Journal of Labelled Compounds and Radiopharmaceuticals
J. Labelled Cpd. Radiopharm. **XLI**, 871-878 (1998)

One Step Synthesis of Deuterium or Tritium Labelled Imines and Aldazine under Mild Conditions

Derek H. R. Barton[a#], Eric Doris[b] and Frédéric Taran[a,b]*

[a] Department of Chemistry, Texas A&M University, P.O. Box 300012, College Station, TX 77842-3012, USA.

[b] CEA/Saclay, Service des Molécules Marquées, Bât. 547, Département de Biologie Cellulaire et Moléculaire, 91191 Gif sur Yvette Cedex, France.

Dedicated to the memory of Sir Derek BARTON

Summary

A novel procedure for the synthesis of labelled imines and aldazines, using a Bu_3P catalyzed decarboxylation reaction, is described.

Key Words: Deuterated imines, tritiated imines, deuterated aldazine, decarboxylation, α-imino acids, tributylphosphine.

Introduction

Aromatic imines are important precursors applied to heterocyclic chemistry. Their interaction with acetylchloride (1,2), phenylacetic acid (3) or a diketene (4), for example, provides easy access to β-lactams in one step. These *Shiff* bases are also able to react with epoxides to give oxazolidines (5, 6). A wide range of products with biological interests could be obtained using

---

[#] Deceased March 16th, 1998.

CCC 0362–4803/98/090871–08$17.50

Received 7 June 1998
Accepted 15 June 1998

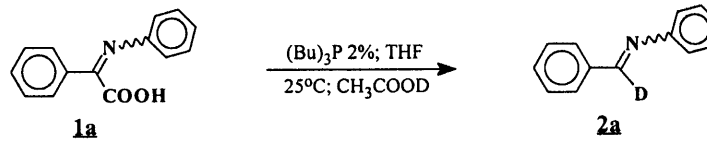
imines as precursors, therefore showing the importance of such labelled compounds. The classical method for the preparation of labelled aromatic imines uses α-deuterated or tritiated benzaldehyde. The synthesis of α-deuterated benzaldehyde has been reported using several procedures such as deuterium oxide hydrolysis of aroyl chlorides derived salts (7), photodeuteriation of phenylglyoxylic acid (8), decarboxylation of deuterated phenylglyoxylic acid (9, 10), or thermal decomposition of deuterated methylbenzylphenyl sulfones (11). It has also been shown that the reaction of a deuterated ylide with nitrosobenzene affords the corresponding α-deuterated imines in reasonable yield (12).

However, these reactions need a large amount of deuterium (tritium) oxide as isotope source and thus can not be reasonably used for tritiated product synthesis. Tritiated benzaldehyde is prepared in most cases by reduction of benzaldehyde with $NaBT_4$ followed by oxidation with silver carbonate (13). Three steps are therefore required for the synthesis of tritiated imines. The purpose of the present article is to report a one step synthesis of deuterium or tritium labelled imines.

Results and Discussion

In a recent publication (14), we described a novel and mild decarboxylation of α-iminoacids catalyzed by tributylphosphine. This reaction affords imines in high yields. During the course of this study, we postulated a mechanism that involves the creation of a P-N bonded intermediate. The formation of this intermediate proceeds with a concomitant proton transfer step. We demonstrated that acetic acid acts as a proton donor and increases the reaction rate. Therefore, we investigated the potentiality of obtaining labelled imines by this method, using readily available deuterated or tritiated acetic acid.

Table 1 shows the influence of the amount of deuterated acetic acid in the Bu_3P catalyzed decarboxylation of (*N*-phenylbenzimidoyl) formic acid **1a**. Using an excess of acetic acid-*d*, the corresponding imine **2a** could be obtained in quantitative yield with high isotopic enrichment.



1a **2a**

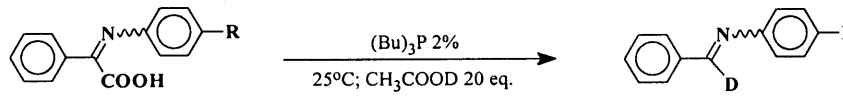
Scheme 1

Table 1. Influence of the amount of CH_3CO_2D in the formation of **2a**

Entry	CH_3CO_2D	Reaction Time	Yields of **2a**	Isotopic Purity*
1	1 eq.	1h 30 min	100 %	45%
2	2 eq.	1 h	100 %	60%
3	5 eq.	30 min	100 %	76%
4	10 eq.	20 min	100 %	87%
5	20 eq.	10 min	100 %	92%

* determined by ^{1}H NMR.

These results, as well as the simple and mild conditions used, prompted us to further investigate the scope and limitations of this labelling strategy. A large number of labelled substituted aromatic imines **2** could be obtained using this procedure (Scheme 2, Table 2). However, it is not suitable for iminoacids with steric hindrance close to the nitrogen atom (14).



1 **2**

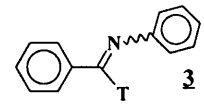
Scheme 2

Table 2. Decarboxylation of iminoacids **1** catalyzed by Bu_3P.

1	R	Solvent	Reaction Time	Yields of **2**	Isotopic Purity*
a	H-	THF	10 min	100%	92%
b	CH_3-	Pyr.	10 min	100%	91%
c	CH_3O-	THF	16 h	100%	83%
d	HO-	THF/Pyr.	2 h	100%	73%
e	$(Me)_2N$-	Pyr.	1 h	100%	87%

* determined by ^{1}H NMR.

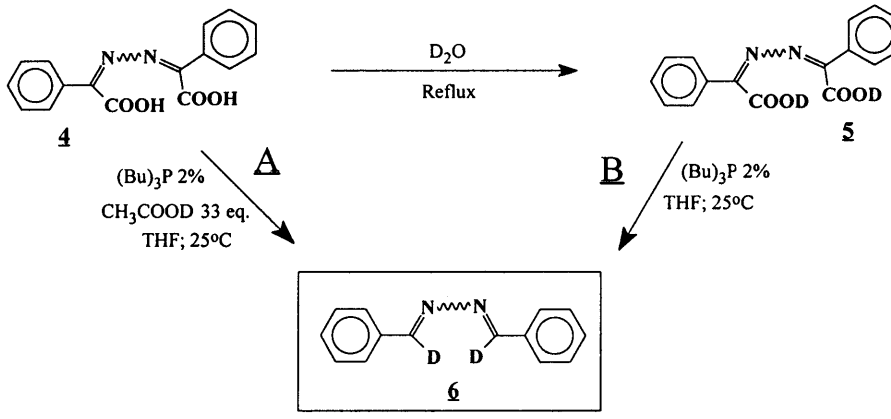
Comparable yields were obtained using tritiated acetic acid (19) as tritium source. The latter was prepared from acetic anhydride that was hydrolyzed with T_2O (from T_2 gas over PtO_2). The expected tritiated imine **3** (Scheme 3) was obtained in quantitative yield and with a specific activity of 12.5 Ci / mmol (unoptimised) upon treatment with 10 eq. of CH_3CO_2T in the presence of Bu_3P.



Scheme 3

In a recent article (15), Ishimoto *et al.* described the thermal decomposition of deuterated azine **5** into aldazine **6** at 180°C. This led to α-deuterated benzaldehyde, after hydrolysis of the corresponding aldazine **6**, in 65% yield and 93 % isotopic purity.

The pyrolysis step is indisputably the cause of the moderate yield obtained. A more convenient decarboxylation reaction can be run efficiently using Bu_3P as catalyst. Indeed, using the same procedure as for iminoacids (*vide supra*), azinodi-phenylacetic acid **4** undergoes facile double decarboxylation to afford deuterated aldazine **6** in quantitative yield (Scheme 4, method **A** and Table 3, entry 1).



Scheme 4

Table 3. Synthesis of bis-deutero aldazine **6**.

Entry	Method	Reaction Time	Yields of **6**	Isotopic Purity*
1	**A**	1h 30 min	100%	92%
2	**B**	1h 30 min	100%	93%

* determined by ^{1}H NMR.

Hydrogen / deuterium exchange can be performed prior to decarboxylation by refluxing **4** in deuterium oxide (Scheme 4, method **B** and Table 3, entry 2). However, this two steps procedure did not increase the isotopic purity of the corresponding aldazine.

In conclusion, α-deuterated, α-tritiated imines and deuterated aldazine were conveniently prepared in quantitative yields. Mild conditions and readily available labelled starting materials are involved in this one step process.

Experimental Section

General procedure for the preparation of α-deuterated imines **2**.

α-iminoacids were prepared from Benzoylformic acid and aromatic amines as previously described (16). To a stirred mixture of the iminoacid (1 mmol) in anhydrous THF or pyridine (20 mL) was added CH_3CO_2D (1.2 mL; 20 mmols). After stirring for 15 min at room temperature under argon, Bu_3P (5 μL; 0.02 mmol) was added. The reaction was monitored by TLC or by GC after derivatization of the starting iminoacid by diazomethane. The solvent was then removed under reduced pressure to afford the imine in quantitative yield.

N-(deutero-phenyl-methylene)-aniline **2a**

white solid; mp = 52-53°C (lit. (12,17,18) 50-53°C); ^{1}H NMR ($CDCl_3$) δ_{ppm} = 7.21-7.29 (m, 3H, Ar), 7.37-7.51 (m, 5H, Ar), 7.90-7.95 (m, 2H, Ar), 8.46 (s, residual CHN); IR (KBr) ν cm^{-1} = 2167 (C-D), 1713 (C=N); MS/EI : m/e = 182.

N-(deutero-phenyl-methylene)-4-methyl-aniline **2b**

yellow solid; mp < 40°C; ^{1}H NMR ($CDCl_3$) δ_{ppm} = 7.13-7.25 (m, 4H, Ar), 7.45-7.51 (m, 3H, Ar), 7.88-7.93 (m, 2H, Ar), 8.47 (s, residual CHN); IR (KBr) ν cm^{-1} = 2165 (C-D), 1617 (C=N); MS/EI : m/e = 196.

N-(deutero-phenyl-methylene)-4-methoxy-aniline **2c**

yellow solid; mp = 65-67°C; ^{1}H NMR ($CDCl_3$) δ_{ppm} = 6.90-6.94 (d, 2H, Ar), 7.22-7.25 (d, 2H, Ar), 7.43-7.47 (m, 3H, Ar), 7.86-7.91 (m, 2H, Ar), 8.47 (s, residual CHN); IR (KBr) ν cm^{-1} = 2161 (C-D), 1608 (C=N); MS/EI : m/e = 212.

N-(deutero-phenyl-methylene)-4-hydroxy-aniline **2d**

yellow solid; mp = 180-183°C; ^{1}H NMR (CD_3OD) δ_{ppm} =6.81-6.85 (d, 2H, Ar), 7.16-7.21 (d, 2H, Ar), 7.44-7.47 (m, 3H, Ar), 7.85-7.88 (m, 2H, Ar), 8.53 (s, residual CHN); IR (KBr) ν cm^{-1} = 2196 (C-D), 1609 (C=N).

N-(deutero-phenyl-methylene)-4-*N',N'*-dimethyl-aniline **2e**

dark green solid; mp = 90-93°C; ^{1}H NMR ($CDCl_3$) δ_{ppm} = 6.74-6.79 (d, 2H, Ar), 7.25-7.31 (d, 2H, Ar), 7.41-7.48 (m, 3H, Ar), 7.87-7.91 (m, 2H, Ar), 8.52 (s, residual CHN); IR (KBr) ν cm^{-1} = 2156 (C-D), 1611 (C=N); MS/EI : m/e = 225.

N-(tritio-phenyl-methylene)-aniline **3**

^{3}H NMR ($CDCl_3$) δ_{ppm} = 8.4 (s). Specific Activity: 12.5 Ci / mmol.

Preparation of bis-(deuterio-phenyl-methylene)-hydrazine **6.**

azinido-phenylacetic acid was prepared from Benzoylformic acid and hydrazine in acetic acid as previously described (15).

Method **A** : To a stirred mixture of carboxy-azine **4** (1 mmol) in anhydrous THF (10 mL) was added CH_3CO_2D (2 mL; 33 mmols). After stirring for 15 min at room temperature and under argon, Bu_3P (5 µL; 0.02 mmol) was added. The reaction was monitored by GC after derivatization of the starting azine by diazomethane. The solvent was then removed under reduced pressure to afford aldazine **6** as a yellow powder in quantitative yield.

Method **B** : A mixture of carboxy-azine **4** (1 mmol) in 3 mL of D_2O was heated to reflux for 30 min under argon. Deuterium oxide was then removed under reduced pressure. The overall procedure was repeated twice. The deuterated carboxy-azine **5** thus obtained was dissolved in anhydrous THF and Bu_3P (5 µL; 0.02 mmol) was added under argon. Carboxy-azine **4** undergoes quantitative double decarboxylation in 1h 30 min.

bis-(deutero-phenyl-methylene)-hydrazine **6**

yellow solid; mp = 88-90°C (lit. (15) 93-94°C); ^{1}H NMR ($CDCl_3$) δ_{ppm} = 7.42-7.49 (m, 6H, Ar), 7.92-7.94 (m, 4H, Ar), 8.69 (s, residual CHN); IR (KBr) ν cm^{-1} = 2132 (C-D), 1717 (C=N); MS/EI : m/e = 210.

Acknowledgments

We thank the Welch Foundation and Unilever Ltd. for the support of this work. We also thank Dr. Bernard Rousseau and Dr. Jean-Christophe Cintrat for helpful discussions. Mr. Alain Valleix, Mr. Frédéric Dupond, and Mrs. Florence Pillon are acknowledged for their help during this work.

References and Notes

(1) Casadei M.A., Moracci F.M. and Inesi A. - J. Chem. Soc. Perkin Trans. 2 419 (1986).

(2) Sheehan J.C. and Ryan J.J. - J. Am. Chem. Soc. 73: 1204 (1951).

(3) Cossio F.P., Ganboa I., Garcia J. M., Lecea B. and Palomo C. - Tetrahedron Lett. 28: 1945 (1987).

(4) Sasaki A., Goda K., Enomoto M. and Sunagawa M. - Chem. Pharm. Bull. 40: 1094 (1992).

(5) Dereig M.E., Early R.I., Fryer R.J., Lopresti R.M., Schweiniger L.H. and Wharton H. - Tetrahedron 27: 2591 (1971).

(6) Hayashi S., Furukawa M., Fujino Y., Okabe H. and Nakao T. - Chem. Pharm. Bull. 19: 2404 (1971).

(7) Scott C.A., Smith D.G and Smith D.J.H. - Synth. Commun. 6: 135 (1976).

(8) Defoin A., Defoin-Stratman R. and Kuhn H.J. - J. Label. Comps. Radiopharm. 19: 891 (1982).

(9) Craig J.C. and Ekwuribe N.N.- Synthesis 909 (1990).

(10) Craig J.C. and Kray L.R.- J. Org. Chem. 33: 871 (1968).

(11) Wladislaw B., Marzorati L. and Uchôa R.V. J. - Synthesis 964 (1986).

(12) Schlosser M. - Chem. Ber. 97: 3219 (1964).

(13) Cornforth R.M. - Tetrahedron 26: 4635 (1970).

(14) Barton D.H.R., Taran F. - Tetrahedron Lett. (1998), in press.

(15) Ishimoto K., Tsukinoki T., Tsuge O. and Tashiro M. - J. Label. Comps. Radiopharm. 36: 267 (1995).

(16) Moustafa A. and Grigg R. - Tetrahedron 44: 7271 (1988).

(17) Luche J.L. and Kagan H.B. - Bull. Chem. Soc. Fr. 5: 1680 (1969).

(18) Robert A., Pommeret J.J., Marchand E. and Foucaud A. - Tetrahedron 29: 463 (1973).

(19) Evans E.A., Tritium and its Compounds, 2nd Ed., Butterworths: London (1974).

