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precipitation from ethanol and diethyl ether, m.p. 240°C (dec.); $[\alpha]_D^{25}$ −140° (*c* 1.0, water). MS: M^+ 700.

N-*(6,14*-endo-*Etheno-7,8-dihydromorphine-7α-carbonyl)*-L--*phenylalanyl*-L-*leucinol* (**14**)

The hydrochloride of **12** (1.63 g, 2.4 mmol) was converted into the base and dissolved in 30 ml of anhydrous 2-propanol. To this solution, 1.5 g (15 mmol) of anhydrous calcium chloride and 1.14 g (30 mmol) of sodium tetrahydroborate were added. The conversion was complete (TLC) after 6 days at 35°C. Water (50 ml) was then added and the mixture acidified with 2 N hydrogen chloride to pH 2–3. Extraction with a mixture of chloroform and 2-propanol (2 : 1) at pH 8 and work up in the usual way, yielded 1.2 g (78 %) of **14**, which was pure according to TLC. It was recrystallized from aqueous ethanol; m.p. 235°C (dec.); $[\alpha]_D^{25}$ −172° (*c* 0.3, 0.1 N hydrogen chloride). Calcd. for $C_{35}H_{43}N_3O_6$ (601.72): C 69.86, H 7.20, N 6.98; found: C 69.5, H 7.3, N 6.7. MS: M^+ 601. Pure according to HPLC.

Acknowledgements

We thank Mr. *P. Kranenburg* for valuable technical assistance and Messrs. *J. A. de Groot*, *L. J. M. Helvensteijn* and *E. F. Lameijer* for carrying out preliminary experiments. We are grateful to the Management of Diosynth B.V., Apeldoorn, The Netherlands, for gifts of chemicals. We thank the U.S.A. Committee on Problems of Drug Dependence and Dr. *A. E. Jacobson*, Biological Coordinator, for the results of the pharmacological studies. We are indebted to Dr. *A. Brossi* (National Institutes of Health, Bethesda, Maryland, U.S.A.) who acted as intermediary in pharmacological screening.

Trimethylacetic formic anhydride. Improved preparation and use as a highly efficient and selective N-formylating reagent

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(Received June 17th, 1982)

Abstract. The title compound was prepared from trimethylacetyl chloride and sodium formate in the presence of 18-crown-6. The mixed anhydride proved to be a very useful reagent for the N--formylation of amines. Even amines which are unstable when deprotonated can be formylated.

Recently, we reported the synthesis of methyl 2-([^{13}C,^{15}N]-isocyano)propionate[1]. A key step in this synthesis is the introduction of the ^{13}C label in the methyl ester of *N*--([^{13}C]formyl)[^{15}N]alanine, the compound from which the isocyanide is prepared. Introduction occurs by reacting [^{15}N]alanine methyl ester with separately prepared acetic [^{13}C]formic anhydride. This reaction also affords the corresponding acetamide in 8 % yield. Presumably this latter compound results from nucleophilic attack of the amine nitrogen on the acetyl moiety of the mixed anhydride and/or the acetic anhydride formed by disproportionation[2]. Suppression of this reaction should be possible by making the acetyl side of the mixed anhydride less susceptible to nucleophilic attack. This can be achieved by substituting the α-carbon atom of the acetyl part with groups having appropriate steric and/or electric properties. The most obvious compound having these features is trimethylacetic formic anhydride.

Although the existence of the latter compound has been suggested in earlier reports, *Schijf* and *Stevens*[3] were the first to unambiguously establish its presence using NMR spectroscopy. They obtained the mixed anhydride in 60 % isolated yield by reacting trimethylacetyl chloride with sodium formate in THF at 0°C for 24 h. The distilled product contained 1–2 mol % of the corresponding symmetrical anhydrides. Closer investigation[4] revealed that the moderate yield is due to decomposition, both thermally, during the long reaction time, removal of the solvent and distillation of the anhydride, and chemically, by sodium formate and traces of carboxylic acids. The instability of the product obtained by the procedure of *Schijf* and *Stevens* was confirmed by *Harman* and *Hutchinson*[5], who failed to isolate the pure anhydride by distillation at room temperature and 18 mm Hg.

We wish to report an improvement on the literature procedure for the preparation of trimethylacetic formic anhydride. In our procedure the compound is formed in a fast reaction and no separation of solvent is necessary, resulting in effective suppression of the various decomposition paths open to the mixed anhydride.

The title compound can be prepared, without using a solvent, from trimethylacetyl chloride and 1.05 equivalent of sodium formate in the presence of 10 mol % 18-crown-6 at 0°C. The reaction is complete within 3 h and the product can be isolated directly from the reaction mixture by distillation into a cold trap at 0.01 mmHg and 0°C. Yields vary from 95 to 98 %. According to ^{1}H NMR, the only contaminants are traces (less than 1 %) of trimethylacetic acid,

[1] *E. J. Vlietstra, R. J. M. Nolte, J. W. Zwikker, W. Drenth* and *R. H. A. M. Janssen*, Recl. Trav. Chim. Pays-Bas **101**, 183 (1982).

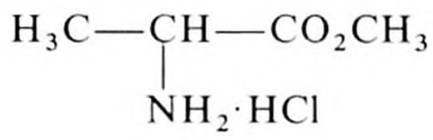
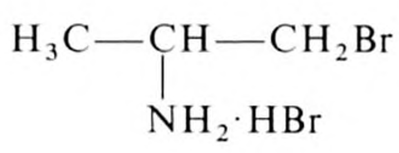
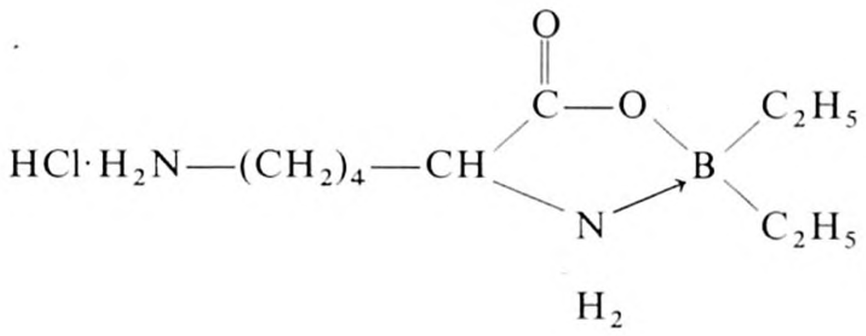
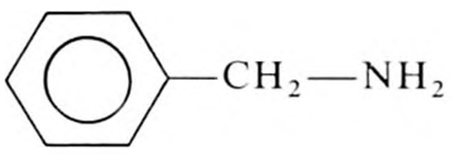
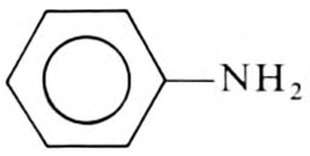
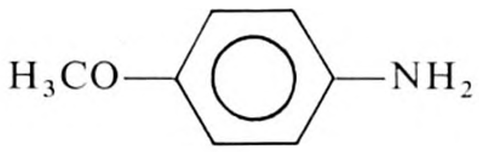
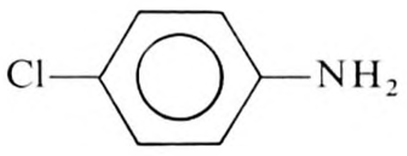
[2] *W. Stevens* and *A. van Es*, Recl. Chim. Pays-Bas **83**, 863 (1964).

[3] *R. Schijf* and *W. Stevens*, Recl. Trav. Chim. Pays-Bas **85**, 627 (1966).

[4] *R. Schijf*, Ph.D. Thesis, State University of Leiden, The Netherlands, 1968.

[5] *A. D. Harmon* and *C. R. Hutchinson*, J. Org. Chem. **40**, 3474 (1975).

Table I N-*Formylation of various amine (salts) by means of trimethylacetic formic anhydride.*

Entry	Amine (salt)	Solvent	Reaction temp./°C	Yield/%[a]
1		$CHCl_3$	25	97
2		$CHCl_3$	0	81
3[b]		CH_3CN	0	91
4		$CHCl_3$	25	94
5		$CHCl_3$	25	96
6		$CHCl_3$	25	93
7		$CHCl_3$	25	95
8		$CHCl_3$	25	100
9		$CHCl_3$	25	95
10		DMSO[c] acetone	25 5	No reaction No reaction

[a] Yields are isolated yields; all products were unambiguously characterised by means of ^1H NMR spectroscopy and, in the cases of solid formamides, melting points. [b] See ref. 6. [c] In DMSO, decomposition of the mixed anhydride with evolution of carbon monoxide occurs.

its anhydride, formic acid and formic anhydride. Because of this, our product can be kept for several months in a freezer without undergoing any detectable change.

The mixed anhydride proved to be an excellent reagent for the N-formylation of a variety of aliphatic, benzylic and aromatic amines. Upon mixing a solution of amine with 1.1 equivalent of anhydride at room temperature, an exothermic reaction occurs. According to ^1H NMR and/or TLC, formylation is complete within 5 minutes. The reaction has a general applicability. Only in the case of 2,4-dinitroaniline was no reaction observed, not even after 4 days. The results obtained with various amines are compiled in Table I. In none of the examples given in Table I could a trace of trimethylacetamide be detected as side-product, thus proving the high selectivity of the reagent.

Due to its high reactivity, trimethylacetic formic anhydride is extremely useful in the formylation of amines which decompose easily via inter- and/or intra-molecular reactions when liberated from their salts (*cf.* entries 1–3 of Table I). Because of this decomposition, the compounds of entries 2 and 3 cannot be formylated using currently available literature methods. However, when these amine salts are deprotonated in the presence of trimethylacetic formic anhydride, the free amine is scavenged and an excellent yield of the corresponding *N*-formamide is obtained.

[6] The preparation of this compound and its use in the functionalisation of the ε-amino group of lysine will be the subject of a forthcoming paper. Its N-formyl derivative melts at 93–94°C.

Experimental

General

Temperatures are uncorrected. All manipulations with water-sensitive compounds were carried out in an atmosphere of dry nitrogen. ^{1}H NMR spectra were obtained using a Varian EM-390 spectrometer, with TMS as internal standard. Melting points were determined using a Mettler-FP5 melting point apparatus. TLC was performed on silica gel (Merck DC-Plasticrolle--Kieselgel 60 F254). Trimethylacetyl chloride and 18-crown-6 were purchased form Aldrich and Fluka, respectively. Trimethylacetyl chloride was distilled immediately before use. Sodium formate (BDH; *pro analysi* quality) was dried at 120°C for 24 h and finely powdered prior to use.

Trimethylacetic formic anhydride

To a vigorously stirred, ice-cooled mixture of 9.69 g (80.4 mmol) of trimethylacetyl chloride and 2.00 g (7.6 mmol) of 18-crown-6 was added 5.74 g (84.4 mmol) of sodium formate in small portions over a period of 15 min. At time intervals of 1 h samples were taken and expanded (0.5 ppm) NMR spectra of the *tert*-butyl pattern were recorded. After 3 h, the reaction was found to be complete. The volatile compounds were distilled at 0°C and 0.01 mmHg into a cold trap affording 9.89 g (95%) of colourless distillate, which proved to be essentially pure trimethylacetic formic anhydride. ^{1}H NMR ($CDCl_3$) δ 1.32 (s, 9 *tert*-butyl), 9.11 (s, 1, formyl H). In addition, the spectrum showed small singlets at δ 1.26, 1.29, 8.02 and 8.75, which are due to traces of trimethylacetic acid, its anhydride, formic acid and formic anhydride, respectively.

Formylation of free amines (general procedure)

To a solution of 1 mmol of amine in 0.5 ml of an appropriate alcohol-free solvent was added dropwise, with vigorous stirring, 1.1 mmol of trimethylacetic formic anhydride. After completion of the reaction (NMR and/or TLC), the solvent was removed *in vacuo*. The oily or solid residue was washed three times with 10 ml portions of hexane in order to remove trimethylacetic acid and its anhydride. Removal of the last traces of hexane *in vacuo* afforded the pure formamide.

Formylation with amine-salts as starting compounds

To a vigorously stirred mixture of 4 mmol of amine salt and 8 ml of solvent was added 4.4 mmol of trimethylacetic formic anhydride. Subsequently, 4 mmol of triethylamine was added dropwise over 15 minutes. After stirring the mixture for 30 min, the solvent was thoroughly removed *in vacuo*. In those cases where the formamide is ether-soluble (entries 1 and 2 of Table), further work up of the residue was performed using procedure A given below. When the formamide is insoluble in ether (entry 3 of Table), work up was accomplished using procedure B.

Procedure A. The residue was washed three times by stirring with 10 ml portions of hexane, followed by decantation. After the final washing, the remaining hexane was thoroughly removed *in vacuo* and the residue extracted three times by stirring with 10 ml portions of ether followed by decantation. Concentration of the combined ether extracts afforded the pure formamide.

Procedure B. The residue was washed three times by stirring with 25 ml portions of ether followed by decantation. After the final washing, the remaining ether was thoroughly removed *in vacuo*. The formamide and triethylamine hydrochloride were separated by column chromatography (column: 20 × 1.5 cm) over silica gel (Merck kieselgel 60: 230–400 mesh) using acetonitrile as eluent.