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BASE-INDUCED GENERATION OF ARYL(1,2,3-TRIAZOL-1-YL)CARBENES FROM 1-[(*N*-PHENYL-SULFONYL)BENZOHYDRAZONOYL]-1,2,3-TRIAZOLES AND THEIR RING ENLARGEMENT TO 3-ARYL-1,2,4-TRIAZINES

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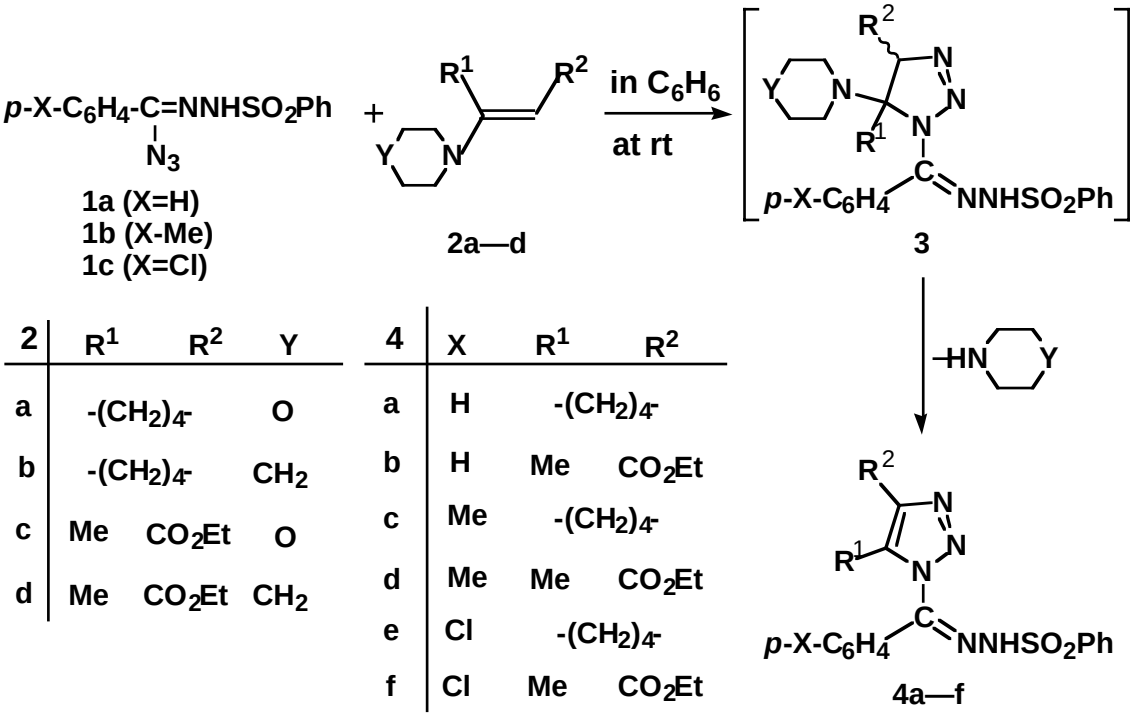
Abstract-The Bamford-Stevens reactions of 1-[*N*-(phenylsulfonyl)-benzohydrazonoyl]-1,2,3-triazole derivatives, readily available from the 1,3-dipolar cycloadditions of *N*-(phenylsulfonyl)benzohydrazonoyl azides with enamines, were examined and the transformation from aryl(1,2,3-triazol-1-yl)carbene intermediates to the corresponding 3-aryl-1,2,4-triazine derivatives was first observed.

Recently much attention have been paid to the preparation of 1,2,4-triazines because of their biological activities. For example, natural antibiotics such as pyrimido[5,4-*e*][1,2,4]triazines, and 4-amino-6-*tert*-butyl-3-methylmercapto-4,5-dihydro-1,2,4-triazin-5-one are used as herbicide[1] and 3,5-disubstituted 1,2,4-triazines are expected their potential activity as its aza analogs of pyrimidine nucleoside bases.[2] There are many preparative methods for 1,2,4-triazine derivatives.[3] Among them, the most convenient and widely used method is the condensation of amidrazones with 1,2-dicarbonyl compounds,[4] and some of the other methods are only variations of this reaction. In connection with our investigation for developing new synthetic utility of arylsulfonylhydrazone derivatives,[5] we interested in the generation of the title carbenes from the Bamford-Stevens reactions[6] of 1-[(*N*-phenylsulfonyl)benzohydrazonoyl]-1,2,3-triazoles. In this paper we report a novel ring-enlargement reaction of aryl(1,2,3-triazol-1-yl)carbenes to 3-aryl-1,2,4-triazines.

The carbene precursors, 1-[*N*-(phenylsulfonyl)benzohydrazonoyl]-1,2,3-triazole derivatives (**4a**—**f**), were synthesized in low to moderate yields (13–69%) by the 1,3-dipolar cycloadditions of *N*-(phenylsulfonyl)benzohydrazonoyl azides (**1a**—**c**) with 1-morpholinocyclohexene (**2a**) or

ethyl 3-morpholinocrotonate (**2c**) in dry benzene at room temperature, followed by the aromatization with the elimination of morpholine. The same products (**4a**—**f**) were also obtained in 15–75% yields from the reactions of azides (**1a**—**c**) with 1-piperidinocyclohexene (**2b**) or ethyl 3-piperidinocrotonate (**2d**). (Scheme 1) The yields of these reactions using 1-morpholinocyclohexene (**2a**) and 1-piperidinocyclohexene (**2b**) as an enamine were better than those using ethyl 3-morpholinocrotonate (**2c**) and ethyl 3-piperidinocrotonate (**2d**). The use of the solvent such as chloroform, acetonitrile, and THF or the reactions in dry benzene at elevated temperature (50°C) caused the decreased yields of the products (**4a**—**f**). In these reactions the primary 1,3-dipolar adducts such as **3** could not be obtained at all. This must be due to the smooth aromatization of the adducts (**3**) to aromatic 1,2,3-triazoles (**4a**—**f**).



2	R^1	R^2	Y
a	-$(CH_2)_4$-		O
b	-$(CH_2)_4$-		CH_2
c	Me	CO_2Et	O
d	Me	CO_2Et	CH_2

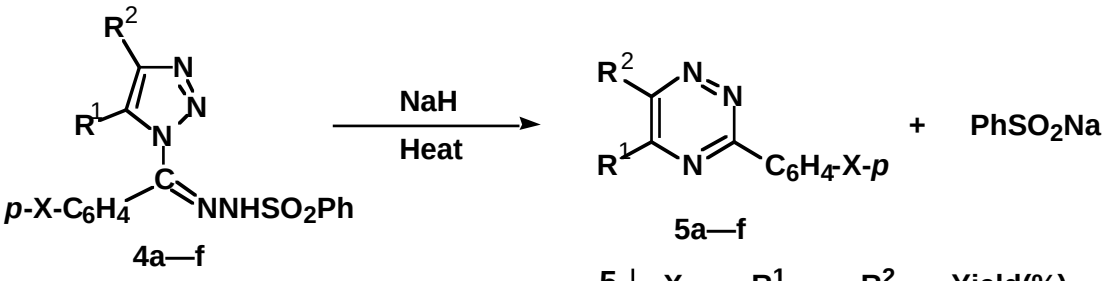
4	X	R^1	R^2
a	H	-$(CH_2)_4$-	
b	H	Me	CO_2Et
c	Me	-$(CH_2)_4$-	
d	Me	Me	CO_2Et
e	Cl	-$(CH_2)_4$-	
f	Cl	Me	CO_2Et

Scheme 1.

The structural assignment for these 1,2,3-triazoles (**4a**—**f**) was mainly accomplished by their analytical and spectral means, and the regioselectivity in adducts (**4b**,**d**,**f**) from azides (**1a**–**c**) and enamines (**2c**,**d**) was determined according to the orientation reported for the reactions of azides with enamines.[7] For example, the elemental analyses for adducts (**4a**—**f**) were in good accord with our proposed compositions and IR spectra clearly exhibited an amino absorption band at 3130–3190 cm^{-1} and two sulfonyl bands at 1155–1182 and 1355–1360 cm^{-1}, respectively, due to the phenylsulfonylhydrazone moiety. The lowered chemical shifts (δ near 2.4) for the 5-methyl group in NMR spectra of **4b**,**d**,**f** indicated that this substituent is on an aromatic carbon of 1,2,3-triazole ring, and no proton signal for a morpholino or piperidino group was observed.

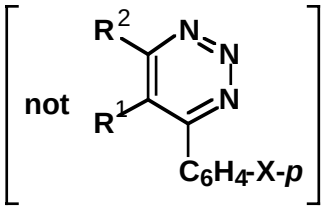
When 1-[*N*-(phenylsulfonyl)benzohydrazonoyl]-1,2,3-triazole derivatives (**4a**—**f**) was heated

with small excess sodium hydride in dry benzene at the reflux temperature under nitrogen, the reaction solution was turned gradually to yellow with the generation of the precipitation of sodium benzenesulfinate. After removal of the insoluble substances by filtration, the chromatographic separation (silica gel) of the reaction mixtures afforded crystalline products, 3-aryl-1,2,4-triazines (**5a**–**f**) in moderate yields (28–54%), together with small amount of unidentified oil. (Scheme 2) Though the insertion reaction of acetyl benzotriazinyl carbene, generated by flash vapor pyrolysis of the corresponding phosphor ylide, on the α-carbon and the α-nitrogen are reported,[8] possible alternatives, 4-aryl-1,2,3-triazines, such as **6** and/or their decomposed products were not detected at all.[9]



4a—f 5a—f

5	X	R^1	R^2	Yield(%)
a	H	-$(CH_2)_4$-		42
b	H	Me	CO_2Et	33
c	Me	-$(CH_2)_4$-		28
d	Me	Me	CO_2Et	54
e	Cl	-$(CH_2)_4$-		51
f	Cl	Me	CO_2Et	28



6

Scheme 2

The elementary analyses for products (**5a**–**f**) were in good accord with our proposed compositions and the IR and ^{1}H-NMR spectra also supported this 1,2,4-triazine structure. For example, the IR spectra of 5,6,7,8-tetrahydro-1,2,4-benzotriazines (**5a**,**c**,**e**) exhibited a characteristic methylene stretching band near 2950 cm^{-1} and those of ethyl 1,2,4-triazine-5-carboxylates (**5b**,**d**,**f**) showed a strong carbonyl band near 1720 cm^{-1}, respectively. The ^{1}H-NMR spectra of **5a**,**c**,**e** showed two sets of proton signals due to each two methylene groups α and β to the aromatic 1,2,4-triazine ring near δ 2.70—3.40 and 1.70—2.25, together with other methyl (near δ 2.5) and/or aromatic proton signals. Similarly, the lowered methyl proton singlet near δ 2.9 in the H^1-NMR spectra of **5b**,**d**,**f** is compatible with that of the methyl group on the heteroaromatic ring. The physical and spectral properties of 3-phenyl-5,6,7,8-tetrahydro-1,2,4-benzotriazine (**5a**) were completely coincided with those of authentic specimen.[10] Furthermore, the X-Ray analysis for **5c** was performed and 5,6,7,8-tetrahydro-1,2,4-benzotriazine structure was finally confirmed. The PLUTO drawing of **5c** was shown in Figure

1.

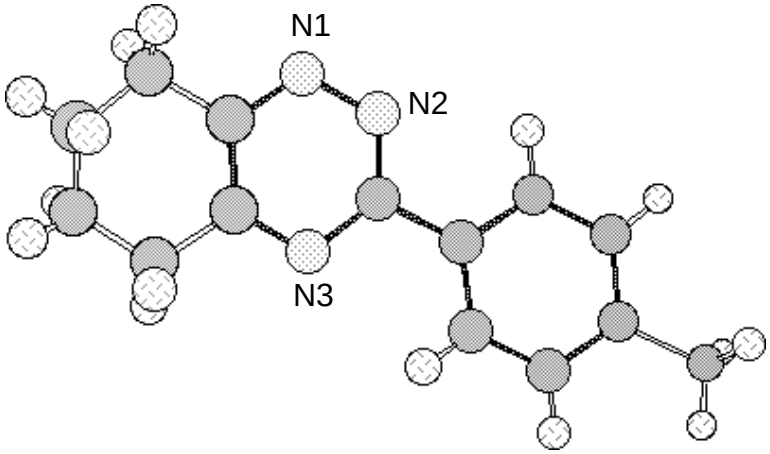
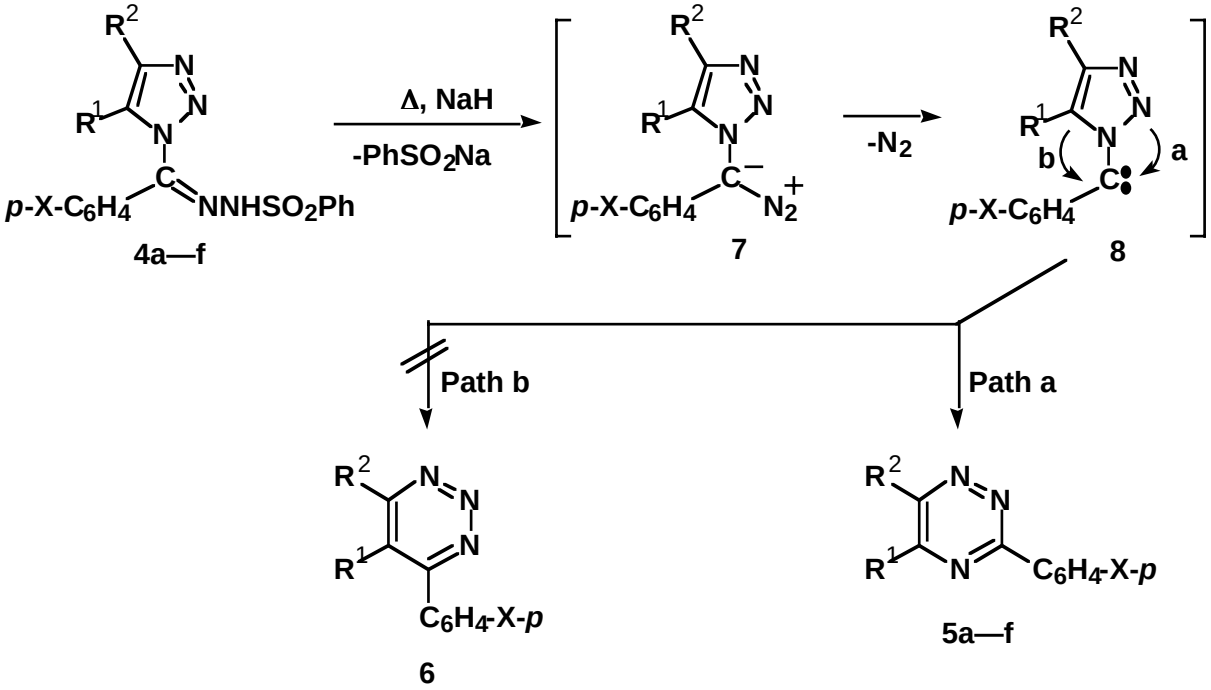


Figure 1 PLUTO drawing of 3-*p*-methylphenyl-5,6,7,8-tetrahydro-1,2,4-benzotriazine (**5c**)

The transformation of 1-benzohydrazonoyl-1,2,3-triazolles (**4a**—**f**) to 1,2,4-triazines (**5a**—**f**) can be considered to proceed *via* the formation and the decomposition of aryl(1,2,3-triazol-1-yl)diazomethanes (**7**) by Bamford-Stevens reaction, followed by the ring enlargement of the resulting aryl(1,2,3-triazol-1-yl)carbenes (**8**), as shown in Scheme 3. Since high electrophilicity of carbenes is well known,[11] the intramolecular attack of carbenes (**8**) to the 2-nitrogen (Path a) rather than the 5-carbon (Path b) is reasonable.



Scheme 3

EXPERIMENTAL

Melting points were measured with a Yanagimoto micromelting point apparatus and were not corrected. Microanalyses were carried out on a Perkin-Elmer 2400 elemental analyzer. The ^{1}H-NMR spectra were determined with a Hitachi R-600 spectrometer (60 MHz) in deuteriochloroform with tetramethylsilane as an internal standard; the chemical shifts are expressed in δ values. The IR spectra were taken with a JASCO FT/IR-5300 IR spectrophotometer.

Preparations of 1-(*N*-Phenylsulfonyl)benzohydrazonoyl-1,2,3-triazoles: *General Method*. A solution of *N*-(phenylsulfonyl)benzohydrazonoyl azide (**1**, 1.5 mmol) and enamine (**2**, 2.0 mmol) in dry benzene (15 mL) was allowed to react under stirring at rt for 1 day. After removal of the solvent from the reaction mixture, the residue was separated by column chromatography on silica gel using benzene-ether (1:1) as an eluent to afford the corresponding 1-[*N*-(phenylsulfonyl)benzohydrazonoyl]-1,2,3-triazole (**4**), but not a primary 1,3-dipolar cycloadduct (**3**), 1-[*N*-(phenylsulfonyl)benzohydrazonoyl]-4,5-dihydro-1,2,3-triazole (**3**), between azide (**1**) and enamine (**2**). The recrystallization from hexane-benzene gave pure **4**.

The use of chloroform, acetonitrile or THF as solvent at rt and the reactions in benzene at the elevated temperature (50℃) resulted in the reduced yields of **4**.

Some data for these reactions are as follows.

1-[(*N*-Phenylsulfonyl)benzohydrazonoyl]-4,5,6,7-tetrahydro-1,2,3-benzotriazole (4a): yield 42% (from **1a** and **2a**), yield 55% (from **1a** and **2b**), mp 174—175°C; IR (KBr) 3190, 1360, 1170 cm^{-1}; ^{1}H-NMR ($CDCl_3$) 1.8—2.8 (8H, m, 4xCH_2), 7.20—8.30 (10H, m, Ar-H), 9.70 (1H, br s, NH). *Anal.* Calcd for $C_{19}H_{19}N_5O_2S$: C, 59.83; H, 5.02; N, 18.36. Found: C, 59.75; H, 5.01; N, 18.43.

Ethyl 5-Methyl-1-[(*N*-phenylsulfonyl)benzohydrazonoyl]-1,2,3-triazole-4-carboxylate (4b): yield 13% (from **1a** and **2c**), yield 15% (from **1a** and **2d**), mp 161—162°C; IR (KBr) 3130, 1730, 1355, 1180 cm^{-1}; ^{1}H-NMR ($CDCl_3$) 1.44 (3H, t, *J*=7.0 Hz, $OCH_2C\underline{H}_3$), 2.40 (3H, s, 5-Me), 4.45 (2H, q, *J*=7.0 Hz, $OC\underline{H}_2CH_3$), 7.20—8.25 (10H, m, Ar-H), 9.05 (1H, br s, NH). *Anal.* Calcd for $C_{19}H_{19}N_5O_4S$: C, 55.20; H, 4.63; N, 16.94. Found: C, 55.03; H, 4.65; N, 16.71.

1-[(*N*-Phenylsulfonyl)(*p*-methylbenzo)hydrazonoyl]-4,5,6,7-tetrahydro-1,2,3-benzotriazole (4c): yield 69% (from **1b** and **2a**), yield 75% (from **1b** and **2b**), mp 187—188°C; IR (KBr) 3160, 1360, 1175 cm^{-1}; ^{1}H-NMR ($CDCl_3$) 1.65—3.00 (8H, m, 4xCH_2), 2.30 (3H, s, Ar-Me), 7.20—8.20 (9H, m, Ar-H), 9.80 (1H, br s, NH). *Anal.* Calcd for $C_{20}H_{21}N_5O_2S$: C, 60.74; H, 5.35; N, 17.71. Found: C, 60.81; H, 5.35; N, 17.77.

Ethyl 5-Methyl-1-[(*N*-phenylsulfonyl)(*p*-methylbenzo)hydrazonoyl]-1,2,3-triazole-4-carboxylate (4d): yield 23% (from **1b** and **2c**), yield 26% (from **1b** and **2d**), mp 184—185°C; IR (KBr) 3150, 1720, 1360, 1155 cm^{-1}; ^{1}H-NMR ($CDCl_3$) 1.43 (3H, t, *J*=7.0 Hz, $OCH_2C\underline{H}_3$), 2.37 (6H, s, 5-Me, Ar-Me), 4.42 (2H, q, *J*=7.0 Hz, $OC\underline{H}_2CH_3$), 7.10—8.15 (9H, m, Ar-

H), 9.05 (1H, br s, NH). *Anal.* Calcd for $C_{20}H_{21}N_5O_4S$: C, 56.19; H, 4.05; N, 16.38. Found: C, 55.95; H, 4.03; N, 16.59.

1-[(*N*-Phenylsulfonyl)(*p*-chlorobenzo)hydrazonoyl]-4,5,6,7-tetrahydro-1,2,3-benzotriazole (4e): yield 54% (from **1c** and **2a**), yield 41% (from **1c** and **2b**), mp 171—173°C; IR (KBr) 3193, 1360, 1175 cm^{-1}; ^{1}H-NMR ($CDCl_3$) 1.65—3.05 (8H, m, 4xCH_2), 7.25—8.15 (9H, m, Ar-H), 9.50 (1H, br s, NH). *Anal.* Calcd for $C_{19}H_{18}N_5O_2ClS$: C, 54.84; H, 4.36; N, 16.84. Found: C, 54.88; H, 4.35; N, 16.78.

Ethyl 5-Methyl-1-[(*N*-phenylsulfonyl)(*p*-chlorobenzo)hydrazonoyl]-1,2,3-triazole-4-carboxylate (4f): yield 31% (from **1c** and **2c**), yield 31% (from **1c** and **2d**), mp 168—169°C; IR (KBr) 3160, 1738, 1357, 1182 cm^{-1}; ^{1}H-NMR ($CDCl_3$) 1.44 (3H, t, *J*=7.0 Hz, $OCH_2C\underline{H}_3$), 2.40 (3H, s, 5-Me), 4.40 (2H, q, *J*=7.0 Hz, $OC\underline{H}_2CH_3$), 7.05—8.15 (9H, m, Ar-H), 9.00 (1H, br s, NH). *Anal.* Calcd for $C_{19}H_{18}N_5O_4ClS$: C, 50.95; H, 4.05; N, 15.64. Found: C, 50.94; H, 4.04; N, 15.66.

Preparations of 3-Aryl-1,2,4-triazines: *General Method*. A mixture of 1,2,3-triazoles (**4**, 1 mmol) and sodium hydride (60%, 60 mg, 1.5 mmol) in dry benzene (10 mL) was refluxed for 1—3 h under nitrogen atmosphere. With the progress of the reaction, the reaction solution was turned to yellow and sodium benzenesulfinate precipitated. After the removal of the insoluble substances, the reaction mixture was separated by column chromatography on silica gel using benzene to give 3-aryl-5,6,7,8-tetrahydro-1,2,4-benzotriazines (**5**) as pale yellow crystals, together with small amount of unidentified oil. Recrystallization from hexane-benzene (**5a**,**b**,**e**,**f**) or methanol-benzene (**5c**,**d**) provided pure products.

Physical and spectral data of 3-phenyl-5,6,7,8-tetrahydro-1,2,4-benzotriazine (**5a**) was completely in accord with an authentic sample which was prepared according to the literature.[10] Some data for these reactions are as follows.

3-Phenyl-5,6,7,8-tetrahydro-1,2,4-benzotriazine (**5a**): yield 42% (from **4a**), mp 93—94°C (lit.,[10] mp 93°C).

Ethyl 3-Phenyl-5-methyl-1,2,4-triazine-6-carboxylate (**5b**): yield 33% (from **4b**), mp 69—70°C, IR (KBr) 1721, 1598 cm^{-1}; ^{1}H-NMR ($CDCl_3$) 1.48 (3H, t, *J*=8.0 Hz, $OCH_2C\underline{H}_3$), 2.90 (3H, s, 5-Me), 4.50 (2H, q, *J*=8.0 Hz, $OC\underline{H}_2CH_3$), 7.33 (5H, br s, Ar-H). *Anal.* Calcd for $C_{13}H_{13}N_3O_2$: C, 64.18; H, 5.39; N, 17.28. Found: C, 64.10; H, 5.41; N, 17.19.

3-(*p*-Methylphenyl)-5,6,7,8-tetrahydro-1,2,4-benzotriazine (**5c**): yield 28% (from **4c**), mp 100—101°C, IR (KBr) 2953, 1610 cm^{-1}; ^{1}H-NMR ($CDCl_3$) 1.70—2.15 (4H, m, 2xCH_2), 2.47 (3H, s, Ar-Me), 2.80—3.30 (4H, m, 2xCH_2), 7.30 (2H, br d, *J*=8.0 Hz, Ar-H), 8.40 (2H, br d, *J*=8.0 Hz, Ar-H). *Anal.* Calcd for $C_{14}H_{15}N_3$: C, 74.64; H, 6.71; N, 18.65. Found: C, 74.42; H, 6.66; N, 18.92.

Ethyl 5-Methyl-3-(*p*-methylphenyl)-1,2,4-triazine-6-carboxylate (**5d**): yield 54% (from **4d**), mp 81—82°C, IR (KBr) 1714, 1610 cm^{-1}; ^{1}H-NMR ($CDCl_3$) 1.47 (3H, t, *J*=8.0 Hz, $OCH_2C\underline{H}_3$), 2.49 (3H, s, Ar-Me), 2.90 (3H, s, 5-Me), 4.45 (2H, q, *J*=8.0 Hz, $OC\underline{H}_2CH_3$), 7.40 (2H,

br d, *J*=8.0 Hz, Ar-H), 8.57 (2H, br d, *J*=8.0 Hz, Ar-H). *Anal.* Calcd for $C_{14}H_{15}N_3O_2$: C, 65.35; H, 5.88; N, 16.33. Found: C, 65.36; H, 5.95; N, 16.07.

3-(*p*-Chlorophenyl)-5,6,7,8-tetrahydro-1,2,4-benzotriazine (**5e**): yield 51% (from **4e**), mp 141—143°C, IR (KBr) 2945, 1590 cm^{-1}; ^{1}H-NMR ($CDCl_3$) 1.80—2.20 (4H, m, 2xCH_2), 2.75—3.35 (4H, m, 2xCH_2), 7.42 (2H, br d, *J*=8.0 Hz, Ar-H), 8.47 (2H, br d, *J*=8.0 Hz, Ar-H). *Anal.* Calcd for $C_{13}H_{12}N_3Cl$: C, 63.55; H, 4.92; N, 17.10. Found: C, 63.52; H, 4.94; N, 16.92.

Ethyl 3-(*p*-Chlorophenyl)-5-methyl-1,2,4-triazine-6-carboxylate (**5f**): yield 28% (from **4f**), mp 106—107°C, IR (KBr) 1726, 1591 cm^{-1}; ^{1}H-NMR ($CDCl_3$) 1.48 (3H, t, *J*=8.0 Hz, $OCH_2C\underline{H}_3$), 2.91 (3H, s, 5-Me), 4.52 (2H, q, *J*=8.0 Hz, $OC\underline{H}_2CH_3$), 7.41 (2H, br d, *J*=8.0 Hz, Ar-H), 8.68 (2H, br d, *J*=8.0 Hz, Ar-H). *Anal.* Calcd for $C_{13}H_{12}N_3O_2Cl$: C, 56.22; H, 4.36; N, 15.13. Found: C, 56.05; H, 4.26; N, 14.87.

Crystallography of 3-(*p*-Methylphenyl)-5,6,7,8-tetrahydro-1,2,4-benzotriazine (5c). A single crystal (0.18 x 0.40 x 0.46 mm) grown from chloroform was used for unit-cell determination and data collection on a Rigaku AFC5S four-circle diffractometer, with graphite-monochromated Mo*K*α radiation (λ=0.71069 Å). Crystal data of **4c**: $C_{14}H_{15}N_3$; *M*=225.29; monoclinic, space group $P2_1/n$ (#14), *Z*=4 with *a*=9.409 (7) Å, *b*=12.406 (4) Å, *c*=10.620 (7) Å; β=104.00 (5)°; *V*=1213 (1) $Å^3$, and D_{calc}=1.244 g/cm^3. All calculations were performed using the TEXSAN package.[12] The structure was solved by a direct method (MITHRIL).[13] The non-hydrogen atoms were refined anisotropically and the hydrogen atoms were refined isotropically. The final *R*- and R_w-factors after full-matrix least-squares refinements were 0.090 and 0.095, respectively, for 965 (I>2.00σ(I)) observed reflections.

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