# The Reaction of *N*-Acyl Imines with *t*-Butyl Isocyanide (1)

*J. A. Deyrup and K. K. Killion*

Department of Chemistry, University of Florida, Gainesville, Florida 32601

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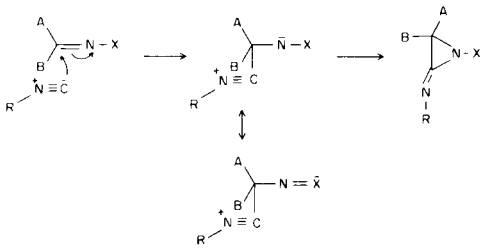
*N*-Acylimines and their derivatives react with *t*-butyl isocyanide only the in presence of acid catalysis. The major products of these reactions are 5-aminooxazoles and 5-iminooxazolines. The structure of these compounds and some of their degradative chemistry is discussed.

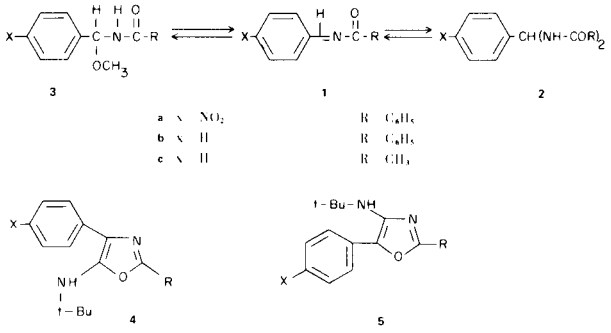
We have previously shown that nucleophilic attack by isocyanides on *N*-aryl imines requires prior nitrogen protonation (2). In order to increase the possibilities of uncatalyzed attack by isocyanides and subsequent ring closure, we have investigated the reaction of isocyanides with imines bearing nitrogen substituents capable of stabilizing negative charge (Scheme I). In addition, in order to extend our earlier work, we have also studied the acid catalyzed addition of isocyanides to these electron deficient imines. In this paper we report our study of the reaction of *t*-butyl isocyanide with X = RCO- and $ArSO_2$- (Scheme I).

*N*-Acyl imines (**1**) are readily available *via* the pyrolysis of benzylidenebisamides (**2**) and purifiable as their methanol adducts (**3**) (3). In spite of the electron withdrawing

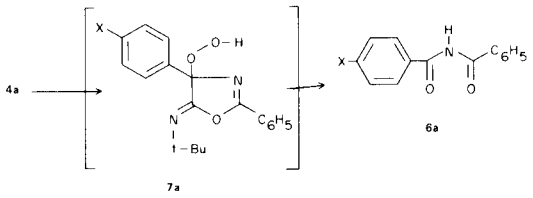
SCHEME I



character of its nitrogen substituent, **1a** failed to react with *t*-butyl isocyanide under a wide variety of conditions in the absence of acid catalysis. Reaction of *t*-butyl isocyanide with **3a** in the presence of boron trifluoride etherate in ether yielded a 1:1 adduct in 65% yield. The same product was obtained in 59% yield from the reaction of **1a** with *t*-butyl isocyanide in carbon tetrachloride at 140°. The presence of N-H stretch and the absence of peaks between 1600 and 2700 $cm^{-1}$ in the infrared spectrum of this adduct suggested oxazole structures **4** and **5**.

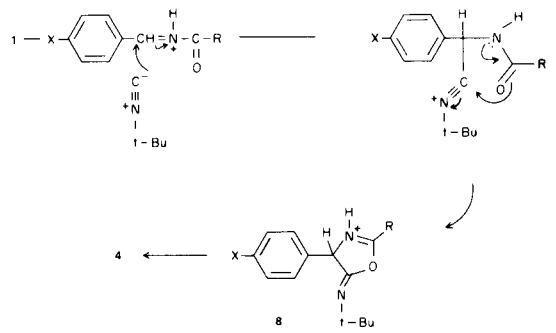


Autoxidation of the 1:1 adduct under basic conditions produced 4-nitrodibenzamide (**6a**). Although the details of the autoxidation process are not totally clear, the postulated formation of an intermediate hydroperoxide **7a** has considerable literature precedent (2,4). Isolation of this autoxidation product excludes structure **5** and supports structure **4** (5).

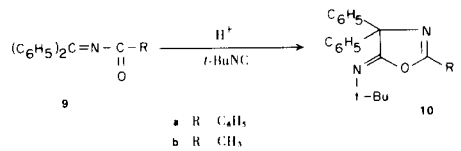


The reactions of **3b** and **3c** with *t*-butyl isocyanide under conditions of acid catalysis also produced aminooxazoles **4b** and **4c**. These aminooxazoles, which were characterized by their nmr spectra, were extremely unstable toward autoxidation (7). The autoxidation products, **6b** and **6c**, were easily purified and compared with known compounds. Formation of **4** can be rationalized in the manner shown in Scheme II. The irreversible

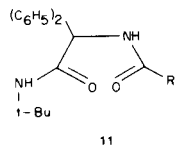
SCHEME II



tautomerism of **8** to **4** prompted our extension of this reaction to diphenylketimine derivatives **9a** and **9b**. Acid catalyzed addition of *t*-butyl isocyanide resulted in the formation of iminooxazoline **10a** in 73% yield. This structure is supported by an infrared peak at 1720 $cm^{-1}$ (9). An isomeric 4-iminooxazoline structure was excluded

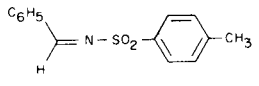


by acidic hydrolysis of **10a** to **11a**. Additional evidence for this structure is found in its pyrolytic reversion to **9a**.



Iminooxazoline **10b** could be characterized spectrally. Its rapid hydrolysis to **11b** precluded isolation of the initial adduct (**10**).

The failure to observe an uncatalyzed reaction of *t*-butyl isocyanide with **1** and **9** prompted us to examine the behavior of **12**. Although the sulfonyl group should make **12** much more susceptible to nucleophilic attack, no reaction was observed between *t*-butyl isocyanide and **12** at 80°. Acid catalysis, in this case, failed to promote incorporation of *t*-butyl isocyanide. It thus appears that *t*-butyl isocyanide is too poor a nucleophile to react with any of the aldehyde or ketone derivatives described herein. Further reactions between other types of imines and isocyanides are under investigation.



## EXPERIMENTAL

The nmr spectra were obtained on a Varian A-60A with TMS as an internal standard. The ir spectra were recorded on a Perkin-Elmer Infracord and the mass spectra on a Hitachi Perkin-Elmer TMU-6E mass spectrometer. All new compounds reported had a molecular ion peak which agreed with the expected value. The CHN analyses are from Galbraith Laboratories, Inc., Knoxville, Tennessee, and from Atlantic Microlab, Inc., Atlanta, Georgia. A Cary 15 Recording spectrophotometer was used for the uv spectra. Melting points are uncorrected and taken in a Thomas-Hoover Capillary M.P. Apparatus. Benzlidenebisacetamide (**3c**). *p*-Nitrobenzylidenebisbenzamide (**3a**) and benzylidenebisbenzamide (**3b**) were prepared according to published procedures (1,2,3).

Methanol Adducts of Benzaldimines.

The methanol adducts of *N*-benzoylbenzaldimine (**1b**), *N*-benzoyl-*p*-nitrobenzaldimine (**1a**), and *N*-acetylbenzaldimine (**1c**) were prepared according to a modified procedure (3). The bisamides were heated in a sublimation apparatus under nitrogen until they melted. Pressure was reduced to 0.5-2 mm and the material was sublimed onto the cold finger. The material thus collected was dissolved in methanol and the latter evaporated. The residue was dissolved in benzene and the solution filtered. The benzene solution was chromatographed on alumina (Fisher neutral, Brockman activity IV) using benzene as elutant. The methanol adducts (**3a**) and (**3b**) were recrystallized from benzene and petroleum ether. Adduct **3c** could not be purified by recrystallization and had to be used immediately after preparation.

*N*-Benzoyl-*p*-nitrobenzaldinime (**1a**).

*p*-Nitrobenzylidenebisbenzamide (0.52 g., 1.4 mmoles) was heated above its melting point (266-267°) under reduced pressure (aspirator) in a nitrogen atmosphere according to the procedure of Breuer, *et al.* (3). The product was taken up in benzene. The benzene solution was filtered and then evaporated; nmr (deuteriochloroform), 8.8 δ (CH=N, s), 7.2-7.8 δ (aromatic, m).

5-*t*-Butylamino-4-*p*-nitrophenyl-2-phenyloxazole (**4a**).

The methanol adduct of *N*-benzoyl-*p*-nitrobenzaldimine (**3a**) (0.20 g., 0.7 mmole) was placed in 20 ml. of dry ether and *t*-butyl isocyanide (0.23 g., 2.8 mmoles) and boron trifluoride etherate (0.06 g., 0.4 mmole) were added. The reaction mixture was stirred under nitrogen for 2.5 hours and then washed with two 15 ml. portions of water. The water washings were washed twice with 10 ml. of ether and the three ether portions combined and dried over magnesium sulfate.

The ether was evaporated and the sample dissolved in benzene and chromatographed on alumina (Fisher neutral, Brockman activity IV). Benzene was used to elute the sample. The oxazole was recrystallized from cyclohexane (0.15 g., 65%); m.p. 123-124°; ir (potassium bromide) $cm^{-1}$ 3280 (NH), 2900 (CH), 1590 (C=N), 1570 (C=C); nmr (deuteriochloroform) 1.40 δ (9H, *t*-Bu, s), 3.68 δ (1H, NH, s), 7.5 and 8.18 δ (9H, aromatic, m); uv (ethanol) 227 nm (16,000), 342 nm (16,000).

*Anal.* Calcd. for $C_{19}H_{19}N_3O_3$: C, 67.64; H, 5.68; N, 12.45. Found: C, 67.80; H, 5.62; N, 12.46.

4-Nitrodibenzamide (**6a**).

The oxazole (**4a**) (0.027 g., 0.78 mmole) was dissolved in 5 ml. of benzene, two drops of pyridine were added, and the solution was stirred under oxygen for 48 hours. The benzene was evaporated and the residue was recrystallized from chloroform

and petroleum ether. The colorless crystals were 4-nitrodibenzamide (0.011 g., 51%); m.p. 169-170°, reported m.p. 174° (13); ir (potassium bromide) $cm^{-1}$ 3220 (NH), 1720 (C=O), 808, 785.

When the same reaction was carried out in the absence of oxygen, no dibenzamide was formed.

Dibenzamide.

The methanol adduct of *N*-benzoylbenzaldimine (**3b**) (0.39 g. 1.6 mmoles), *t*-butyl isocyanide (0.47 g., 5.8 mmoles), and 10 ml. of carbon tetrachloride were heated in a sealed tube at 120° for 36 hours. The carbon tetrachloride was evaporated and nmr and ir spectra of the reaction mixture were run immediately; ir (potassium bromide) $cm^{-1}$ 3200 (NH), 1610 (C=N), 1590 (C=C); nmr (deuteriochloroform) 1.30 δ (9H, *t*-Bu, s), 3.05 δ (1H, NH, s), 7-8 (10H, aromatic, m). The product was 5-*t*-butylamino-2,4-diphenyloxazole. When the residue was partially dissolved in benzene, the only product isolable was an insoluble material which was dibenzamide. The insoluble material was filtered and recrystallized from carbon tetrachloride (0.13 g., 35%); m.p. 144-145°, reported m.p. 146° (14); ir (potassium bromide) $cm^{-1}$ 3200 (NH), 1720 (C=O).

Acetobenzamide.

The methanol adduct of *N*-acetylbenzaldimine (**3c**) (0.08 g., 0.42 mmole) was dissolved in 9 ml. of ether and *t*-butyl isocyanide (0.01 g., 1.2 mmoles) and borontrifluoride etherate (0.06 g., 0.04 mmole) were added. The solution was stirred under nitrogen for 2.5 hours and then washed with two 8 ml. portions of water. The water washings were washed with two 5 ml. portions of ether, the ether portions were combined, dried with magnesium sulfate, and evaporated to dryness. The residue was an orange oil. The nmr spectrum was obtained immediately: nmr (deuteriochloroform) 1.21 δ (9H, s, *t*-Bu), 3.05 δ (1H, NH, s), 7-8 δ (5H, aromatic, m), 2.39 δ (3H, $CH_3$, s). The oil was 5-*t*-butylamino-2-methyl-4-phenyloxazole (**4c**). When the oil was dissolved in hot cyclohexane, a white solid acetobenzamide, came out of solution when it cooled (0.036 g., 52%), m.p. 112-113° reported m.p. 114° (15), ir (potassium bromide) $cm^{-1}$ 3260 (NH), 2950 (CH), 1750 (C=O).

Reaction of *N*-Benzoyl-*p*-nitrobenzaldimine (**1a**) with *t*-Butyl Isocyanide.

Crude **1a** (0.20 g., 3.5 mmoles) and 7 ml. of carbon tetrachloride were heated in a sealed tube at 117° for 42 hours. Ether was added to the carbon tetrachloride solution and insoluble material was removed by filtration. The solvent was evaporated and the residue was dissolved in benzene and chromatographed on alumina (Fisher neutral, Brockman activity IV) using benzene as elutant.

The oxazole (**4a**) was recrystallized from cyclohexane (0.12 g., 59%); m.p. 120-121°; nmr (deuteriochloroform) 1.40 δ (9H, *t*-Bu, s), 3.68 δ (1H, NH, s), 7.5 and 8.1 δ (9H, aromatic, m).

5-*t*-Butylimino-4,4-diphenyl-2-phenyloxazoline (**10a**).

*N*-Benzoyldiphenyl ketimine (**9a**) (0.50 g., 1.7 mmoles) and boron trifluoride etherate (0.12 g., 0.8 mmole) were added to 25 ml. of benzene. The reaction mixture was stirred for 1 hour under nitrogen and then washed with two 15 ml. portions of water. The water washings were washed twice with 10 ml. of benzene and the three benzene portions combined and dried with magnesium sulfate.

The benzene was evaporated to an oil and petroleum ether was added. The white crystals which came out of the petroleum ether were recrystallized from hot *n*-hexane (0.46 g., 73%); m.p. 121-122°; ir (potassium bromide) $cm^{-1}$ 2900 (CH), 1720 (exo (C=N), 1650 (ring C=N); nmr (deuteriochloroform) 1.40 δ (9H, *t*-Bu, s), 7.25 δ, 7.6 δ, and 8.1 δ (15H, aromatic, m); uv (Ethanol) 246 nm (19, 600).

*Anal.* Calcd. for $C_{25}H_{26}N_2O_2$: C, 77.69; H, 6.78; N, 7.25. Found: C, 77.54; H, 6.91; N, 7.15.

Hydrolysis of 5-*t*-Butylimino-4,4-diphenyl-2-phenyloxazoline (**10a**).

The oxazoline (32 mg., 0.088 mmole) was allowed to stand for 12 hours in a solution of acetone (3 ml.) -water (2 ml.) to which 3 drops of 5% hydrochloric acid had been added. The acetone was then removed by evaporation and the resultant solid removed by filtration (26 mg., 77%), m.p. 168.5-169.5°. Recrystallization from benzene-petroleum ether produced an analytical sample of identical m.p.; ir (potassium bromide) $cm^{-1}$ 3310 cm- (NH), 1660 (C=O); nmr (deuteriochloroform) 1.26 δ (9H, *t*-Bu, s), 5.64 δ (1H, -NH-CO, s) 7.5-7.90 δ (15H, aromatic,(m) and 8.68 δ (1H, -NH-C=O, s).

*Anal.* Calcd. for $C_{25}H_{26}N_2O_2$: C, 77.69; H, 6.78; N, 7.25. Found: C, 77.54; H, 6.91; N, 7.15.

Pyrolysis of 5-*t*-Butylimino-4,4-diphenyl-2-phenyloxazoline (**10a**).

The oxazoline (**10**) (0.066 g., 0.18 mmole) was heated in a sandbath at 220° for 1.5 hours. Petroleum ether was added to the resulting oil and colorless crystals precipitated. These were recrystallized from chloroform and petroleum ether. The white crystals were *N*-benzoyldiphenylketimine (0.001 g., 20%); m.p. 114-115°; ir (potassium bromide) $cm^{-1}$ 3000 (CH), 1660 (C=O), 1610 (C=N).

Reaction of *N*-Acetyldiphenylketimine (16) (**10b**) and *t*-Butyl Isocyanide.

The ketimine (0.66 g., 3.0 mmoles) was dissolved in 10 ml. of benzene and *t*-butyl isocyanide (0.69 g., 8.3 mmoles) and boron trifluoride etherate (0.06 g., 0.4 mmole) were added. The solution was stirred under nitrogen for 45 minutes. The benzene solution was then washed with two 10 ml. portions of water and the water was then washed with 10 ml. of benzene. The benzene portions were combined and dried with magnesium sulfate. The benzene was evaporated. The residue was a green oil to which petroleum ether was added. The crystals which formed were recrystallized from benzene and petroleum ether. The resulting colorless crystals were the *t*-butyl amide of 2,2-diphenyl-*N*-acetylglycine (**11b**) (0.21 g., 21%); m.p. 196-197°; ir (potassium bromide) $cm^{-1}$ 3250 (NH), 2900 (CH), 1680 (C=O); nmr (deuteriochloroform) 1.25 δ (9H, *t*-Bu, s), 1.98 δ (3H, $CCH_3$, s), 5.65 δ (1H, -NHCO, s), 8.4 δ (10H, aromatic, m), 8.6 (1H, $-C(C_6H_5)_2NH-\overset{O}{\overset{\|}{C}}-$, s).

*Anal.* Calcd. for $C_{20}H_{24}N_2O_2$: C, 74.05; H, 7.46; N, 8.63. Found: C, 74.17; H, 7.39; N, 8.57.

In order to see if the oxazoline was initially formed, the reaction was run again as before, but, after stirring for 45 minutes, the benzene was evaporated; ir (neat) $cm^{-1}$ 2900 (CH), 1730 (exo C=N), 1680 (ring C=N); nmr (deuteriochloroform) 1.30 δ (9H, *t*-Bu, s), 2.19 δ (3H, $CH_3$, s), 7.08-7.85 δ (10H, aromatic, m), no peak for NH.

Attempted Reaction of *N*-Tosylbenzaldimine and *t*-Butyl Isocyanide.

*N*-Tosylbenzaldimine (26) and *t*-butyl isocyanide were stirred for 24 hours in dichloromethane and for 24 hours in benzene. An nmr spectrum showed that no reaction had occurred; nmr (deuteriochloroform) 2.42 δ (3H, $CH_3$, s), 7.5 and 8.9 (9H, aromatic, m), 9.1 (1H, N-CH, s). Refluxing in benzene and in *t*-butyl isocyanide as solvent did not cause any significant

incorporation of a *t*-butyl group; nmr (deuteriochloroform) 1.2 δ (*t*-Bu, m), 2.4 δ ($CH_3$, m). Bubbling hydrogen chloride gas into a benzene solution of the benzaldimine and isocyanide gave the same results as refluxing.

Attempted Reaction of *p*-Nitrobenzylidenebisbenzamide with *t*-Butyl Isocyanide.

The benzamide, *t*-butyl isocyanide, and 7 ml. of carbon tetrachloride were heated in a sealed tube at 120° for 36 hours. Nmr spectroscopy showed no oxazole had formed; nmr (deuteriochloroform) 1.35 δ (small *t*-Bu, s), no NH peak.

## REFERENCES

(1) This research was supported by the National Science Foundation.

(2) J. A. Deyrup, M. M. Vestling, W. V. Hagan and H. Y. Yun, *Tetrahedron*, **25**, 1467 (1969).

(3) S. W. Brewer, T. Bernath and D. Ben-Ishai, *ibid.*, **23**, 2869 (1967).

(4) B. Wilkop and J. B. Patrick, *J. Am. Chem. Soc.*, **73**, 2196 (1967).

(5) Kille and Fleury have prepared 5-amino-oxazoles *via* a different procedure. These compounds did not appear to show oxygen sensitivity (6).

(6) G. Kille and J. P. Fleury, *Bull. Soc. Chem. France*, 4619 (1967).

(7) Other examples of stabilization toward autoxidation afforded by the electron-withdrawing *p*-nitro group have been found (8).

(8) A. G. Davies, "Organic Peroxides," Butterworths, London, 1961, p. 14.

(9) *cf.*, H. W. Heine, *J. Am. Chem. Soc.*, **85**, 2743 (1963).

(10) While this work was in progress, a reference was found in which Gambaryan reported that *N*-acylamine of perfluoro ketones react with isocyanides to give oxazolines (11).

(11) N. P. Gambaryan, E. M. Rokhlin, Yu. V. Zeifman, L. A. Simongan and L. L. Knunyants, *Dokl. Akadi Nauk SSSR.*, **166**, 864 (1966).

(12) W. A. Noyes, and D. B. Forman, *J. Am. Chem. Soc.*, **55**, 3493 (1933).

(13) A. Lamberton and A. E. Standage, *J. Chem. Soc.*, 2957 (1960).

(14) D. Davidson and H. Skovronek, *J. Am. Chem. Soc.*, **80**, 376 (1958).

(15) R. E. Dunbar and G. C. White, *J. Org. Chem.*, **23**, 915 (1958).

(16) J. E. Banfield, G. M. Brown, F. H. Davey, W. Davies, and T. H. Ramsey, *Aust. J. Sci. Res.*, **A1**, 330 (1948).