Conversion of Aliphatic Amides into Amines with [*I,I*-Bis(trifluoroacetoxy)iodo]benzene. 1. Scope of the Reaction

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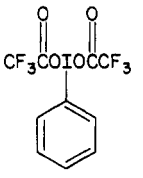
Received April 9, 1984

The reagent [*I,I*-bis(trifluoroacetoxy)iodo]benzene, PIFA, brings about the facile oxidative rearrangement of aliphatic amides to amines in mildly acidic (pH 1-3) mixed aqueous-organic solvents. Aromatic amines are further oxidized by the reagent and therefore cannot be prepared by this method. The rearrangement, which is in effect an "acidic Hofmann rearrangement", occurs with complete retention of configuration in the migrating group, and the rate of the reaction follows approximately the migratory aptitudes of the migrating groups determined for other similar reactions. Isocyanates are intermediates in the rearrangement but are rapidly hydrolyzed to the product amines under the mildly acidic conditions. The acidic conditions protect the product amines from reacting with the isocyanate intermediates and forming ureas. The reaction is accelerated by addition of pyridine to a pH of approximately 3. The scope of the reaction is discussed.

There has been a substantial amount of recent interest in compounds containing hypervalent iodine as reagents in organic synthesis.[1] Many of the properties and uses of these reagents have been summarized in a recent review.[1a] Our interest in these compounds stemmed from the need for a reagent that would effect the Hofmann rearrangement (the conversion of a primary amide into an amine with one less carbon atom) under acidic or neutral conditions without affecting secondary or tertiary amides. For this reason we were particularly intrigued by a report that iodobenzene diacetate effects exactly this transformation.[2] Although the substance of this report turned out to be erroneous, it started our research in a direction that eventually led to the use of the trifluoroacetoxy derivative of iodobenzene diacetate, [*I,I*-bis(trifluoroacetoxy)iodo]benzene[3] (1), for effecting the Hofmann rearrangement of primary amides under mildly acidic conditions. Compound 1, to which we refer by the acronym PIFA,[4] has been found[5] to be particularly useful in the rearrangement of amides derived from peptides and acylamino acids. In this paper we report our studies on the synthetic aspects of the rearrangement of primary amides to amines with PIFA. In the following paper[6] we consider the mechanism of this reaction.



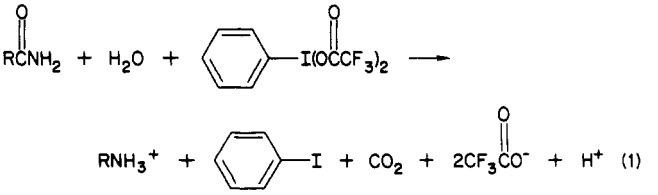
1 (PIFA)

Results and Discussion

Preparation of PIFA. PIFA is prepared very simply by recrystallizing iodobenzene diacetate[7] from trifluoroacetic acid. It is important to adhere to the proportions of trifluoroacetic acid and iodobenzene diacetate given in the Experimental Section. Although a higher yield of crystals can be obtained by using less trifluoroacetic acid, the product is not as effective in promoting the reactions discussed in this paper.

At least one chemical supplier reports that PIFA is light-sensitive, and indeed the reagent does become yellow if stored in a clear bottle. The discolored reagent is ineffective in promoting the rearrangement of amides. Although we have not characterized the decomposition reaction, iodobenzene diacetate is known to be an excellent source of methyl radicals if heated,[8] and perhaps the photodecomposition involves similar reactions. We have found that PIFA stored under inert atmosphere in a dark bottle remains stable to decomposition for reasonable periods of time.

Rearrangement of Amides. Primary amides are rearranged by PIFA in 1:1 (v/v) acetonitrile-water according to eq 1. In Table I are given a representative series of



(1)

(1) (a) Varvoglis, A. *Chem. Soc. Rev.* **1981**, *10*, 377-407. (b) Spyroudis, S.; Varvoglis, A. *J. Org. Chem.* **1981**, *46*, 5231-5233. (c) Koser, G. F.; Rebrovic, L.; Wettach, R. H. *J. Org. Chem.* **1981**, *46*, 4324-4326. (d) Moriarty, R. M.; Gupta, S. C.; Hu, H.; Berenschot, D. R.; White, K. B. *J. Am. Chem. Soc.* **1981**, *103*, 686-688. (e) Hummfray, A. A.; Imberger, H. E. *J. Chem. Soc., Perkin Trans. 2* **1981**, 382-387. (f) Waki, M.; Kitajima, Y.; Izumiya, N. *Synthesis* **1981**, 266-268. (g) Soby, L. M.; Johnson, P. *Anal. Biochem.* **1981**, *113*, 149-153. (h) Spyroudis, S.; Varvoglis, A. *J. Chem. Soc., Perkin Trans. 1* **1984**, 135-137. (i) Moriarty, R. M.; Hou, K.-C. *Tetrahedron Lett.* **1984**, *25*, 691-694.

(2) Swaminanthan, K.; Venkatasubramanian, N. *J. Chem. Soc., Perkin Trans. 2* **1975**, 1161-1176.

(3) Radhakrishna, A. S.; Parham, M. E.; Riggs, R. M.; Loudon, G. M. *J. Org. Chem.* **1979**, *44*, 1746-1747.

(4) This reagent has been known in the literature, including *Chemical Abstracts*, by a variety of names: iodobenzene bis(trifluoroacetate), phenyl iodosyl bis(trifluoroacetate), and phenylbis(trifluoroacetato-*O*)-iodine; the last name is the one currently in use in *Chemical Abstracts*. The acronym PIFA is based on the name phenyl *i*odosyl bis(trifluoroacetate).

(5) (a) Pallai, P. V.; Richman, S.; Struthers, R. S.; Goodman, M. *Int. J. Pept. Prot. Res.* **1983**, *21*, 84-92. (b) Pallai, P. V.; Goodman, M. *J. Chem. Soc., Chem. Commun.* **1982**, 280-281. (c) Loudon, G. M.; Parham, M. E. *Tetrahedron Lett.* **1978**, 437-440. (d) Parham, M. E.; Loudon, G. M. *Biochem. Biophys. Res. Commun.* **1978**, *80*, 1-6.

(6) Boutin, R. H.; Loudon, G. M. *J. Org. Chem.*, following paper in this issue.

(7) Sharefkin, J. G.; Saltzman, H. "Organic Syntheses"; Wiley: New York, 1973; Collect. Vol. V, pp 660-3. We use the commercially available material from Aldrich Chemical Co.

(8) Leffler, J. E.; Story, L. J. *J. Am. Chem. Soc.* **1967**, *89*, 2333.

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Table I. Rearrangements of Primary Amides to Amines with PIFA

amide $RCONH_2$, product $RNH_3^+Cl^-$, R =	yield, %	mp, °C
CH_3CH_2	85	108–110 (110)[a]
$CH_3(CH_2)_4$	92	222–224 (227–228)[b]
$(CH_3)_3C$	92	275–280 (270–280)[c]
$C_6H_5CH(CH_3)$	84	157–159 (158)[d]
p-$CH_3OC_6H_4CH_2$	70	228–232 (230–233)[e]
$O_2NC_6H_4CH_2$	85	221–223 (220)[f]
cyclobutyl	78	181–183 (183–184)[g]
cyclopentyl	91	204–206 (206–207)[h]
cyclohexyl	90	207–209 (204–205)[i]
cycloheptyl	85	244–246 (242–246)[j]
1-adamantyl	85	>330[k] (360)[l]
3-cyclohexenyl	75	178–179 (181–182)[m]
1-naphthyl-CH_2	85	261–264 (262–264)[n]
$EtO_2CCH_2CH_2$[o]	86	69–70 (69–70)[p]
$HO_2CCH_2CH_2$[o]	81	123–125 (122–123)[q]
$Et_2NCOCH(NHAc)CH_2CH_2$[r,s]	55	175–177
Ac-Ala-NH-CH(CH$_2$CH$_2$-)-CO-Ala-Gly[s,t]	79	
AcNHCH(CH$_2$C$_6$H$_5$)-[u]	79	140–142 (dec)[v]
AcNHCH(CH(CH$_3$)$_2$)-[w]	75	121–123 (dec)[v]

[a] Watt, G. W.; Otto, J. B. *J. Am. Chem. Soc.* **1947**, *69*, 837–878. [b] Olomucki, M.; Hebrard, P. French Patent 1579561 (August, 1969); *Chem. Abstr.* **1970**, *72*, 100003*h*. [c] von B. Brauner, *Liebigs Ann. Chem.* **1878**, *192*, 65–80. [d] Tagel, J. *Chem. Ber.* **1889**, *22*, 1856. [e] Goldschmidt, H.; Polonowska, N. *Chem. Ber.* **1887**, *20*, 2407. [f] Hagner, A. *Chem. Ber.* **1890**, *23*, 338. [g] Reference 17d. [h] Barber. H. E.; Lunt, E. *J. Chem. Soc.* **1960**, 1187–1194. [i] Braun, C. E. *J. Am. Chem. Soc.* **1933**, *55*, 1280. [j] Prelog, V.; Fausy El Neweihy, M.; Häfliger, O. *Helv. Chim. Acta* **1950**, *33*, 365–369. [k] The hydrochloride was converted into the free amine with NaOH; the melting point of the 1-adamantamine was 206–208 °C. There is considerable disagreement in the literature on the melting point of this amine. Examples are 160–190 °C, 180–192 °C. Our melting point agrees with that of a commercial supplier, Aldrich Chemical Co. [l] (a) Stetter, H.; Mayer, J.; Schwarz, M.; Wolff, K. *Chem. Ber.* **1960**, *93*, 226–230. (b) Haaf, W. *Angew. Chem.* **1961**, *73*, 144. [m] Reference 21. [n] von Braun, J.; Blessing, G.; Zobel, F. *Chem. Ber.* **1923**, *56*, 1990. [o] Reaction run at 60–62 °C. [p] Treibs, W.; Hauptman, S. *Chem. Ber.* **1956**, *89*, 117. [q] Moe, O. A.; Warner, D. T. *J. Am. Chem. Soc.* **1949**, *71*, 1253. [r] Product hydrolyzes (6 N HCl, 22 h) to DABA: NMR (Me_2SO-d_6) δ 7.9–8.4 (1 H, d, J = 9 Hz, exchanges in D_2O), 6.6–7.6 (2 H, two br s, exchanges in D_2O), 4.4–4.5 (1 H, m, collapses to t, J = 7 Hz, on addition of D_2O), 2.8–3.8 (4 H, m), 1.35–2.3 (7 H, overlapping s and m), 0.6–1.3 (6 H, two overlapping t). [s] Ac = acetyl; DABA = 2,4-diaminobutyric acid residue. [t] Product amino acid analysis: Ala (2.01), DABA (1.00), Gly (1.02). [u] Anal. (C, H, N) Calcd. 55.94, 6.99, 13.05. Found: 55.69, 7.24, 13.24. NMR (Me_2SO-d_6) δ 8.5–9.5 (4 H, br s at 8.85 overlapping d, J = 8.5 Hz, exchanged in D_2O), 7.4 (5 H, s), 4.7–5.4 (1 H, m, collapses to dd on addition of D_2O), 2.9–3.4 (2 H, m), 1.85 (3 H, s). [v] All compounds of this type showed similar melting behavior: a sintering and partial melting at the indicated temperature followed by resolidification. [w] Anal. (C, H, N) Calcd 43.24, 9.07, 16.81. Found: 43.01, 8.99, 16.81. NMR (Me_2SO-d_6) δ 8.1–9.3 (4 H, br s partially overlapping a doublet, J = 8.5, both exchange out with D_2O), 4.4–4.9 (1 H, br t, collapses to d, J = 8 Hz, on addition of D_2O), 1.5–2.4 (4 H, s overlapping a multiplet), 0.7–1.1 (6 H, d, J = 7 Hz).

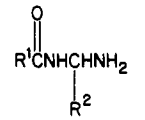
amines that have been produced by this reaction. As noted in the Experimental Section, it is important to use glass-distilled water in this preparation, and the amide must be completely free of halide ion.

The reaction is not useful for the preparation of amines in which the nitrogen is directly bonded to an aromatic ring. For example, if benzamide is subjected to the conditions of the reaction, a dark reaction mixture is formed that shows many components by thin-layer chromatography. Presumably this result is due to the further oxidation of aniline by PIFA.[9] Indeed, if aniline itself is subjected to the reaction conditions, a similar reaction mixture is obtained. In view of this result, the original observation[2] that iodobenzene diacetate oxidizes benzamides to acetanilides in acetic acid is particularly strange, since this reaction cannot be observed in either our or others' laboratories.[10] The original report was a kinetic study in which the disappearance of iodobenzene diacetate was followed. Indeed, iodobenzene diacetate is undoubtedly reduced, but the yield of anilines or (in acetic acid) acetanilides is small or negligible. In the original report the experimental section notes that acetanilide was isolated as the product, but neither yields or experimental details were given.

It is also interesting to consider the PIFA-promoted oxidation of amides that would formally give enamine products. Oxidation of 1-cyclohexenecarboxamide gave a moderate yield of cyclohexanone, presumably via the enamine 1-aminocyclohexene. The oxidation of *trans*-cinnamamide was followed in an NMR tube. After 60% of the amide had reacted, NMR showed that a 42% conversion to phenylacetaldehyde was achieved (25% yield). The amount of PIFA consumed exceeded the amount of aldehyde produced presumably because the enamine intermediate is oxidized further. For the conversion of compounds of this type into protected amines or carbonyl compounds, the Curtius reaction is clearly superior.[11]

Because iodobenzene diacetate and related iodine(III) derivatives are known to attack carbon–carbon double bonds,[1a] it was of interest to determine whether an amide in a molecule containing an isolated carbon–carbon double bond could be rearranged. Indeed, 3-cyclohexene-1-carboxamide was rearranged in excellent yield (Table I) without oxidation of the double bond provided that only 1 equiv of PIFA was used. If the reaction mixture contained excess PIFA, substantial decomposition was observed.

An interesting class of compounds is obtained from the rearrangement of the amides of acylamino acids. The products of these compounds are geminal amino amides (*N*-[1-aminoalkyl]amides). Although the derivatives with

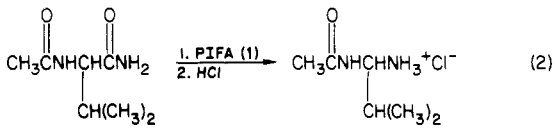


geminal amino amides

R^2 = H have long been known, derivatives in which R^2 = alkyl had not been previously isolated until they were discovered by Bergmann and Zervas.[12] Despite these authors' comments that this interesting class of compounds deserves further investigation, they were not studied again until relatively recently when Goodman and his group

(9) Pausacker, K. H. *J. Chem. Soc.* **1953**, 1989–1990.
(10) Barlin, G. B.; Pausacker, K. H.; Riggs, N. V. *J. Chem. Soc.* **1954**, 3122–3125.
(11) Jessup, P. J.; Petty, C. B.; Roos, J.; Overman, L. G. *Org. Synth.* **1979**, *59*, 1–9.
(12) Bergmann, M.; Zervas, L. *J. Biol. Chem.* **1936**, *113*, 341–357.

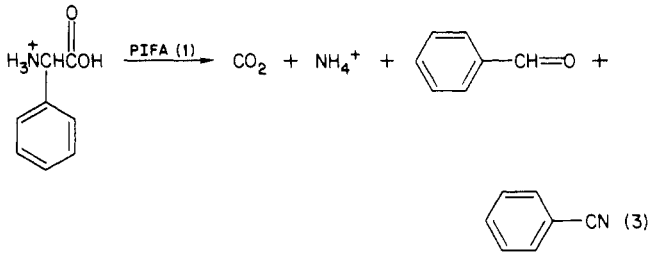
employed them in the synthesis of retroinverso peptide analogues,[5a,b] we encountered them as intermediates in our carboxyl-terminal peptide degradation,[5c,d] and Bundgaard employed them as protecting groups for drug molecules.[13] Perhaps one reason that these compounds were not studied further is that they are thinly masked aldehydes, and the common perception might be that these compounds would not be stable enough to be isolable under the conditions of the usual synthetic reactions. However, Loudon, Jacob, and Almond[14] studied the hydrolysis rates of geminal amino amides and found that in many cases the compounds are rather stable in aqueous solution. These compounds are synthesized quite easily by the rearrangement of N^{α}-acylamino acid amides:



(2)

Other examples of this reaction are also given in Table I. Notice in this and other examples that oxidation of the primary amide occurs without effect on secondary or tertiary amides in the same molecule.

It has been reported[1g] that PIFA converts free asparagine into 2,3-diaminopropionic acid and free glutamine into 2,4-diaminobutyric acid. These observations seemed strange to us in view of the fact that lead tetraacetate, a reagent with some similarity to PIFA, oxidizes α-hydroxy acids.[15] Thus it was of interest to investigate the reaction of PIFA with amino acids that do not contain N-acyl groups on the α-amino group. Accordingly, PIFA was allowed to react with several amino acids under the usual conditions. α-Phenylglycine gave benzaldehyde (isolated in 43–45% yield as the 2,4-dinitrophenylhydrazone) along with 8–10% of benzonitrile; evolution of gas, presumably CO_2, was noted immediately upon addition of the reagent to the amino acid (eq 3). Under similar conditions phenylalanine and alanine were also oxidatively decarboxylated to the corresponding aldehydes, phenylacetaldehyde and propionaldehyde, respectively, in about the same yield. If α-phenylglycine, PIFA (2 equiv), and pyridine (5 equiv) are heated on a steam bath for an hour under anhydrous conditions, benzonitrile is isolated in about 50% yield. Furthermore, in direct contrast to the earlier report,[1g] we have found that no diamino acids are obtained when PIFA reacts with asparagine or glutamine. However, it has been shown that N^{α}-acylated asparagine can be rearranged by PIFA to N^{2}-acylated 2,3-diaminopropionic acid in good yield[1f] with pyridine catalysis; we have observed a similar reaction with N-acylglutamine derivatives (see below and Figure 1).



(3)

We and others[1f] have found that the PIFA reaction is catalyzed by bases such as pyridine. The effect of pyridine on the rearrangement of the amide side chain in the glutamine residue of the peptide Ac-Ala-Gln-Ala-Gly is shown in Figure 1. The reaction mixtures contained, relative to peptide, 1.5 molar equiv of PIFA and either 2.0 equiv of pyridine or no added pyridine in 1:1 (v:v) acetonitrile–water. The pH meter readings of the solutions were 1.25 (absence of added pyridine) or 3.16 (presence of pyridine). In this reaction the addition of pyridine gives a rate enhancement of about 30- to 50-fold. The reason for the promotion of the reaction by added bases is clear from our mechanistic studies, which are described in the accompanying paper. We have discovered no instances to date in which the addition of pyridine has any effect other than acceleration of the reaction; however, the examples in Table I were run without pyridine, which is therefore not strictly necessary.

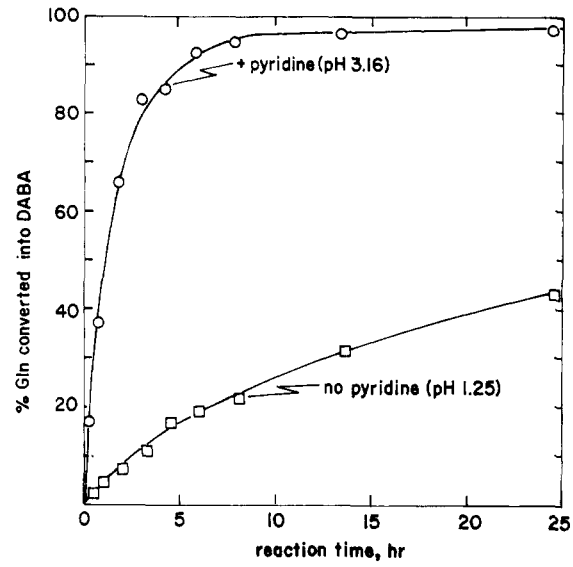
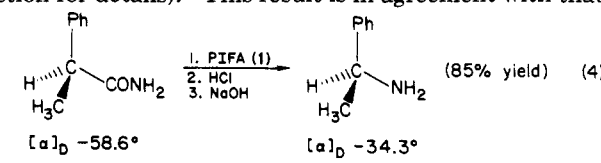


Figure 1. Effect of pyridine on the PIFA-promoted rearrangement of the peptide Ac-Ala-Gln-Ala-Gly. In the rearrangement the side-chain amide of the glutamine residue is converted into a primary amine; that is, the Gln residue is converted into a 2,4-diaminobutyric acid (DABA) residue. The amount of DABA formed at a given time was determined by amino acid analysis and equaled, within experimental error, 100 – the amount of Glx present. The curves drawn through the points have no theoretical significance.

Stereochemistry of the Rearrangement. The rearrangement of amides to amines proceeds with retention of stereochemical configuration at the migrating carbon. This point was established by the following experiment. Hydratropic acid was resolved with strychnine and converted into its amide. The observed specific rotation (58.6°) for the (*S*)-(+)-amide compares well with the literature value[16] of 58.3°. The optical purity of the amide was also examined by NMR by using the chiral shift reagent tris[3-[(heptafluoropropyl)hydroxymethylene]-*d*-camphorato]europium(III). PIFA promotes the rearrangement of this amide to (*R*)-(−)-α-phenethylamine with retention of configuration that is complete within the limits of detection of the shift reagent method (see Experimental Section for details). This result is in agreement with that



(85% yield) (4)

(13) (a) Bundgaard, M.; Johansen, M. *J. Pharm. Sci.* **1980**, *69*, 44. (b) Johansen, M.; Bundgaard, H. *Arch. Pharm. Chem., Sci. Ed.* **1980**, *8*, 141.

(14) Loudon, G. M.; Almond, M. R.; Jacob, J. N. *J. Am. Chem. Soc.* **1981**, *103*, 4508–4515.

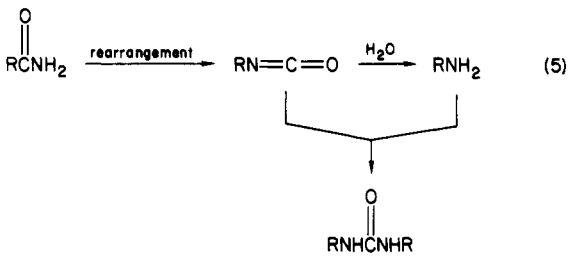
(15) Bunton, C. A. "Oxidation in Organic Chemistry", Part A; Wiberg, K. B., Ed.; Academic Press: New York, 1965; p 403ff.

(16) Arcus, C. L.; Kenyon, J. *J. Chem. Soc.* **1939**, 916–920.

of Pallai and Goodman,[5b] who found that a series of *N*-acyldipeptidyl amides could be rearranged to the corresponding amines uncontaminated by their diastereomers. In those reactions, however, there exists at least the formal, if unlikely, possibility that the stereochemical purity of the product is due to asymmetric induction caused by the penultimate chiral amino acid residue of the dipeptide. The reaction shown in eq 4 rigorously demonstrates that the rearrangement occurs with retention of configuration.

Structure vs. Reactivity of Amides. The rate of the reaction of amides with PIFA can in many cases be followed either by monitoring the release of protons or by NMR spectroscopy. The rate of the rearrangement varies significantly with the structure of the amide, as shown in Table II. The variation of rearrangement rates with structure roughly corresponds to that observed in the Lossen rearrangement; that is, compounds with highly substituted migrating groups or migrating groups that, taken alone, would make relatively stable carbonium ions react most rapidly. This is the same trend that is followed in other reactions in which migration to electron-deficient centers occurs. However, the relative rates in Table II cannot be taken simply as migratory aptitudes because the mechanism of the reaction involves a complexation of the reagent with the amide prior to rearrangement.[6]

Isocyanate Intermediates in the Rearrangement. If this reaction is in fact analogous to the Hofmann rearrangement, the corresponding isocyanate should be an intermediate in the reaction. Indeed, during the rearrangement of hexanamide, *n*-pentyl isocyanate was isolated from the reaction mixture in 29% yield after the conversion of PIFA to iodobenzene was 60 ± 5% complete. The isocyanate survives long enough to be isolated because it hydrolyzes somewhat more slowly than it is formed.[6] However, authentic *n*-pentyl isocyanate does hydrolyze to the amine under the reaction conditions. This finding means that the amine product and the isocyanate intermediate are present together in the reaction mixture in significant concentrations during the reaction. A typical side reaction expected from the simultaneous presence of isocyanates and amines is the formation of ureas (eq 5).

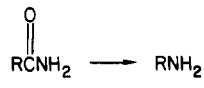


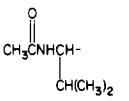
(5)

However, ureas are not observed as products in PIFA-promoted rearrangements because trifluoroacetic acid is liberated as a byproduct. As a result the amine is protonated and therefore protected from undergoing nucleophilic reactions. The liberated trifluoroacetic acid performs the additional function of catalyzing the hydrolysis of the isocyanate.[17]

These results demonstrate that the rearrangement of carboxamides with PIFA is a useful reaction. This reaction formally resembles the similar reaction of lead tetraacetate with amides;[18] however, PIFA is noteworthy for its mildness as an oxidizing reagent. Because of its utility, it seemed appropriate for us to study the mechanism of the reaction. The results of these studies are reported in the accompanying paper.

Table II. Effect of Structure on the Rate of Rearrangement of Amides with PIFA[a]



R	relative rate at pH 2.7	relative rate at pH 1.2
n-C_5H_{11}	(1.00)	(1.00)
$(CH_3)_2CH$	7.6	
$(CH_3)_3C$	5.6	4.8
CH_3	0.09	
cyclohexyl	3.8	
cyclopentyl		2.0
benzyl	2.0	3.9
	56	

[a] 1:1 (v/v) acetonitrile:water. The reactions at pH 2.7 were followed by release of protons; the pH was adjusted with pyridine. The reactions at pH 1.2 were followed in an NMR tube under conditions very similar to those used in the synthetic procedures, except that CD_3CN and D_2O were used as solvent.

Experimental Section

Preparation of [*I*,*I*-Bis(trifluoroacetoxy)iodo]benzene (PIFA, 1). Trifluoroacetic acid was purified by distillation from a small amount of P_2O_5. In 45 mL of purified trifluoroacetic acid was dissolved, with heating, 22.5 g of [*I*,*I*-diacetoxyiodo]benzene[7] (iodobenzene diacetate, Aldrich). PIFA crystallized after the solution was allowed to stand at room temperature, and the PIFA was isolated by suction filtration, mp 124–126 °C (lit.[19] mp 119°; 122–124 °C). It has been the authors' experience that crystallization should be completed within 2 h. The PIFA obtained from solutions that have stood substantially longer than this time does not give good yields in the rearrangement. If PIFA does not crystallize, scratching or seeding the solution generally will induce crystallization. PIFA should be stored in a dark bottle under nitrogen. The importance of using no less trifluoroacetic acid than the 1:2 (weight:volume) proportions indicated above is discussed in the test of this paper.

Representative Procedure for Rearrangement of Amides. Rearrangement of 3-Cyclohexene-1-carboxamide. (a) Preparation of 3-Cyclohexene-1-carboxylic Acid. To an Erlenmeyer flask was added 5.5 g (50 mmol) of 3-cyclohexene-1-carbaldehyde (Aldrich), 50 mL of THF, 8 mL of water, and 10 g (43.1 mmol) of silver oxide. After stirring at room temperature for 4 h, 2 mL of 30% aqueous NaOH was cautiously added, and a vigorous reaction ensued. After about 15 mL of water was added to abate the reaction, another 20 mL of 30% NaOH solution was added very slowly, and the reaction mixture was stirred for 45 min and then filtered on a sintered-glass funnel. The reaction mixture was diluted with water to 300-mL total volume and extracted with two 200-mL portions of ether. The alkaline aqueous layer was cooled and acidified to litmus with concentrated HCl. This solution was then extracted with two 100-mL portions of ether. The combined ether layers were washed with water (2 × 100 mL), dried (anhydrous $MgSO_4$), and concentrated at reduced pressure to afford a 3-cyclohexene-1-carboxylic acid as a pale yellow oil (75% yield). This material was used without further purification in the subsequent procedure.

(b) Preparation of 3-Cyclohexene-1-carboxamide. 3-Cyclohexene-1-carboxylic acid (1.25 g, 10 mmol) and purified

(17) Williams, A.; Jencks, W. P. *J. Chem. Soc., Perkin Trans. 2* **1974**, 1753.

(18) (a) Acott, B.; Beckwith, A. L. *J. Chem. Soc., Chem. Commun.* **1965**, 161. (b) Acott, B.; Beckwith, A. L.; Hassanali, A.; Redmond, J. W. *Tetrahedron Lett.* **1965**, 4039. (c) Baumgarten, H. E.; Staklis, A. *J. Am. Chem. Soc.* **1965**, *87*, 1141. (d) Baumgarten, H. E.; Smith, H. L.; Staklis, A. *J. Org. Chem.* **1975**, *40*, 3554–3661.

(19) (a) Maletina, I. I.; Orda, V. V.; Yagupol'shii, L. M. *J. Org. Chem. (USSR)* **1974**, *10*, 294. (b) Makarchenka, S. S.; Moskal'chuk, A. S.; Glushkova, V. V.; Kogai, T. I.; Polyakova, L. G. *Ibid.* **1975**, *11*, 1246.

thionyl chloride (4 mL) were heated at reflux under anhydrous conditions for 1 h, and the excess thionyl chloride was removed under reduced pressure. The residue was added slowly with a pipet to a stirred ice-cold, concentrated ammonium hydroxide solution. The solid that precipitated was filtered by suction, washed with cold water, and dried in vacuo. Crystallization from chloroform–hexanes afforded 3-cyclohexane-1-carboxamide (0.6 g, 48–49% yield), mp 152–154 °C (lit.[20] mp 155–156 °C).

(c) Preparation of 4-Aminocyclohexene. PIFA (1, 1.73 g, 4.0 mmol) was dissolved in 6 mL of acetonitrile, and 6 mL of distilled water was added. To this solution was added 3-cyclohexene-1-carboxamide (0.50 g, 4 mmol), and the solution was stirred at room temperature for 6 h. The reaction mixture was diluted with 75 mL of water, 8 mL of concentrated HCl was added, and the mixture was extracted with 75 mL of ether. (The addition of HCl converts any remaining PIFA into the ether-soluble iodobenzene dichloride, and also converts the amine into its hydrochloride.) The aqueous layer was concentrated at reduced pressure to give a sticky solid which was thoroughly dried in vacuo. Crystallization from ethanol–ether afforded the hydrochloride of 4-amino-1-cyclohexene in 75% yield: mp 178–179 °C; lit.[21] mp 181–182 °C; NMR (60 MHz, D_2O) δ 5.4–5.6 (m, 2 H, alkene protons); HDO singlet at δ 5.7, 3.15–3.8 (m, 1 H), 1.3–2.7 (m, 6 H).

Precautions. It has been found that the use of glass-distilled water in PIFA-promoted rearrangements is imperative. In the authors' laboratory the deionized water had been passed through a tank with metal fixtures. When water from this tank was used, light green reaction mixtures were produced and the yields were poor. Substitution of glass-distilled water and use of the same batch of PIFA gave good results. We strongly suspect that adventitious metal ions, perhaps Fe(III), may be responsible for the aberrant results.

It is also important that the starting amide used in the rearrangement be completely free from chloride ion. (Chloride can, for example, be a trace contaminant if the amide is prepared from an acid chloride or in any method in which amine hydrochloride salts are present.) The absence of chloride ion may be checked with the silver nitrate test. If chloride ion is present, some of the iodine(III) is precipitated as a yellow gum, presumably iodobenzene dichloride. In addition, the reactions become very dark yellow and the yields are very poor. (Satisfactory reactions are water-white.)

The reaction times required vary with the structure of the amide. The 6-h reaction time used in the representative procedure above is very typical, and reactions can be allowed to run overnight without any apparent ill effect. Some idea of the variation of reaction times with structure can be obtained from the reaction rate data in Table II. As a benchmark we note that hexanamide required about 5.5 h for complete reaction.

Stereochemistry of the Rearrangement. Studies with Chiral Shift Reagent. The amide of 2-phenylpropionic acid (6.5 mg) was dissolved in 1 mL of $CDCl_3$ containing 1% Me_4Si, and 61.2 mg of the shift reagent tris[3-[(heptafluoropropyl)-hydroxymethylene]-*d*-damphorato]europium(III) [Eu(hfc)$_3$] was added. Under these conditions the methyl group doublet appears at 9.74 and 9.83 ppm for one enantiomer and 10.01 and 10.10 ppm for the other. The same experiment with authentic (*S*)-(+)-amide showed that the resonances at the higher field are due to this enantiomer. The resolved amide contained only a trace of the methyl group doublet due to its antipode. These resonances were assigned to the methyl group by observing the shift of the methyl doublet as a function of concentration of the shift reagent. Rearrangements of both racemic and resolved amide were carried out in separate vessels, and, after the usual workup and isolation of free amine, 6 mg of the amine product was dissolved in $CDCl_3$ containing 1% Me_4Si followed by 50 mg of Eu(hfd)$_3$. The methyl group doublets appear at 10.51 and 10.60 ppm for one enantiomer and 10.63 and 10.72 ppm for the other. The product of the reaction of the (*S*)-(+)-amide was found to be the (*S*)-(−)-amine, and its NMR spectrum in the presence of shift reagent under essentially the same conditions showed the doublet at higher field, with only a trace of the other doublet (probably corresponding to the trace of the enantiomer in the starting amide).

Oxidative Decarboxylation of Free α-Amino Acids. A mixture of α-phenylglycine (0.604 g, 4 mmol) and PIFA (1.73 g, 4 mmol) was added to a stirred solution of pyridine (4 mL) in 12 mL of 1:1 (v:v) acetonitrile–water. Immediate evolution of a gas (presumably CO_2) was observed with frothing. After stirring the reaction mixture for 30 min, water (35 mL) was added and the reaction mixture was extracted with two 75-mL portions of ether. The solution was dried (Na_2SO_4) and concentrated to about 10 mL. Addition of an alcoholic solution of 2,4-dinitrophenylhydrazine gave an orange-red precipitate, which was purified by crystallization from 95% ethanol and shown (by comparison with an authentic sample) to be the 2,4-dinitrophenylhydrazone of benzaldehyde. Yield: 0.47 g (42%).

α-Phenylglycine (0.60 g, 4 mol), PIFA (3.41 g, 8 mmol), and pyridine (1.58 g, 20 mmol) were heated in 25 mL of anhydrous benzene on a steam bath. The initially heterogeneous reaction mixture became homogeneous after 30 min of heating. It was heated for an additional 30 min, cooled, and added to 75 mL of water and extracted with two 50-mL portions of ether. The organic layer was washed with three 20-mL portions of 20% aqueous HCl and then with water. The organic layer was dried over anhydrous Na_2SO_4 and concentrated in vacuo to give a pale yellow liquid residue. Analysis by gas chromatography showed that benzonitrile was formed in 50% yield.

Acknowledgment. We gratefully acknowledge the support of this work by the National Institute of General Medical Sciences.

Registry No. 1, 2712-78-9; DABA, 1758-80-1; $CH_3CH_2CONH_2$, 79-05-0; *n*-$C_5H_{11}CONH_2$, 628-02-4; $(CH_3)_3CCONH_2$, 754-10-9; (±)-$C_6H_5CH(CH_3)CONH_2$, 2328-25-8; (*S*)-(±)-$C_6H_5CH(CH_3)$-$CONH_2$, 13490-74-9; *p*-$Ch_3OC_6H_4CH_2CONH_2$, 6343-93-7; O_2N-$C_6H_4CH_2CONH_2$, 91862-01-0; $EtO_2C(CH_2)_2CONH_2$, 53171-35-0; $HO_2C(CH_2)_2CONH_2$, 638-32-4; $Et_2NCOCH(NHAc)(CH_2)_2CONH_2$, 91861-94-8; Ac-Ala-NH-CH[$(CH_2)_2CONH_2$]-CO-Ala-Gly, 91861-95-9; $AcNHCH(CH_2C_6H_5)CONH_2$, 7376-90-1; $AcNHCH(CH$-$(CH_3)_2)CONH_2$, 37933-88-3; $(CH_3)_2CHCONH_2$, 563-83-7; CH_3CO-NH_2, 60-35-5; $C_6H_5CH_2CONH_2$, 103-81-1; $CH_3CH_2NH_2$·HCl, 557-66-4; *n*-$C_5H_{11}NH_2$·HCl, 142-65-4; $(CH_3)_3CNH_2$·HCl, 10017-37-5; (±)-$C_6H_5CH(CH_3)NH_2$, 618-36-0; (±)-$C_6H_5CH(CH_3)NH_2$·HCl, 13437-79-1; (*S*)-(-)-$C_6H_5CH(CH_3)NH_2$, 2627-86-3; *p*-$CH_3OC_6H_4CH_2NH_2$·HCl, 17061-61-9; $O_2NC_6H_4CH_2NH_2$·HCl, 91861-96-0; $EtO_2C(CH_2)_2NH_2$·HCl, 4244-84-2; $HO_2C(CH_2)_2$-NH_2·HCl, 6057-90-5; $Et_2NCOCH(NHAc)(CH_2)_2NH_2$·HCl, 91861-97-1; Ac-Ala-NH-CH[$(CH_2)_2NH_2$]-CO-Ala-Gly·HCl, 91861-98-2; $AcNHCH(NH_2)CH_2C_6H_5$·HCl, 91861-99-3; AcNHC-$H(NH_2)CH(CH_3)_2$·HCl, 91862-00-9; $(CH_3)_2CHNH_2$·HCl, 15572-56-2; CH_3NH_2·HCl, 593-51-1; $C_6H_5CH_2NH_2$·HCl, 3287-99-8; $C_6H_5I(OAc)_2$, 3240-34-4; CF_3CO_2H, 76-05-1; Cl^-, 16887-00-6; C_6H_5CN, 100-47-0; cyclobutylcarboxamide, 1503-98-6; cyclopentylcarboxamide, 3217-94-5; cyclohexylcarboxamide, 1122-56-1; cycloheptylcarboxamide, 1459-39-8; 1-adamantylcarboxamide, 5511-18-2; 3-cyclohexene-1-carbaldehyde, 100-50-5; 3-cyclohexene-1-carboxylic acid, 4771-80-6; 3-cyclohexene-1-carboxamide, 4771-81-7; 1-naphthylacetamide, 86-86-2; α-phenylglycine, 69-91-0; cyclobutylamine hydrochloride, 6291-01-6; cyclopentylamine hydrochloride, 13803-73-1; cyclohexylamine hydrochloride, 4998-76-9; cycloheptylamine hydrochloride, 69163-89-9; 1-adamantylamine hydrochloride, 665-66-7; 1-adamantylamine, 768-94-5; 3-cyclohexenyl-1-amine hydrochloride, 22615-33-4; 1-naphthylmethylamine hydrochloride, 39110-74-2; benzaldehyde 2,4-dinitrophenylhydrazone, 1157-84-2.

(20) Nelson, N. A.; Mortimer, G. A. *J. Org. Chem.* **1957**, *22*, 1146–1153.
(21) Taub, W.; Denss, R.; Oetermayer, F. S. African Patent 67 04 453 (July, 1968); *Chem. Abstr.* **1969**, *70*, P60827e.