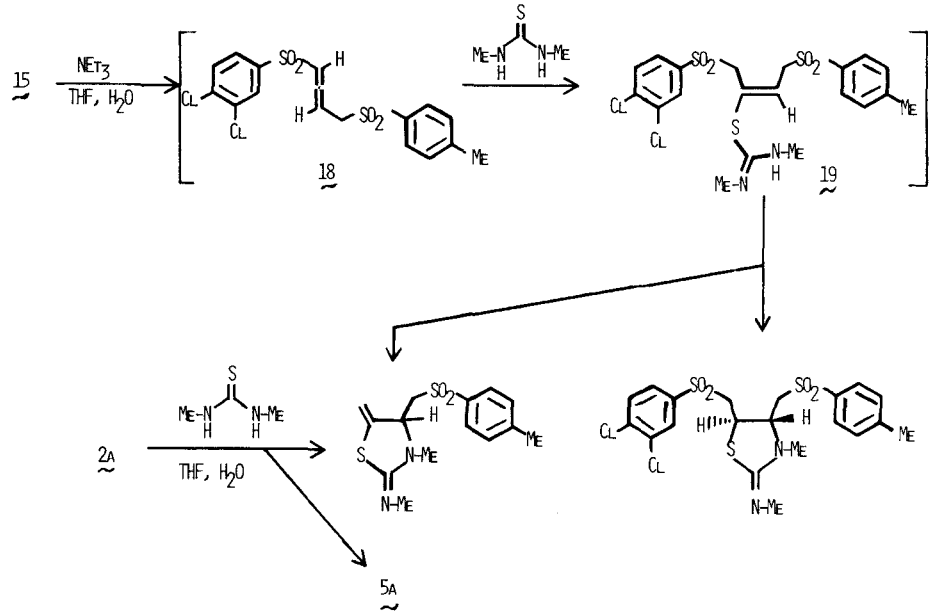
15



16 17

anticipate formation of the allene on the side of the more acidic methylene.[5] This would be followed by addition of the sulfur atom from thiourea to the allenic central carbon and would yield **19**. The latter would then cyclize to the thiazolidine **16** and its corresponding exomethylene **6a** as shown below.

The selective loss of the haloarylsulfinate from the dissymmetrical intermediate **19** adds confirmatory evidence for the site of attachment of the sulfur atom in the thiazolidine (see **5a** and **6a**). The obtention of one and the same exomethylene derivative (**6a**) from two totally different butynes such as **2a** and **15** thus confirms the selective loss of the arylsulfinate carrying the stronger electron-withdrawing group. All these reactions are summarized in Scheme 6.



SCHEME 6

The present work, therefore, represents an unusually interesting, regiospecific, ring-forming addition of thioureas to derivatives of 2-butynes.[7]

EXPERIMENTAL

General Comments. Melting points were determined by using a Buchi SMP-20 capillary melting point apparatus and are uncorrected Nuclear magnetic resonance spectra were recorded on Varian T-60A spectrometer, using tetramethylsilane as the internal standard in $CDCl_3$ and d_6-DMSO solutions. Elemental analyses were carried out by Midwest Microlab of Indianapolis, Indiana.

TABLE I

Thiazolidines **5** and **16**

Compd. no. **5**	*R*	*R* × *n.* Time (min.)	% Yld.	mp. (°C)	Analyses calc. fd.	^{1}H NMR Data (δ in $CDCL_3$, ppm)
a	CH_3	40	70	165.5–167.0	C: 54.08 54.00 H: 5.58 5.50	8.08–7.42(q, 8H), 4.33(m, 2H), 3.40(m, 4H), 2.92(s, 3H), 2.70 (s, 3H), 2.43(s, 6H)
b	H	30	75	154.0–155.0	C: 52.05 52.13 H: 5.02 5.30	8.08–7.22(m, 10H), 4.55–4.05 (m, 2H), 3.62–3.12(m, 4H), 2.90 (s, 3H), 2.67(s, 3H)
c	Cl	20	61	157.0–158.0	C: 45.06 44.36* H: 3.95 3.99	8.03–7.43(q, 8H), 4.63–4.07 (m, 2H), 3.70–3.13(m, 4H), 2.93 (s, 3H), 2.72(s, 3H)
d	Br	10	55	160.0–160.5	C: 38.26 38.46 H: 3.36 3.35	8.03–7.53(q, 8H), 4.67–4.07 (m, 2H), 3.70–3.10(m, 4H), 2.93 (s, 3H), 2.70(s, 3H)
16	3,4-Cl_2, 4-CH_3	20	55	149.0–150.0	C: 46.15 46.09 4.23 4.16	8.23–7.27(m, 7H), 4.63–4.07 (m, 2H), 3.73–3.10(m, 4H), 2.93 (s, 3H), 2.72(s, 3H).

* Mass spectrum obtained on this material confirms its homogeneity and purity.

Preparation of 2-(N-methyl)imino-3-N-methyl-4,5-bis(4-methyl benzenesulfonylmethyl)-thiazolidine; **5**. To a solution of *N,N'*-dimethylthiourea (0.0150 moles, 1.56 g) in THF (50 ml), NEt_3 (0.0019 moles, 0.19 g) was added. The mixture was added in one lot to a stirred solution of 4,5-bis(4-methylbenzenesulfonyl)-2-butyne[8] (0.0150 moles, 5.34 g) in THF (150 ml). The reaction mixture was stirred at ambient temperature, under nitrogen, until the starting materials were consumed (TLC: 7 ml benzene, 2 ml acetonitrile, 5 drops NH_4OH). After disappearance of the starting materials, the reaction mixture was diluted with benzene (200 ml), washed with water (5 × 150 ml), and dried (Na_2SO_4). Concentration (*in vacuo*) to ca. 30 ml gave 30–40% of the crude product which was removed by filtration. The filtrate was concentrated by a gentle stream of air to ca. 20 ml. This solution, once chilled, gave an additional 10–20% of crude product. The two crops were combined and recrystallized from chloroform/pet. ether or methylene chloride/pet. ether resulting in an analytically pure sample.

The other compounds were synthesized using identical conditions. Some differences were observed in the relative rates of reaction as well as in overall yields. These are presented in the accompanying table (see Table I).

Preparation of 2-(N-methyl)imino-3-N-methyl-4-(4-methylbenzenesulfonylmethyl)-5-methyleneothiazolidine; **6**. To a solution of 1,4-bis(4-methylbenzenesulfonyl)-2-butyne (0.0120 moles, 4.34 g) and *N,N'*-dimethylthiourea (0.0120 moles, 1.25 g) was made in THF (290 ml) and DMF (100 ml). Water (300 ml) was slowly added until the solution turned cloudy white. This was immediately followed by the addition of NEt_3 (0.0030 moles, 0.30 g) in THF (10 ml) and MgO (0.0060 moles, 0.24 g). The heterogeneous mixture was stirred at ambient temperature under nitrogen (ca. 10 minutes, at most), and was monitored for disappearance of the starting materials (TLC: 7 ml benzene, 2 ml acetonitrile, 5 drops NH_4OH). Dilution with benzene (400 ml) was followed by several water washes (5 × 200 ml). The product mixture was dried (Na_2SO_4) and concentrated to an oil under a vacuum. (TLC of the product mixture revealed the presence not only the exomethylene compound but also the thiazolidine 1. The separation of these two was accomplished through flash column chromatography.)

What follows is a description of the general method for the separation of the exomethylene compound from the thiazolidines in all the examples cited in Table I. A column ($1\frac{1}{2} \times 2''$) of silica (Aldrich, Merck, grade 60, 230–400 mesh, 60 A) was prepared as described by Still.[9] The product mixture (1.00 g), dissolved in 4 ml of a (60/40) hexane/acetone mixture, was placed on the column. Initially, 500 ml of 100% hexane were passed through the column. Following this, 500 ml of a (95/5) hexane/acetone mixture were eluted. Compound **6** was observed to elute with an (80/20) hexane/acetone solution in all compounds in the series. This solvent ratio was used until the fractions eluted did not contain **2**. At this point, the column was eluted with 600 ml of chloroform followed by 800 ml of methanol. Compound **5** was isolated in these later fractions.

TABLE II

Thiazolidine **6**

Compd. No. **6**	*R*	mp. (°C)	Analyses calc. fd.	^{1}H NMR Data (δ in $CDCl_3$, ppm)
a	CH_3	82.0–83.0	C: 54.19 54.16 H: 5.81 5.96	7.83–7.37(q, 4H), 5.42(t, 1H), 5.21(t, 1H), 4.73(t, 1H), 3.41(d, 2H), 3.00(s, 3H), 2.83(s, 3H), 2.46(s, 3H)
b	H	90.5–91.5	C: 52.70 52.45 H: 5.41 5.48	8.08–7.45(m, 5H), 5.45(t, 1H), 5.22(t, 1H), 4.78(t, 1H), 3.43(d, 2H), 3.00(s, 3H), 2.87(s, 3H)
c	Cl	134.0–135.0	C: 47.27 47.15 H: 4.55 4.53	7.93–7.43(q, 4H), 5.50(t, 1H), 5.27(t, 1H), 4.82(t, 1H), 3.43(d, 2H), 3.00(s, 3H), 2.92(s, 3H)
d	BR	132.0–133.0	C: 41.60 41.38 H: 4.00 4.23	7.80(s, 4H), 5.47(t, 1H), 5.23(t, 1H), 4.77(t, 1H), 3.40(d, 2H), 3.03(s, 3H), (s, 3H), 2.88(s, 3H),

Further purification by recrystallization from ethyl ether/hexane resulted in the pure samples for spectroscopic and elemental analyses shown in Table II.

Preparation of 2-(N-methylimino-3-N'-methyl-4-(4-methylbenzenesulfonylmethyl)-5-methylene thiazolidine; **6** from **15**. The Bissulfone **15** (0.0096 moles, 4.00 g) and *N,N'*-dimethylthiourea (0.0096 moles, 1.00 g) were dissolved in a mixture of THF (40 ml) and DMF (40 ml) and stirred. Water (45 ml) was added slowly until the homogeneous solution remained slightly cloudy. At this point, NEt_3 (0.0024 moles, 0.24 g) was added. The reaction mixture was stirred under nitrogen for *10 minutes* and was immediately diluted with benzene (200 ml). (The reaction mixture was diluted with benzene, once it was revealed by TLC that the starting materials were absent.TLC: 7 ml benzene, 2 ml acetonitrile, 5 drops NH_4OH). The biphasic solution was washed with water (5 × 200 ml) and dried (Na_2SO_4). The dried solution was concentrated to an oil and purified by Flash Column Chromatography.

Preparation of 1,4-bis(4-methylsulfonyl)-2-(2-mercaptobenzimidazolyl)-2-butene; **12**. To a suspension of 1,4-bis(4-methylbenzenesulfonyl)-2-butyne (0.0138 moles, 5.00 g) in benzene (250 ml), 2-mercaptobenzimidazole (0.0152 moles, 2.28 g) and NEt_3 (0.0035 moles, 0.35 g) in DMF (70 ml) were added in one lot. The mixture was stirred for 30 minutes at ambient temperature under nitrogen. (Completion of the reaction was observed by disappearance of the starting materials (TLC: 7 ml benzene, 2 ml acetonitrile). The reaction mixture was diluted with benzene (400 ml), washed with water (6 × 300 ml), dried (Na_2SO_4), and concentrated *in vacuo* to ca. 35 ml. Upon chilling, the crude vinyl sulfide was precipitated by dropwise addition of pet. ether (ca. 2 ml). The solid was removed by vacuum filtration (ca. 50–60%). The filtrate was further concentrated to ca. 25 ml, chilled, and treated with pet. ether (ca. 2 ml) for additional precipitation of 10–15% of crude vinyl sulfide. Both crops were combined and recrystallized from a chloroform/pet. ether solution to give an analytically pure sample. Other compounds prepared similarly are listed in Table III.

Preparation of 1-(4-methylbenzenesulfonyl)-3-(2-mercaptobenzimidazolyl)-2-butene; **13**. The vinyl sulfide **12** (0.0039 moles, 2.00 g) was dissolved in a mixture of THF (60 ml) and methanol (4 ml) and stirred. Dry $NaBH_4$ (0.0117 moles, 0.45 g) was added to the homogeneous solution and stirred at ambient temperature for 10 minutes. Completion of the reaction was observed by disappearance of the starting material by TLC (7 ml benzene, 5 ml acetone) as well as the cessation of evolution of hydrogen gas.

At the completion of the reaction, the reaction mixture was filtered through two inches of sand in a Buchner funnel. The filtrate was diluted with benzene (300 ml), washed with water (6 × 200 ml) to remove the THF and methanol, dried (Na_2SO_4), and concentrated under a vacuum to ca. 25 ml. When the concentrate was chilled and treated with pet. ether (ca. 2 ml), the butene precipitated as a mixture of E and Z isomers (60–70%). Purification was achieved by two recrystallizations from chloroform/pet. ether. Other compounds obtained analogously are listed under Table IV.

Preparation of **14**. Compound **13** (0.0091 moles, 3.25 g) was dissolved in DMF (55 ml) and stirred under nitrogen at room temperature. DBU (0.0091 moles, 1.38 g in DMF (5 ml) was added in one lot and the reaction mixture was stirred for three and one quarter hours. (The reaction was monitored by

TABLE III

Vinyl sulfides **12**.

Compd. No. **12**	*R*	*R* × *n*. Time (min.)	% Yld.	mp. (°C)	Analyses calc. fd.	^{1}H NMR Data (δ in $CDCL_3$, ppm)
a	CH_3	30	68	97.0–99.0	C: 58.59 58.36 H: 4.69 4.76	7.88–7.05(m, 12H), 6.22(t, 1H), 4.22(d, 2H), 4.01(s, 2H), 2.37(s, 6H)
b	H	60	60	146.0–147.0	C: 57.02 56.82 H: 4.13 4.23	8.10–7.33(m, 14H), 6.43(t, 1H), 4.37(d, 2H), 4.27(s, 2H)
c	Cl	10	66	152.0–153.0	C: 49.91 50.07 H: 3.25 3.37	8.03–6.97(m, 12H), 6.23(t, 1H), 4.70(s, 2H), 4.47(d, 2H)
d	Br	10	59	150.0–151.0	C: 42.99 42.79 H: 2.80 2.77	8.01–7.02(m, 12H), 6.30(t, 1H), 4.73(s, 2H), 3.68(d, 2H)

TABLE IV

Vinyl sulfides **13**.

Compd. No. **13**	*R*	*R* × *n*. Time (min.)	% Yld.	mp. (°C)	Analyses calc. fd.	^{1}H NMR Data (δ in $CDCl_3$, ppm)
a	CH_3	10	71	167.0–168.0	C: 60.34 60.09 H: 5.03 5.02	7.88–6.97(m, 8H), 5.78(t, 1H), 4.08(d, 2H), 2.35(s, 3H), 2.05(s, 3H)
b	H	20	84	138.5–139.5	C: 59.30 59.18 H: 4.66 4.73	7.97–7.00(m, 9H), 5.85(t, 1H), 4.23(d, 2H), 2.07(s, 3H)
c	Cl	10	78	184.0–185.0	C: 53.97 54.18 H: 3.97 3.95	8.07–6.70(m, 8H), 5.88(t, 1H), 4.38(d, 2H), 2.03(s, 3H)
d	Br	10	78	186.0–188.0	C: 48.23 48.44 H: 3.55 3.66	8.00–7.03(m, 8H), 5.88(t, 1H), 4.38(d, 2H), 2.07(s, 3H)

TABLE V

Thiazolidines **14**.

Compd. No. **14**	*R*	(min.)	Yld.	mp. (°C)	Analyses calc. fd.	^{1}H NMR Data (δ in $CDCL_3$, ppm)
a	CH_3	180	90	129.5–131.0	C: 60.34 60.58 H: 5.03 5.10	7.93–6.93(m, 8H), 4.93–4.03(m, 2H) 3.73–3.00(m, 2H), 2.43(s, 3H), 1.67(d, 3H)
b	H	180	70	103.0–104.0	C: 59.30 59.28 H: 4.65 4.53	8.03–6.87(m, 9H), 4.97–4.30(m, 2H), 3.77–3.03(m, 2H), 1.70(d, 3H)
c	Cl	60	85	157.5–159.0	C: 53.97 54.35 H: 3.97 3.88	8.23–7.00(m, 8H), 5.17–4.27(m, 2H), 4.10–3.80(m, 2H), 1.51(d, 3H)
d	Br	90	80	130.5–132.0	C: 48.23 48.32 H: 3.55 3.54	7.83–6.87(m, 8H), 4.57–4.20(m, 2H), 3.70–2.10(m, 2H), 1.60(d, 3H)

TLC—7 ml benzene, 6 ml acetone—for the disappearance of starting material.) After the starting material was consumed, the reaction mixture was diluted with benzene (300 ml) and washed with water (6 × 250 ml) to remove the DMF. The washed solution was dried (Na_2SO_4) and concentrated *in vacuo* to ca. 30 ml. The concentrate was chilled and the crude product precipitated in ca. 60% yield when pet. ether was added dropwise (ca. 2 ml). The material was purified by recrystallization from benzene/pet. ether. This and the other analogously obtained compounds are listed in the accompanying table (see Table V).

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