purification. Linde molecular sieves were purchased from Alpha Chemicals, Danvers, Mass. Neutral alumina was purchased from Bio-Rad Laboratories (AG-7, 100–200 mesh) and used as obtained. Toluene was dried by distillation from sodium and benzophenone under a nitrogen atmosphere. All ^1H NMR and IR spectra were recorded using Varian A-60 and Beckman Acculab 7 spectrometers, respectively. Product mixtures were analyzed by GLC on a Hewlett Packard Model 5830A flame ionization instrument. Culture tubes were used as reaction vessels (25 × 150 mm Corning no. 9826 tubes) and were equipped with a Teflon-lined screw cap and a Teflon-coated magnetic stirring bar.

Impregnation of NaCN on Alumina (Reagent 1). A 50-mL round-bottom flask was charged with 2.0 g (40.8 mmol) of sodium cyanide dissolved in 5 mL of distilled water, and 4.0 g of neutral alumina was added to it in one portion. The flask was transferred to a rotary evaporator, and water was removed under reduced pressure, keeping the bath temperature below 65 °C. Impregnated alumina was then dried [4 h, 110 °C (0.05 mm)].

General Procedure for Small-Scale Reactions. Procedures similar to that described for the conversion of 1-bromooctane to 1-cyanooctane were followed for all of the small-scale reactions described in Table II. A mixture of 0.19 g (1.0 mmol) of 1-bromooctane, 1.49 g of 1, 4.0 mL of toluene, and an internal standard was placed in a 25 × 150 mm Corning no. 9826 culture tube equipped with a Teflon-coated magnetic stirring bar. The flask was placed in an oil bath (90 °C), stirred for 24 h, withdrawn, and cooled to room temperature. The liquid phase was analyzed using a UCW-982 on Chromosorb W column.

Conversion of 1-Bromododecane to 1-Cyanododecane. A mixture of 2.5 g (10.0 mmol) of 1-bromododecane, 15.0 g of 1, and 30 mL of toluene was placed in a 100-mL round-bottom flask and stirred with a Teflon-coated magnetic stirring bar for 45 h at 90 °C. The nitrile product was isolated by filtering the mixture, washing the spent and unused reagent with 100 mL of toluene, and removing the solvent from the combined filtrate under reduced pressure to yield 1.96 g (100%) of 1-cyanododecane, obtained as a colorless liquid. The infrared and NMR spectra were identical with those of an authentic sample.

Registry No.—1-Bromobutane, 109-65-9; 1-chlorobutane, 109-69-3; 1-iodooctane, 629-27-6; 1-bromooctane, 111-83-1; 1-chlorooctane, 111-85-3; 1-bromododecane, 143-15-7; 1-chlorododecane, 112-52-7; 2-bromooctane, 557-35-7; 1-cyanobutane, 110-59-8; 1-cyanooctane, 2243-27-8; 1-cyanododecane, 629-60-7; 2-cyanooctane, 2570-96-9; NaCN, 143-33-9; alumina, 1344-28-1.

References and Notes

(1) Supported by the National Science Foundation (Grant No. CHE-77-28366).
(2) Regen, S. L.; Koteel, C. *J. Am. Chem. Soc.* **1977**, *99*, 3837.
(3) Acetonitrile has also been examined as a solvent and found to give greater reaction rates. However, we have observed significant displacement using sodium cyanide in the absence of alumina with this more polar solvent.[4]
(4) Cook, F. L.; Bowers, C. W.; Liotta, C. L. *J. Org. Chem.* **1974**, *39*, 3416.
(5) A control experiment carried out in which reagent **1** was replaced by finely ground NaCN plus nonimpregnated alumina (used as obtained or dried prior to reaction [4 h, 110 °C (0.05 mm)]) did show significant displacement. However, the yield of nitrile was consistently low, and, in contrast to **1**, the experiment gave substantial amounts of 1-octanol plus an unidentified side product. A further control experiment in which **1** was replaced by an aqueous sodium cyanide solution plus nonimpregnated alumina showed no evidence of displacement after heating for 24 h at 90 °C.
(6) Shaw, J. E.; Hsia, D. Y.; Parries, G. S.; Sawyer, T. K. *J. Org. Chem.* **1978**, *43*, 1017.
(7) Surprisingly, 1-iodooctane was much less reactive toward **1** than 1-bromooctane. The origin of this unusual selectivity is not clear at present and is under investigation.

Indole Syntheses with *o*-Tolyl Isocyanide. 3-Acylindoles and 2-Substituted Indoles

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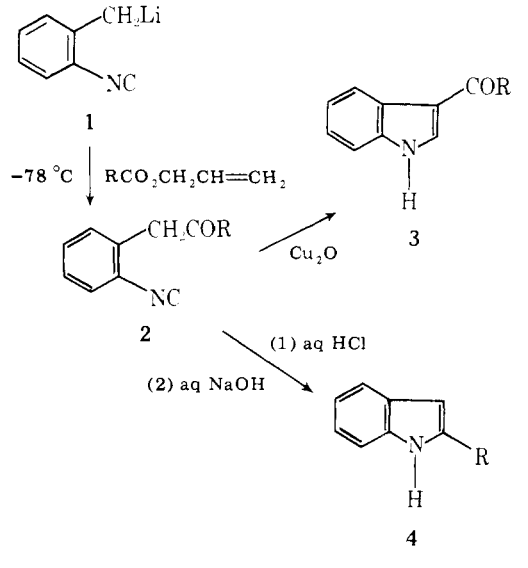
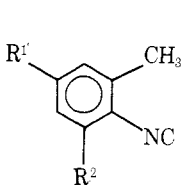
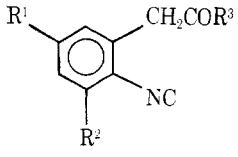
In the preceding paper we described syntheses of some indole derivatives by elaboration of *o*-(lithiomethyl)phenyl isocyanide (1) with electrophiles such as alkyl halides,[1] alkylene oxides,[1] and isocyanates,[2] followed by cyclization. Herein, we wish to report that acylation of the ortho methyl group of *o*-tolyl isocyanide can be best performed by treating *o*-(lithiomethyl)phenyl isocyanide (1) with allyl carboxylates and that *o*-(acylmethyl)phenyl isocyanides (2) thus prepared were readily converted to 3-acylindoles (3) and 2-alkyl(or 2-aryl)indoles (4). Preparation of 3-acylindoles (3) and 2-substituted indoles (4) by the previous methods[3,4] is not always satisfactory in respect to the yields and the reaction conditions. The present reaction provides a convenient synthetic method for preparation of 3-acylindoles and 2-alkyl(or 2-aryl)indoles starting with *o*-tolyl isocyanide,[5] which is readily prepared from commercially available *o*-toluidine.



Acylation of *o*-tolyl isocyanide was successfully carried out by treating a solution of *o*-(lithiomethyl)phenyl isocyanide[1] in diglyme, which was generated at −78 °C from *o*-tolyl isocyanide and 2 equiv of lithium diisopropylamide (LDA), with 2 equiv of allyl carboxylate. Use of an acyl halide instead of an allyl carboxylate gave unsatisfactory results. Acylations of the ortho methyl group of 4-chloro-2-methylphenyl isocyanide, 2,4-dimethylphenyl isocyanide, and 2,6-dimethylphenyl isocyanide could be similarly carried out, producing the corresponding *o*-(acylmethyl)phenyl isocyanides **2** in moderate yields. Some results on the acylations of *o*-methylphenyl isocyanides are summarized in Table I.

Table I. Acylations of the Ortho Methyl Group of *o*-Methylphenyl Isocyanides



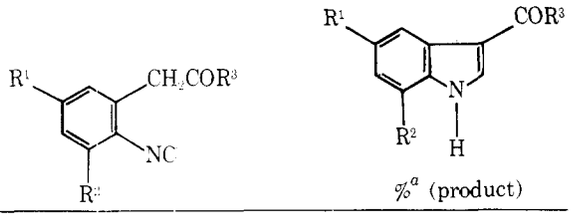


$R^3CO_2CH_2$-CH=CH_2	% [a] (product)
R^1 = H, R^2 = H; R^3 = CH_3	48 (**2-i**)
R^1 = H, R^2 = H; R^3 = n-C_3H_7	57 (**2-ii**)
R^1 = H, R^2 = H; R^3 = i-C_4H_9	55 (**2-iii**)
R^1 = H, R^2 = H; R^3 = t-C_4H_9	57 (**2-iv**)
R^1 = H, R^2 = H; R^3 = n-C_7H_{15}	71 (**2-v**)
R^1 = H, R^2 = H; R^3 = Ph	95 (**2-vi**)
R^1 = Cl, R^2 = H; R^3 = t-C_4H_9	48 (**2-vii**)
R^1 = CH_3, R^2 = H; R^3 = i-C_4H_9	62 (**2-viii**)
R^1 = CH_3, R^2 = H; R^3 = t-C_4H_9	50 (**2-ix**)
R^1 = CH_3, R^2 = H; R^3 = Ph	72 (**2-x**)
R^1 = H, R^2 = CH_3; R^3 = t-C_4H_9	63 (**2-xi**)

[a] Isolated yields.

0022-3263/79/1944-2030$01.00/0

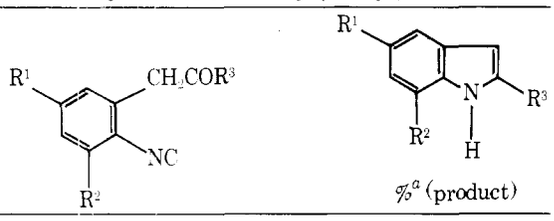
Table II. Syntheses of 3-Acylindoles



	%[a] (product)
R^1 = H, R^2 = H, R^3 = CH_3 (**2-i**)	80 (**3-i**)[b]
R^1 = H, R^2 = H, R^3 = n-C_3H_7 (**2-ii**)	71 (**3-ii**)
R^1 = H, R^2 = H, R^3 = i-C_4H_9 (**2-iii**)	71 (**3-iii**)
R^1 = H, R^2 = H, R^3 = t-C_4H_9 (**2-iv**)	60 (**3-iv**)
R^1 = H, R^2 = H, R^3 = n-C_7H_{15} (**2-v**)	68 (**3-v**)
R^1 = H, R^2 = H, R^3 = Ph (**2-vi**)	80 (**3-vi**)[c]
R^1 = CH_3, R^2 = H, R^3 = i-C_4H_9 (**2-viii**)	63 (**3-viii**)
R^1 = CH_3, R^2 = H, R^3 = Ph (**2-x**)	71 (**3-x**)
R^1 = H, R^2 = CH_3, R^3 = t-C_4H_9 (**2-xi**)	85 (**3-xi**)

[a] Isolated yields. [b] Reference 3a. [c] Reference 3b.

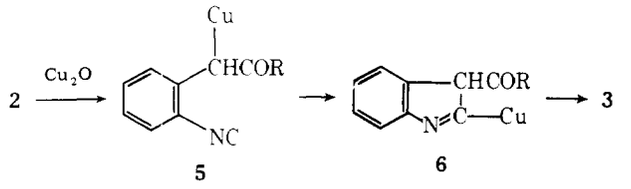
Table III. Syntheses of 2-Alkyl(2-Aryl)indoles



	%[a] (product)
R^1 = H, R^2 = H, R^3 = i-C_4H_9 (**2-iii**)	60 (**4-iii**)[b]
R^1 = H, R^2 = H, R^3 = t-C_4H_9 (**2-iv**)	79 (**4-iv**)[c]
R^1 = H, R^2 = H, R^3 = n-C_7H_{15} (**2-v**)	63 (**4-v**)
R^1 = H, R^2 = H, R^3 = Ph (**2-vi**)	85 (**4-vi**)[d]
R^1 = Cl, R^2 = H, R^3 = t-C_4H_9 (**2-vii**)	43 (**4-vii**)
R^1 = CH_3, R^2 = H, R^3 = t-C_4H_9 (**2-ix**)	64 (**4-ix**)[b]
R^1 = CH_3, R^2 = H, R^3 = Ph (**2-x**)	61 (**4-x**)[e]
R^1 = H, R^2 = CH_3, R^3 = t-C_4H_9 (**2-xi**)	82(**4-xi**)

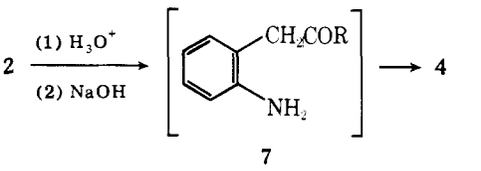
[a] Isolated yields. [b] Reference 8. [c] Reference 9. [d] Reference 10. [e] Reference 10b.

Unlike o-isocyanophenyl acetates[1] and N-substituted o-isocyanophenylacetamides,[2] o-(acylmethyl)phenyl isocyanides (**2**) could not be converted to 3-acylindoles by means of the benzylic lithiation of **2** with n-butyllithium. However, the cyclization of **2** was efficiently catalyzed with Cu_2O to produce 3-acylindoles (**3**) in moderate to fair yields. For instance, when a mixture of o-(acetylmethyl)phenyl isocyanide (**2-i**) and ~15 mol % of Cu_2O in benzene was heated at reflux for 2 h under nitrogen, 3-acetylindole was produced in 80% yield, which was identified by comparison of its IR spectrum with that[6] of an authentic sample. Syntheses of 3-acylindoles are summarized in Table II. The Cu_2O-catalyzed cyclization of **2** may be explained in terms of intramolecular isonitrile insertion into the copper–carbon linkage of organocopper(I) **5**, which is assumed to be a key intermediate.[7]



5 **6**

It is well known that the isocyano group readily undergoes acid hydrolysis to produce a primary amine. Now we have found that acid hydrolysis of o-(acylmethyl)phenyl isocyanides followed by neutralization with alkali affords 2-alkyl(or 2-aryl)indoles in moderate yields (Table III).



7

Experimental Section

Diglyme, diisopropylamine, and benzene were dried over sodium and distilled under nitrogen. Allyl carboxylates were prepared from acyl halides and allyl alcohol and distilled under nitrogen. Aryl isocyanides were prepared from the corresponding N-arylformamide according to Ugi's procedure.[5] Cu_2O was commercially available and dried in vacuo prior to use.

General Procedure for Preparation of o-(Acylmethyl)phenyl Isocyanide (2). To a stirring solution of o-(lithiomethyl)phenyl isocyanide (1.5 mmol) in 4 mL of diglyme at −78 °C prepared according to the reported procedure[1] was added dropwise 384 mg (3.0 mmol) of allyl butyrate. After the reaction mixture was stirred at the same temperature for 10 min, it was quenched with aqueous NH_4Cl and extracted with ether. The ether solution was evaporated and distilled to afford o-(n-butyroylmethyl)phenyl isocyanide (**2-ii**) [bp 82 °C (0.4 mm)] in 57% yield: IR (neat) 2115, 1713 cm^{-1}; NMR (CCl_4 with Me_4Si) δ 0.96 (t, 3 H), 1.70 (m, 2 H), 2.54 (t, 2 H), 3.84 (s, 2 H), 7.27 (m, 4 H).

2-i: bp 105 °C (1 mm); IR (neat) 2120, 1714 cm^{-1}; NMR (CCl_4 with Me_4Si) δ 2.19 (s, 3 H), 3.78 (s, 2 H), 7.22 (m, 4 H).

2-iii: bp 108 °C (0.4 mm); IR (neat) 2120, 1718 cm^{-1}; NMR (CCl_4 with Me_4Si) δ 0.93 (d, 6 H), 2.2 (m, 1 H), 2.35 (d, 2 H), 3.68 (s, 2 H), 7.13 (m, 4 H).

2-iv: bp 120 °C (0.4 mm); IR (neat) 2110, 1708 cm^{-1}; NMR (CCl_4 with Me_4Si) δ 1.36 (s, 9 H), 3.82 (s, 2 H), 7.16 (m, 4 H).

2-v: TLC on silica gel, R_f 0.52 (benzene); IR (neat) 2115, 1718 cm^{-1}; NMR ($CDCl_3$ with Me_4Si) δ 0.88 (t, 3 H), 1.2–1.8 (m, 10 H), 2.52 (t, 3 H), 3.80 (s, 2 H), 7.23 (m, 4 H).

2-vi: TLC on silica gel, R_f 0.41 (benzene); mp 89–91 °C; IR (KBr disk) 2125, 1681 cm^{-1}; NMR ($CDCl_3$ with Me_4Si) δ 4.38 (s, 2 H), 7.2–8.0 (m, 9 H).

2-vii: bp 110 ° (0.6 mm); IR (neat) 2125, 1710 cm^{-}; NMR (CCl_4 with Me_4Si) δ 1.20 (s, 9 H), 3.79 (s, 2 H), 7.0–7.2 (m, 3 H).

2-viii: bp 114 °C (0.4 mm); IR (neat) 2120, 1718 cm^{-1}; NMR (CCl_4 with Me_4Si) δ 0.97 (d, 6 H), 2.1 (m, 1 H), 2.35 (broad s, 5 H), 3.67 (s, 2 H), 6.9–7.2 (m, 3 H).

2-ix: bp 107 °C (0.6 mm); IR (neat) 2125, 1710 cm^{-1}; NMR ($CDCl_3$ with Me_4Si) δ 1.23 (s, 9 H), 2.16 (s, 3 H), 3.75 (s, 2 H), 6.7–7.0 (m, 3 H).

2-x: TLC on silica gel, R_f 0.50 (benzene); mp 87–90 °C; IR (KBr disk) 2120, 1678 cm^{-1}; NMR ($CDCl_3$ with Me_4Si) δ 2.32 (s, 3 H), 4.34 (s, 2 H), 7.0–8.1 (m, 9 H).

2-xi: mp 89–90 °C; IR (KBr disk) 2125, 1707 cm^{-1}; NMR (CCl_4 with Me_4Si) δ 1.15 (s, 9 H), 2.33 (s, 3 H), 3.76 (s, 2 H), 6.8–7.1 (m, 3 H).

General Procedure for Preparation of 3-Acylindoles (3). A mixture of 302 mg (1.5 mmol) of o-[(3-methylbutyroyl)methyl]phenyl isocyanide (**2-iii**) and 29 mg (0.2 mmol) of Cu_2O in 5 mL of benzene was heated at reflux for 2 h under nitrogen. The cyclization reaction was monitored by the disappearance of the characteristic IR band ($\nu_{N\equiv C}$) of the starting phenyl isocyanide in the reaction mixture. The reaction mixture was filtered to remove Cu_2O, and the filtrate was concentrated. The residue was chromatographed on silica gel with 1:1 $CHCl_3$–AcOEt to give 3-(isobutyroyl)indole (**3-iii**) (TLC, R_f 0.76): mp 135.5–137 °C, IR (KBr disk) 3170, 1629 cm^{-1}; NMR ($CDCl_3$ with Me_4Si) δ 0.97 (d, 6 H), 2.28 (m, 1 H), 2.59 (d, 2 H), 7.0–7.3 (m, 3 H), 7.71 (d, 1 H), 8.3 (m, 1 H), 9.4 (broad, 1 H).

3-i: TLC on silica gel, R_f 0.60 (4:1 AcOEt–$CHCl_3$); mp 194 °C; IR (KBr disk) 3150, 1610 cm^{-1}; NMR ($CDCl_3$ with Me_4Si) δ 2.43 (s, 3 H), 6.9–7.2 (m, 3 H), 7.65 (d, 1 H), 8.2 (m, 1 H), 9.0 (broad, 1 H).

3-ii: TLC on silica gel, R_f 0.71 (1:1 $CHCl_3$–AcOEt); mp 181–183 °C; IR (KBr disk) 3150, 1614 cm^{-1}; NMR ($CDCl_3$ with Me_4Si) δ 1.01 (t, 3 H), 1.8 (m, 2 H), 2.84 (t, 2 H), 7.1–7.3 (m, 3 H), 7.75 (d, 1 H), 8.3 (m, 1 H), 9.0 (broad, 1 H).

3-iv: TLC on silica gel, R_f 0.73 (1:1 $CHCl_3$–AcOEt); mp 170 °C; IR (KBr disk) 3200, 1609 cm^{-1}; NMR ($CDCl_3$ with Me_4Si) δ 1.48 (s, 9 H), 7.1–7.4 (m, 3 H), 7.8 (d, 1 H), 8.4 (m, 1 H), 8.8 (broad, 1 H).

3-v: mp 170 °C; IR (KBr disk) 3150, 1614 cm^{-1}; NMR ($CDCl_3$ with Me_4Si) δ 0.84 (t, 3 H), 1.2–1.9 (m, 10 H), 2.80 (t, 2 H), 7.0–7.3 (m, 3 H), 7.82 (d, 1 H), 8.3 (m, 1 H), 9.0 (broad, 1 H).

3-vi: TLC on silica gel, R_f 0.37 (20:1 $CHCl_3$—acetone); mp 252 °C; IR (KBr disk) 3130, 1595 cm^{-1}; NMR (acetone-d_6) δ 6.6–8.0 (m, 11 H).

3-viii: TLC on silica gel, R_f 0.85 (1:1 $CHCl_3$–AcOEt); mp 177 °C; IR (KBr disk) 3200, 1615 cm^{-1}; NMR ($CDCl_3$ with Me_4Si) δ 0.99 (d, 6 H), 2.1 (m, 1 H), 2.43 (s, 2 H), 2.66 (d, 2 H), 7.1–7.2 (m, 2 H), 7.70 (d, 1 H), 8.23 (m, 1 H), 8.9 (broad, 1 H).

3-x: TLC on silica gel, R_f 0.56 (10:1 $CHCl_3$–AcOEt); mp 228 °C; IR (KBr disk) 3150, 1585 cm^{-1}; NMR (Me_2SO-d_6) δ 2.43 (s, 3 H), 6.9–7.9 (m, 8 H), 8.15 (m, 1 H), 11.3 (broad, 1 H).

3-xi: TLC on silica gel, R_f 0.47 ($CHCl_3$); mp 175–177 °C; IR (KBr disk) 3250, 1610 cm^{-1}; NMR (Me_2SO-d_6) δ 1.36 (s, 9 H), 2.49 (s, 3 H), 6.8–7.2 (m, 2 H), 8.0–8.3 (m, 2 H), 11.5 (broad, 1 H).

General Procedure for Preparation of 2-Alkyl(or 2- Aryl)-indoles (4). A mixture of 215 mg (1.0 mmol) of 2-(pivaloylmethyl)-6-methylphenyl isocyanide (**2-xi**) and 3 mL of 10% HCl in methanol–water (1:1) was stirred for 15 min at room temperature. Then the mixture was made alkaline by adding 10% aqueous NaOH and stirring for 15 min at room temperature. The reaction mixture was extracted with ether, and the ether extract was evaporated. The residue was chromatographed on silica gel with $CHCl_3$ to afford 2-*tert*-butyl-7-methylindole (**4-xi**) in 82% yield: TLC, R_f 0.89; mp 98–99 °C; IR (KBr disk) 3425 cm^{-1}; NMR (CCl_4 with Me_4Si) δ 1.29 (s, 9 H), 2.26 (s, 3 H), 5.90 (d, 1 H). 6.4–7.1 (m, 3 H), 7.3 (broad, 1 H).

4-iii: bp 115 °C (0.4 mm); IR (neat) 3390 cm^{-1}; NMR (CCl_4 with Me_4Si) δ 0.88 (d, 6 H), 1.8 (m, 1 H), 2.27 (d, 2 H), 5.90 (m, 1 H), 6.7–7.2 (m, 4 H), 7.4 (broad, 1 H).

4-iv: mp 74–76 °C; IR (KBr disk) 3420 cm^{-1}; NMR ($CDCl_3$ with Me_4Si) δ 1.37 (s, 9 H), 6.18 (d, 1 H), 6.9–7.5 (m, 4 H), 7.8 (broad, 1 H).

4-v: TLC on silica gel, R_f 0.81 ($CHCl_3$); mp 61 °C; IR (KBr disk) 3400 cm^{-1}; NMR ($CDCl_3$ with Me_4Si) δ 0.83 (t, 3 H), 1.1–1.8 (m, 10 H), 2.60 (t, 3 H), 6.05 (m, 1 H), 6.8–7.4 (m, 4 H), 7.6 (broad, 1 H).

4-vi: TLC on silica gel, R_f 0.83 (20:1 $CHCl_3$–AcOEt); mp 177 °C; IR (KBr disk) 3425 cm^{-1}; NMR ($CDCl_3$ with Me_4Si) δ 6.72 (m, 1 H), 6.9–7.7 (m, 10 H), 8.3 (broad, 1 H).

4-vii: TLC on silica gel, R_f 0.53 (2:1 $CHCl_3$–benzene); mp 62–66 °C; IR (KBr disk) 3430 cm^{-1}; NMR ($CDCl_3$ with Me_4Si) δ 1.30 (s, 9 H), 5.97 (d, 1 H), 6.95 (m, 2 H), 7.30 (m, 1 H), 7.8 (broad, 1 H).

4-ix: TLC on silica gel, R_f 0.88 (1:1 $CHCL_3$–benzene); mp 101–103 °C; IR (KBr disk) 3420 cm^{-1}; NMR ($CDCl_3$ with Me_4Si) δ 1.34 (s, 9 H), 2.29 (s, 3 H), 5.93 (d, 1 H), 6.5–7.1 (m, 3 H), 7.4 (broad, 1 H).

4-x: TLC on silica gel, R_f 0.80 ($CHCl_3$); mp 216–217 °C; IR (KBr disk) 3420 cm^{-1}; NMR (Me_2SO-d_6 with Me_4Si) δ 2.30 (s, 3 H), 6.46 (d, 1 H), 6.7–7.6 (m, 8 H), 10.7 (broad, 1 H).

Registry No.—**2-i,** 69622-45-3; **2-ii,** 69622-46-4; **2-iii,** 69622-47-5; **2-iv,** 69622-53-3; **2-v,** 69622-48-6; **2-vi,** 69622-49-7; **2-vii,** 69622-55-5; **2-viii,** 69622-50-0; **2-ix,** 69622-51-1; **2-x,** 69622-52-2; **2-xi,** 69622-54-4; **3-i,** 703-80-0; **3-ii,** 22582-67-8; **3-iii,** 69622-34-0; **3-iv,** 69622-35-1; **3-v,** 69622-36-2; **3-vi,** 15224-25-6; **3-viii,** 69622-37-3; **3-x,** 69622-38-4; **3-xi,** 69622-39-5; **4-iii,** 3623-86-7; **4-iv,** 1805-65-8; **4-v,** 54687-20-6; **4-vi,** 948-65-2; **4-vii,** 69622-40-8; **4-ix,** 69622-41-9; **4-x,** 13228-36-9; **4-xi,** 69622-42-0; $CH_3CO_2CH_2CH{=}CH_2$, 591-87-7; n-$C_3H_7CO_2$-$CH_2CH{=}CH_2$, 2051-78-7; i-$C_4H_9CO_2CH_2CH{=}CH_2$, 2835-39-4; t-$C_4H_9CO_2CH_2CH{=}CH_2$, 15784-26-6; n-$C_7H_{15}CO_2CH_2CH{=}CH_2$, 4230-97-1; $PhCO_2CH_2CH{=}CH_2$, 583-04-0; 1-isocyano-2-methylbenzene, 10468-64-1; 4-chloro-1-isocyano-2-methylbenzene, 60515-59-5; 1-isocyano-2,4-dimethylbenzene, 3100-93-4; 2-isocyano-1,3-dimethylbenzene, 2769-71-3.

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Novel Synthesis of 3,4-Dihydro-1*H*-2,1,3-benzothiadiazine 2,2-Dioxides

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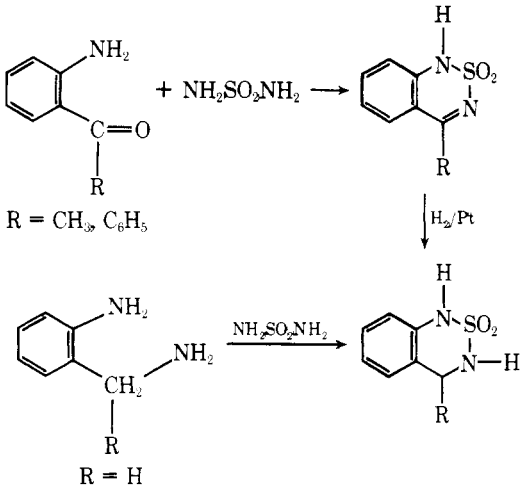
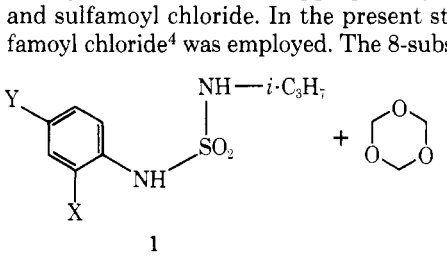
In 1965, Wright reported the first synthesis of 1*H*-2,1,3-benzothiadiazine 2,2-dioxides from the reaction of sulfamide with 2-aminobenzophenones and 2-aminoacetophenones.[1] Catalytic hydrogenation of the 1*H*-2,1,3-benzothiadiazine



2,2-dioxides in acetic acid solution using Adams catalyst gave the 3,4-dihydro derivative. 3,4-Dihydro-1*H*-2,1,3-benzothiadiazine 2,2-dioxides have also been prepared from the reaction of 2-aminobenzylamines with either sulfuryl chloride[2] or sulfamide.[3] We wish to report here a novel synthesis of 3,4-dihydro-1*H*-2,1,3-benzothiadiazine 2,2-dioxides involving cyclization by intramolecular sulfonylamidomethylation. We have found that the reaction of trioxane with *N*-aryl-*N'*-alkylsulfamides in methanesulfonic acid–methylene chloride solution at ice bath to room temperature provides a facile method for the preparation of a number of the substituted title compounds (see Table I). The sulfamide precursors are readily available from the appropriately substituted aniline and sulfamoyl chloride. In the present study, isopropylsulfamoyl chloride[4] was employed. The 8-substituted derivatives



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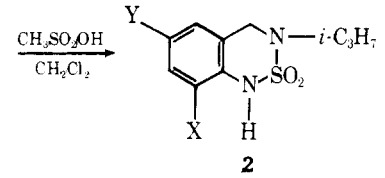

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readily undergo nitration or bromination in the 6 position. In the presence of a tertiary base, the N–H moiety is acetylated.

A comparison of the present cyclization with the phenylmethanesulfonamide system described by Orazi and Corral is of interest.[5] The kinetic product **3** is obtained in 54% yield after 2 min at 35 °C whereas the thermodynamic product **4** was obtained in 67% after 3 h. The formation of a triazine was not observed in the present study. The trimerization of the

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