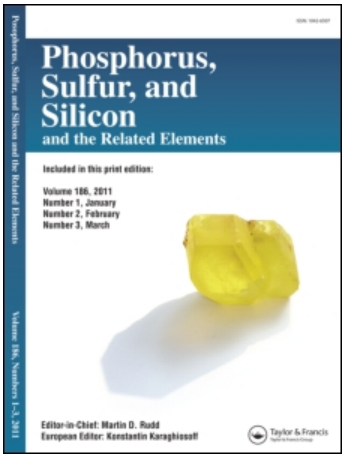

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1,3,4-THIADIAZOLO[3,2-a]BENZIMIDAZOLES AND *N*-AMINOBENZIMIDAZOLONES VIA RING TRANSFORMATIONS OF 3-(2-NITROARYL)-1,3,4-OXADIAZOL-2(3H)-ONES

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1,3,4-THIADIAZOLO[3,2-a]BENZIMIDAZOLES AND *N*-AMINOBENZIMIDAZOLONES VIA RING TRANSFORMATIONS OF 3-(2-NITROARYL)-1,3,4-OXADIAZOL-2(3H)-ONES

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The reaction of (3-(2-nitroaryl)-1,3,4-oxadiazol-2(3H)ones, **1**, with phosphorus pentasulfide in refluxing xylene leads to the formation in good yields of 1,3,4-thiadiazolo(3,2-a)benzimidazoles, **3**, which form water soluble methiodide salts. Chemical evidence in support of a reaction pathway is presented.

Key words: 3-(2-Nitroaryl)-1,3,4-oxadiazol-2(3H)-ones; Ring transformations; Phosphorus pentasulfide; 1,3,4-Thiadiazolo(3,2-a)benzimidazoles.

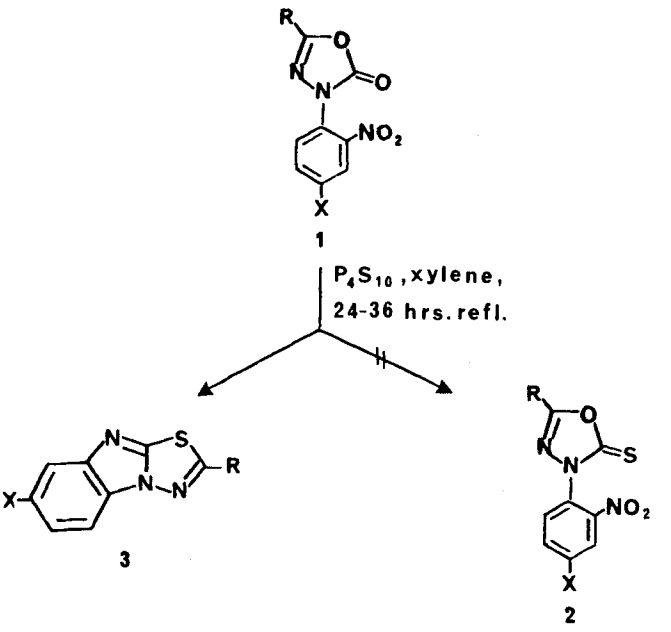
INTRODUCTION

The attempted preparation of the 2-thione **2b** from the corresponding 1,3,4-oxadiazol-2(3H)-one **1b** with phosphorus pentasulfide in refluxing xylene was unsuccessful. The 2-thione **2b** was not isolated as it underwent ring transformation leading to the isolation of the 1,3,4-thiaziazolo[3,2-a]benzimidazole derivative **3b**. In view of the novelty of this reaction, a brief study was carried out to examine the scope of the reaction.

RESULTS AND DISCUSSION

The reaction of the 3,5-disubstituted-1,3,4-oxadiazol-2(3H)-one **1a** with an excess of phosphorus pentasulfide (P_4S_{10}) in refluxing xylene (36 hrs) did not give the desired 2-thione **2a**. Instead, the 1,3,4-thiadiazolo[3,2-a]benzimidazole derivative **3a** was the only product, isolated in 35% yield by silica chromatography techniques. Both **1b** and **1c** reacted analogously with P_4S_{10} in refluxing xylene (24–36 hrs) to give **3b** and **3c** in 50% and 73% yield, respectively. When **3b** and **3c** were allowed to react with methyl iodide at room temperature, the water soluble methiodide salts, **4b** and **4c**, were isolated (Scheme 1, Table II, Experimental).

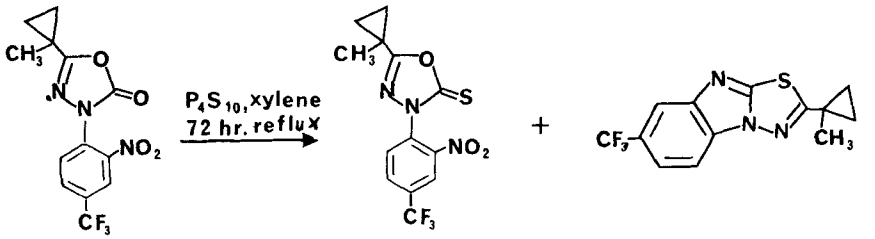
The reaction with P_4S_{10} of the oxadiazolone **1d** proceeded much more sluggishly in refluxing xylene. For example, after 72 hrs the reaction mixture contained the 2-thione **2d**, isolated in 19% yield, and the fused heterocycle, **3d** isolated in 29% yield.



1 3 2

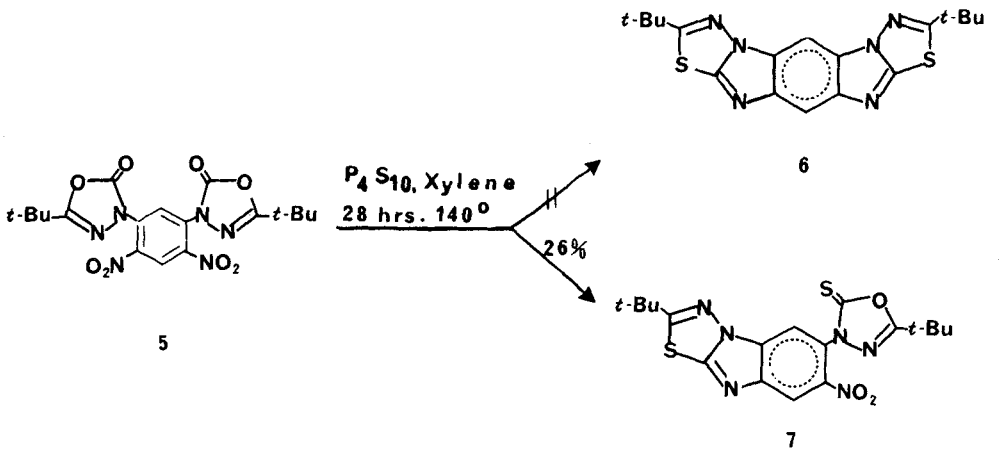
a: R=t-Bu, X=H; b: R=t-Bu, X=CF_3; c: R=CH_2-t-Bu, X=CF_3

Scheme 1



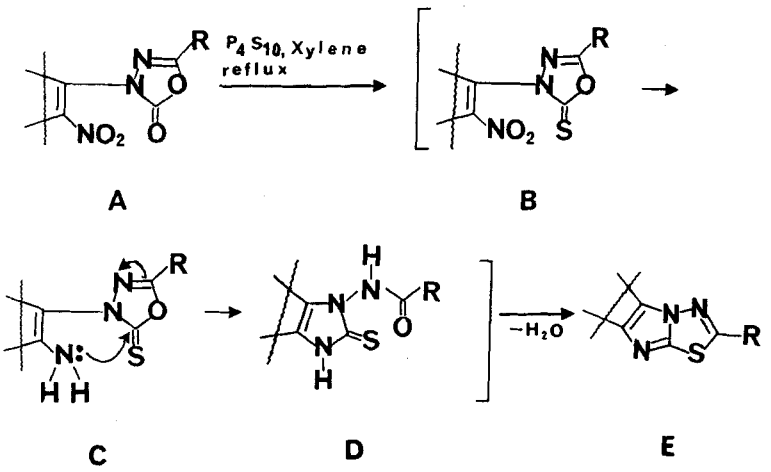
1d 2d (19%) 3d (29%)

Reaction of the "bis-oxadiazolone" **5** with P_4S_{10} in refluxing xylene was only partially successful. After 28 hrs, the reaction mixture still contained starting material **5** (9%). The only reaction product, isolated in 21% yield by silica chromatography techniques, was the highly insoluble heterocycle **7** (m.p. 247–248°). The structure of **7** follows from correct elemental analysis (C, H, N, S), its infrared spectrum (NO_2 1540 and 1320, and C=S 1460 cm^{-1}), and the chemical ionization mass spectrum which shows $(MH)^+$ at m/z 433. The inability to isolate or detect **6** resulting from the interaction of **7** with P_4S_{10} may be due to insolubility of **7** in refluxing xylene.



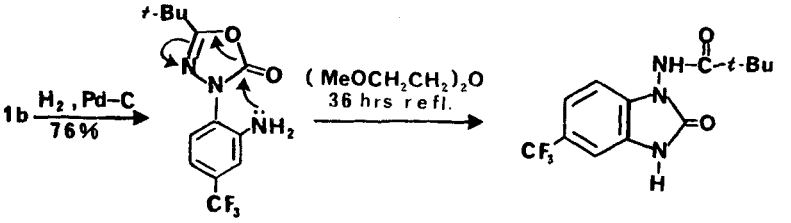
The conversion of the 3-(2-nitroaryl)-1,3,4-oxadiazol-2(3H)-ones of generalized structure **A** into 1,3,4-thiadiazolo(3,2-a)benzimidazoles **E** can be explained in terms of the mechanism outlined in Scheme 2. The proposed mechanism includes thiation (**A**→**B**), reduction, nitro to amino (**B**→**C**), internal nucleophilic attack by amino on (thio)carbonyl carbon leading to **D**, and dehydration (**D**→**E**).

The source of hydrogen for the second step (**B**→**C**) is the system P_4S_{10}-xylene. After an induction period of approximately 10 hrs, the system, P_4S_{10}-refluxing xylene, is beginning to generate hydrogen sulfide which, in turn, is capable of reducing the nitro group. The *ortho*-amino group is the required nucleophile for attack on (thio)carbonyl carbon to build up the dihydrobenzimidazole-2-thione ring system **D**. The dehydration step, **D**→**E**, completes the sequence.



Scheme 2. Reaction Mechanism

The *N*-amination of certain 4 (or 5)-substituted imidazoles and benzimidazoles can give two isomers. A distinction between isomers is often difficult.[1] The above reaction sequence, **C**→**D**, might offer an alternative to direct *N*-amination of benzimidazol-2-ones. In order to test the feasibility of this approach, the oxadiazolone **8** was heated in refluxing diethylene glycol dimethyl ether.[2] After 24 hrs, the desired N-pivaloyl derivative **9** was obtained in 29% yield from the dark reaction mixture by silica chromatography.



8 **9**

EXPERIMENTAL

Materials and Methods

Melting points were determined with a Thomas–Hoover capillary melting point apparatus and are uncorrected, as are boiling points. Routinely, reaction courses and product mixtures were monitored by thin layer chromatography (TLC) or gas–liquid chromatography (GLC). Thin layer separations were accomplished on silica gel GF^{254} plates with visualization by iodine vapor, phosphomolybdic acid spray, or UV light. Infrared (IR) spectra were measured on a Digilab FTS-15E or Beckman Acculab I spectrophotometer, and only pertinent and other strong absorptions are listed. Bruker WM-360 or General Electric QE-300 spectrometers were used to obtain nuclear magnetic resonance (NMR) data. Peak positions are given in ppm downfield from tetramethylsilane as an internal standard. Mass spectra were determined at 70 eV on a Finnigan 4000 spectrometer, either through gas chromatographic (GC/MS) or solid probe (SP/MS) sample introduction, and only the pertinent or more abundant fragment peaks are recorded. In the absence of clearly detectable molecular ions, chemical ionization (CI) using CH_4 was employed on the same instrument.

5-Substituted-1,3,4-oxadiazol-2(3H)-ones were prepared in analogy to published[3] methods by reaction of the corresponding hydrazide with phosgene. 5-(1,1-Dimethylethyl)-1,3,4-oxadiazol-2(3H)-one was obtained in 99% yield, b.p. 85–88° (0.01 mm). 5-(1-Methylcyclopropyl)-1,3,4-oxadiazol-2(3H)-one was obtained in 85% yield, m.p. 77–78°. 5-(2,2-Dimethylpropyl)-1,3,4-oxadiazol-2(3H)-one was obtained in 94% yield, m.p. 65–70°.

2-Chloronitrobenzenes reacted with these 5-substituted-1,3,4-oxadiazol-2(3H)-ones in the presence of sodium hydride to give the starting materials, **1** and **5**[3] (Table I). All reactions were carried out in DMF at ambient or elevated (80–100°) temperature. Products, **3** and **7** (Table II) were isolated by diluting the cooled reaction mixture with water, followed by filtration and crystallization or silica chromatography.

Representative examples are described below.

5-(1,1-Dimethylethyl)-3-[2-nitro-4-(trifluoromethyl)phenyl]-1,3,4-oxadiazol-2(3H)-one, **1b**. A mixture containing 14.2 g (0.1 mol) of 5-(1,1-dimethylbenzyl)-1,3,4-oxadiazol-2(3H)-one, 4.8 g (0.1 mol) of sodium hydride, 55% in oil, and 22.6 g (0.1 mol) of 4-chloro-3-nitrobenzotrifluoride in 200 ml DMF was gradually heated to 135° (0.4 hr), poured into ice water, neutralized (HCl), extracted with ether, dried, and concentrated. Recrystallization from ether-hexane (1:10) gave 21.5 g (65%) of **1b** light yellow leaflets; m.p. 90–92°; IR (KBr); ν 1800 (C=O), 1635 (C=), 1560 and 1330 (NO_2) cm^{-1}; ^1H NMR ($CDCl_3$); δ 1.4 (9H, s, $(CH_3)_3C$) and 8.0 (3H, m, $(CH=)_3$).

1,3-Dinitro-4,6-bis(5-(1,1-dimethylethyl)-1,3,4-oxadiazol-2(3H)-one-3-yl)benzene, **5**. This compound was prepared analogously from 1,3-dichloro-4,6-dinitrobenzene and 5-(1,1-dimethylethyl)-1,3,4-

TABLE I

3-(2-Nitroaryl)-5-subst.-1,3,4-oxadiazol-2(3H)-ones

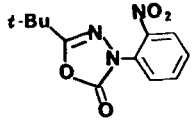
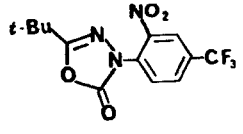
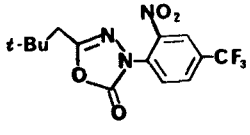
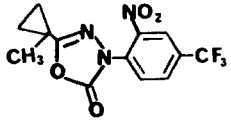
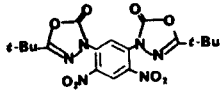
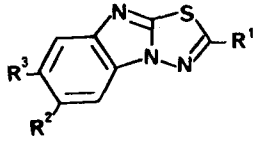
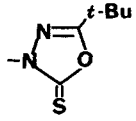
No. of compound	Structure	Formula (mol. wt.)	% Yield	MP, °C	C		H		N	
					Calcd	Fd	Calcd	Fd	Calcd	Fd
1a		$C_{12}H_{13}N_3O_4$ (263.24)	18	101–102	54.8	54.8	4.9	5.0	16.0	15.9
1b		$C_{13}H_{12}F_3N_3O_4$ (331.25)	65	90–92	47.1	46.9	3.6	3.6	12.7	12.9
1c		$C_{14}H_{14}F_3N_3O_4$ (345.27)	84	liq.	48.7	48.8	4.1	4.0	12.1	11.9
1d		$C_{13}H_{10}F_3N_3O_4$ (329.23)	81	67–68	47.4	47.3	3.0	3.1	12.8	12.9
5		$C_{18}H_{20}N_6O_8$ (448.39)	98	206–207	48.2	48.1	4.5	4.4	18.7	18.7

TABLE II

1,3,4-Thiadiazolo[3,2-a]benzimidazoles



No. of compound	R_1	R_2	R_3	Formula (mol. wt.)	% Yield	MP°C	C Calcd	C Fd	H Calcd	H Fd	N Calcd	N Fd	S Calcd	S Fd
3a	$C(CH_3)_3$	H	H	$C_{12}H_{13}N_3S$ (231.31)	35	oil	62.3	62.6	5.7	5.9	18.2	18.0	13.9	13.7
3b	$C(CH_3)_3$	CF_3	H	$C_{13}H_{12}F_3N_3S$ (299.32)	30	111–113	52.2	52.3	4.0	4.0	14.0	14.2	10.7	10.7
3c	$CH_2C(CH_3)_3$	CF_3	H	$C_{14}H_{14}F_3N_3S$ (313.34)	73	98–100	53.8	53.9	4.5	4.6	13.5	13.5	10.3	10.3
3d		CF_3	H	$C_{13}H_{10}F_3N_3S$ (297.30)	29	113–115	52.2	52.1	4.0	3.7	14.0	14.2	—	—
7	$C(CH_3)_3$		NO_2	$C_{18}H_{20}N_6O_3S_2$ (432.56)	26	247–248	50.0	50.4	4.6	4.6	19.4	19.1	14.8	14.8

oxadiazol-2-(3H)-one (molar ratio 1:1) in DMF at 20° and in the presence of 2 equiv. of sodium hydride. An aqueous work-up after 2 hrs gave **5** in 98% yield, m.p. 206–207° (from ethanol), colorless solid; IR; ν (KBr) 1800 (C=O), 1540 and 1350 (NO_2) cm^{-1}; CI/MS (m/z) 449 (MH^+); ^1H NMR (DMSO-d6); δ 1.5 (18H, s, $2(CH_3)_3C$) and ≈8.0 (2H, m, $(=CH)_2$).

2-(1,1-Dimethylethyl)-7-(trifluoromethyl)-1,3,4-thiadiazolo[3,2-a]benzimidazole, **3b**, *and Methiodide,* **4b**. A mixture containing 10.0 g (30 mmol) of **1b** and 22.2 g (50 mmol) of P_4S_{10} in 400 ml of xylene was heated at reflux for 29 hrs, cooled to 60°, and treated with 500 ml of H_2O. After 1 hr, the organic layer was dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residual dark oil, 21.0 g, was purified by silica chromatography using the solvent mixture (by vol): THF (80), AcOEt (500), hexane (1420), to give 4.5 g (50%) of cream colored **3b**, m.p. 111–113°; ^1H NMR ($CDCl_3$); δ 1.5 (9H, s, $(CH_3)_3C$), and 7.0–8.1 (3H, m, $(=CH)_3$).

The methiodide **4b** precipitated after 10 days from a solution of 2.0 g (6.7 mmol) of **3b** in 25 ml of methyl iodide. Yield, 1.0 g (34%), light yellow crystals, m.p. 243–245° (decomp.), insoluble in ether, soluble in H_2O. *Anal.* Calcd for $C_{14}H_{15}F_3IN_3S$ (441.26): C, 38.1; H, 3.4; N, 9.5; S, 7.3; I, 28.8. Found: C, 37.9; H, 3.3; N, 9.5; S, 7.2; I, 29.2.

2-(2,2-Dimethylpropyl)-7-(trifluoromethyl)-1,3,4-thiadiazolo[3,2-a]benzimidazole, **3c**, *and Methiodide,* **4c**. A mixture of 14.2 g (32 mmol) of P_4S_{10} and 10.0 g (29 mmol) of **1c** in 300 ml of xylene was stirred and heated to reflux for 36 hrs. After 9 hrs, a new product began to form (by TLC). The reaction mixture was cooled to room temperature and treated with 250 ml of water. The organic layer was dried ($MgSO_4$) and concentrated. The residue was chromatographed over silica gel. By using the solvent system (by vol): THF (4), hexane (96), a solid fraction of 6.6 g (73%) of colorless solid **3c** was obtained, m.p. 98–100°; IR (KBr); ν no C=O, 1630 (C=C), 1535 and 1320 (NO_2) cm^{-1}; ^1H NMR ($CDCl_3$); δ 1.1 (9H, s, $(CH_3)_3C$), 2.9 (2H, s, CH_2), 7.0 and 8.1 (3H, m, $(=CH)_3$).

The methiodide **4c**, formed and isolated in 45% from **3c** and methyl iodide on standing at room temperature (3 days), is a colorless solid, m.p. 230–231° (decomp.); IR (KBr) 1630 (C=) cm^{-1}; ^1H NMR (DMSO-d6) δ 1.1 (9H, $(CH_3)_3C$), 3.3 (2H, CH_2), 4.3 (3H, CH_3) and 8.0–8.7 (3H, $(=CH)_3$). *Anal.* Calcd for $C_{15}H_{17}F_3IN_3S$ (455.29): C, 39.5; H, 3.7; N, 9.2. Found: C, 39.5; H, 3.8; N, 9.2.

5-(1-Methylcyclopropyl)-3-[2-nitro-4-(trifluoromethyl)]phenyl-1,3,4-oxadiazole-2(3H)-thione, **2d**, *and 2-(1-methylcyclopropyl)-7-(trifluoromethyl)-1,3,4-thiadiazolo[3,2-a]benzimidazole,* **3d**. A solution of 15.5 g (35 mmol) of P_4S_{10} in 200 ml of xylene was stirred and refluxed during the slow addition of a solution 11.5 g (35 mmol) of **1d** in 600 ml of xylene. After 72 hrs, the mixture was cooled to room temperature, treated with 900 ml of H_2O and phase-separated. The organic layer was washed with H_2O, dried ($MgSO_4$), and concentrated by rotary evaporation. The residue was absorbed on silica gel and purified by chromatography using the following solvent system (by vol): THF (4), hexane (80), AcOEt (14). Two fractions were obtained.

The first fraction, 2.3 g (19%), was off-white solid **2d,** m.p. 113–115°; EI/MS (m/z) 345 (M^+), 329 (M^+-O), 326 (M^+-F), 315 (M^+-NO), 297 (M^+-SO), 281, 266 (M^+-S), HNO_2), 216, 186, 172, 158, 126, 83, 67 (CF_3^+), 55 (cyclopropylmethyl$^+$); ^1H NMR ($CDCl_3$); δ 1.02 (2H, m, CH_2), 1.42 (2H, m, CH_2), 1.48 (3H, s, CH_3), 8.04 (2H, m (=$CH)_2$), 8.35 (1H, s, =CH); ^{13}C NMR ($CDCl_3$); δ 13.07 (s, C), 16.43 (t, CH_2); 19.05 (q, CH_3), 122.3 (s, CF_3) (J = 273.1 Hz), 123.2 (d, =CH), 129.7 (d, =CH), 130.4 (d, =CH), 132.5 (s, C—CF_3), 144.32 (s, =C), 167.22 (s, =C or C=O), 175.95 (s, C=O or C=S). *Anal.* Calcd for $C_{13}H_{10}F_3N_3SO_3$ (345.30): C, 45.2; H, 2.9; N, 12.2. Found: C, 45.3; H, 2.9; N, 12.0.

The second fraction, 3.0 g (29%), was off-white solid **3d**, m.p. 113–115°; EI/MS (m/z) 297 (M^+), 282 (M^+-CH_3), 264, 255, 216 (M^+-$C_4H_7CN^+$), 147 (*m/z* 216-CF_3), 69 (CF_3^+); ^1H NMR ($CDCl_3$); δ 1.12 (2H, m, CH_2), 1.37 (2H, m, CH_2), 1.63 (3H, s, CH_3), 7.53 (1H, m, =CH), 7.85 (1H, m, =CH), 8.03 (1H, s, =CH); ^{13}C NMR ($CDCl_3$); δ 19.02 (t, CH_2), 19.13 (s, C), 21.99 (q, CH_3), 110.71 (d, =CH), 117.2 (d, =CH), 118.6 (d, =CH), 124.7 (s, CF_3) (J = 272 Hz), 125.7 (s, C-CF_3) (J = 33 Hz), 145.67 (s, =C), 154.75 (s, =C), 170.18 (s, =C or C=O).

5-(1,1-Dimethylethyl)-3-(2-(1,1-dimethylethyl)-6-nitro-1,3,4-thiadiazolo[3,2-a]benzimidazol-7-yl)-1,3,4-oxadiazol-2(3H)-thione, **7**. To a stirred and refluxing solution of 22.2 g (50 mmol) of P_4S_{10} in 400 ml of xylene was slowly added a solution of 22.4 g (50 mmol) of **5** in 400 ml of xylene. The mixture was stirred and refluxed for 28 hrs, cooled to room temperature, and diluted with 500 ml of H_2O. After 1 hr, the organic layer was washed with water, dried ($MgSO_4$), filtered, and concentrated under rotary evaporation. The residual oil, 18.0 g, was purified by silica chromatography using the solvent mixture (by vol): THF (4), hexane (80), AcOEt (16). The first fraction consisted of 2.0 g (9.0%) of **5**. The second fraction was characterized as **7**, 5.0 g (23%); m.p. 247–248°; CI/MS (m/z) 433 (MH^+); IR (KBr); ν 1540 and 1320 (NO_2), 1460 (C=S) cm^{-1}; ^1H NMR (DMSO-d6); δ 1.5 (18H, s, 2 $(CH_3)_3C$) and 7–8 (2H, m, $(=CH)_2$).

3-[2-Amino-4-(trifluoromethyl)phenyl]-5-(1,1-dimethylethyl)-1,3,4-oxadiazol-2(3H)-one, **8**. Catalytic hydrogenation in a Parr shaker (5% Pd–C, H_2, 60 psig, THF) of **1b** gave a 76% yield of **8**; m.p. 208–210°. *Anal.* Calcd for $C_{13}H_{14}F_3N_3O_2$ (301.26): C, 51.8; H, 4.7; N, 13.9. Found: C, 51.5; H, 4.5; N, 13.6.

1-(Pivaloylamino)-5-(trifluoromethyl)benzimidazol-2(3H)-one, **9.** A solution of 7.2 g (25 mmol) of **8** in 160 ml of diethylene glycol dimethyl ether was heated to reflux for 36 hrs while a slow stream of dry N_2 was passed through. Removal of solvent under reduced pressure gave an oil which was purified by silica chromatography (solvent (by vol): THF (4), AcOEt (16), hexane (80)). The first fraction consisted of 1.2 g of *m*-(trifluoromethyl)pivalanilide, *m/z* 245 (M^+). The second fraction, 2.2 g (29%) was identified as **9**, colorless crystalline solid, m.p. 79–81°; EI/MS (*m/z*) 217 (M^+-$(CH_3)_3CCO$), 174. *Anal.* Calcd for $C_{13}H_{14}F_3N_3O_2$ (301.26): C, 51.8; H, 4.7; N, 13.9. Found: C, 51.6; H, 4.4; N, 14.0.

REFERENCES AND NOTES

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2. Refluxing xylene was ineffective.
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