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# Novel Synthetic Reactions Using 1-Fluoro-2, 4, 6-trinitrobenzene. An Efficient Direct Esterification Method

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Synthetic utility of 1-fluoro-2, 4, 6-trinitrobenzene (FTNB) as a condensing agent was investigated. The use of FTNB and DMAP was found to be very effective for direct esterification of carboxylic acids with alcohols or thiols. However, this system was not very effective for macrolactonization. Reaction of 2, 4, 6-trinitrophenyl esters with several nucleophiles was investigated briefly. Plausible reaction mechanisms of esterification are presented. It seems that the reaction proceeds via the intermediacy of 2, 4, 6-trinitrophenyl esters by initial formation of 2′, 4′, 6′-trinitrophenyl-4-dimethylaminopyridinium salt from which the trinitrophenyl group is transferred to the carboxylic acid.

## Introduction

Esterification of carboxylic acids to the corresponding esters plays an important role in organic synthesis. In synthetic applications such conversions often must be accomplished in complex molecules containing other functional groups. Consequently, it is important that esterification proceeds under mild conditions in high yields.

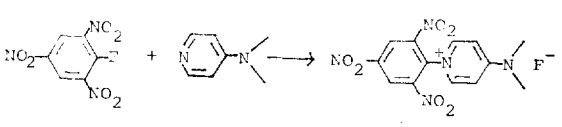
As part of our continuous efforts directed toward the development of new condensing agents, we recently outlined in a preliminary account[1] a convenient method for direct esterification of carboxylic acids using 1-fluoro-2,4,6-trinitrobenzene (FTNB)[2] as a condensing agent under mild conditions. Recent efforts in our laboratory have centered around mechanistic insights of esterification reaction and synthetic usefulness of FTNB in the related reactions. This paper describes a detailed account of our results.

## Results and Discussion

*Preparation of Carboxylic Esters.* It has been previously demonstrated that treatment of equimolar amounts of carboxylic acids and FTNB with 1 equiv of triethylamine in acetonitrile at room temperature for 2 hrs, followed by the addition of equimolar amounts of an alcohol and triethylammine results in the formation of the corresponding esters.[3] The reported procedure was found to be effective only for simple carboxylic acids and alcohols. Esterification of hindered carboxylic acids like pivalic acid gave low yields of esters even under forcing conditions.

Direct esterification using equimolar amounts of benzoic acid, cyclohexanol and FTNB in the presence of 2 equiv of triethylamine at room temperature for 12 hrs was attempted. As the reaction proceeded, it turned to dark brown and cyclohexyl benzoate was obtained in poor yield (24%). Presumably, low yield is due, in part, to the fact that an alcohol also reacts with FTNB in the presence of triethylamine to form its 2,4,6-trinitrophenyl ether. It is known that the reaction of 2,4-dinitrofluorobenzene with alcohols in the presence of triethylamine affords the corresponding 2,4-dinitrophenyl ethers, which are suitable in many instances for the characterization of alcohols.[4] We have indeed observed that treatment of equimolar amounts of FTNB and methanol with excess of triethylamine readily afforded methyl 2,4,6-trinitrophenyl ether. The use of various amine bases such as diisopropylethylamine, imidazole, and pyridine was also found to be ineffective.

$$RCOOH + R'OH \xrightarrow[FTNB]{DMAP} RCOOR' \quad (1)$$



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[I]

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We have found that the use of 4-dimethylaminopyridine (DMAP)[5] as a base proved to be exceedingly effective in the direct conversion of carboxylic acids into carboxylic esters in high yields under mild conditions (eq. 1). The reaction proceeded smoothly at room temperature and only one spot of the desired product was observed on tlc. No trace of 2,4,6-trinitrophenyl ether was observed on tlc. We speculated that the origin of remarkable improvement using DMAP instead of triethylamine may lie in inablity of the formation of 2,4,6-trinitrophenyl ether. Treatment of equimolar amounts of FTNB and DMAP in acetonitrile at room temperature immediately gave the precipitate (eq. 2). The precipitate could be assumed to be 2′, 4′, 6′-trinitrophenyl-4-dimethylaminopyridinium fluoride (I) although the structure of compound I was not vigorously established.[6] There was no indication of the salt formation with FTNB and triethylamine on tlc. As we expected, compound I did not react with simple alkyl alcohols like methanol but slowly react with some acidic alcohols, *i.e.*, β-naphthol and β, β, β-trichloroethanol. These results conclusively suggest that compound I selectively reacts with carboxylic acids or carboxylate anions in the presence of alcohols.

Using similar conditions, several equimolar reactions of carboxylic acids and alcohols by the use of FTNB and DMAP were carried out in acetonitrile at room temperature and good results were obtained as shown in Table 1. As mentioned above, in case of the preparation of β, β, β-trichloroethyl or β-naphthyl esters, it is desirable to use a carboxylic acid with strictly equimolar amounts of FTNB to suppress the formation of the corresponding 2,4,6-trinitrophenyl ether.

Not only simple carboxylic acids but hindered carboxylic acids work well with unhindered alcohols. However, the possibility of synthesizing *t*-butyl esters reaches a limit with even simple carboxylic acids. Higher reaction temperature and the change of solvent did not help the reaction. It is of considerable interest to note that this method is applicable to the preparation of benzyl, β, β, β-trichloroethyl[7] and *trans*-cinnamyl esters[8] important as protecting groups.

**TABLE 1: Direct Esterification of RCOOH with R′OH with FTNB and DMAP in Acetonitrile at Room Temperature**

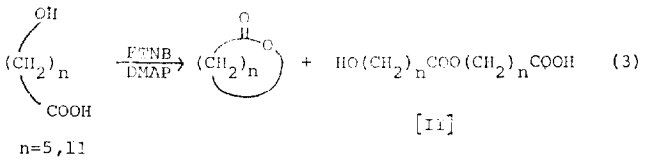
| RCOOH | R′OH | Time | Yield[a] |
|---|---|---|---|
| Benzoic | Cyclohexanol | 6 | 84 %, 24 %[b] |
| Benzoic | Benzyl alcohol | 3 | 94, 54[b] |
| Benzoic | Isopropanol | 6 | 90 |
| Benzoic | t-Butanol | 12 | Trace |
| *trans*-Cinnamic | β, β, β-Trichloroethanol | 2 | 98, 51[c] |
| *trans*-Cinnamic | β-Naphthol | 4 | 98 |
| Isobutylic | Benzyl alcohol | 12 | 84 |
| Diphenyl acetic | Cinnamyl alcohol | 6 | 99 |
| Diphenyl acetic | Isopropanol | 24 | 92 |
| Pivalic | Cinnamyl alcohol | 20 | 93 |
| Pivalic | β-Naphthol | 3 | 92 |
| Pivalic | t-Butanol | 24 | 0 |

[a] The yields refer to isolated yields of pure products; [b] With 2 equiv or triethylamine; [c] With 2 equiv of triethylamine and a catalytic amount of DMAP.

*Preparation of Macrocyclic lactones.* The importance of macrolactonization in organic synthesis has been recognized in recent years and a number of macrolactonization methods have been developed.[9]

We have attempted to extend our esterification method to macrolide synthesis (eq. 3). In order to determine the effectiveness of this method in macrolactonization, we chose two simple model compounds, *i.e.* 12-hydroxydodecanoic acid and 6-hydroxyhexanoic acid.

When equimolar amounts of 12-hydroxydodecanoic acid and FTNB were treated with 2 equiv of DMAP in acetonitrile at reflux for 24 hrs, the isolated yield (20 %) of 12-dodecanolide was disappointingly low. The product was characterized by comparison with an authentic sample, prepared by triphenylphosphine-2,2′-dipyridyl disulfide method,[10] by spectroscopic methods (nmr, ir, gc) and chromatographic behaviors in a variety of solvents.



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The major byproduct, more polar than 12-dodecanolide on tlc, was also isolated in 15-35% yield after chromatographic separation. In order to establish the structure of the major byproduct, we treated it with methanol in the presence of a catalytic amount of *p*-toluenesulfonic acid at reflux. Its nmr spectrum exhibited a singlet (3H) at 3.75 ppm, indicative of the methyl ester, and multiplets (4H) at 3.6-3.8 ppm and its ir spectrum exhibited carbonyl absorption at 1730 and 1710 $cm^{-1}$. On the basis of spectroscopic data, we concluded that the product must be compound II resulting from intermolecular esterification.

Several experiments were further carried out using 6-hydroxyhexanoic aicd. The lactonization was somewhat improved, albeit with still unattractive efficiency. As shown in Table 2, no remarkable solvent effect was observed. Similarly, the changes of reaction temperature did not help the reaction. These results indicate that this method is not effective for macrolactonization unlike analogous esterification.

*Preparation of thiol Esters.* Thiol esters have attracted a great deal of recent attention as active acylating agents,[11] especially in the synthesis of macrocyclic lactones.[9]

**TABLE 2: Cyclization of ω-Hydroxycarboxylic Acids with FTNB and DMAP to Lactones**

| ω-Hydroxyacid | Solvent | Temperature | Time | Isolated Yield |
|---|---|---|---|---|
| $HO(CH_2)_{11}COOH$ | $CH_3CN$ | 80°C | 25h | 25% |
| $HO(CH_2)_{11}COOH$ | $CH_3CN$ | 25 | 35 | 15 |
| $HO(CH_2)_{11}COOH$ | $CH_2Cl_2$ | 50 | 46 | 11 |
| $HO(CH_2)_5COOH$ | $CH_3CN$ | 25 | 24 | 34 |
| $HO(CH_2)_5COOH$ | $CH_3CN$ | 80 | 24 | 40 |
| $HO(CH_2)_5COOH$ | $CH_2Cl_2$ | 25 | 24 | 33 |
| $HO(CH_2)_5COOH$ | $C_6H_5CH_3$ | 110 | 24 | 36 |

We have observed that treatment of equimolar amounts of carboxylic acids and FTNB with 2 equiv of DMAP in acetonitrile at room temperature for 10 mins, followed by the addition of 1 equiv of a thiol results in the conversion of carboxylic acids into thiol esters in high yields. It is required to use equimolar amounts of a carboxylic acid and FTNB, and to follow the sequence of mixing to suppress the formation of the corresponding 2,4,6-trinitrophenyl thioether. For instance, when equimolar amounts of a carboxylic acid and a thiol were treated with FTNB and DMAP, a small amount of 2,4,6-trinitrophenyl thioether was observed on tlc. In addition to the desired thiol ester, the pale yellow spot was sometimes observed on tlc. The pale yellow spot was a trace amount of impurity, not detectable by nmr spectrum and could be removed by silica gel column chromatography. This impurity is presumed to be the disulfide formed by air oxidation of the thiol.

To determine the scope and the limitation of this reaction, the preparation of thiol esters has been performed on both arene- and alkanecarboxylic acids utilizing primary, secondary, tertiary, and aryl alcohols as shown in Table 3. Generally, arene- and simple carboxylic acids give thiol esters in high yields. However, hindered carboxylic acids like pivalic acid or diphenylacetic acid do not work well with thiols, yielding thiol esters in poor yields irrespective to steric hindrance of thiols.

A noteworthy feature of this method is a facile preparation of *t*-butyl thiol esters[12] from simple carboxylic acids. This method is advantageous when it is not practical to convert the carboxylic acid to an acid chloride and when it is necessary to avoid strong acids or strong bases.

**TABLE 3. Preparation of Thiol Esters' Using FTNB and DMAP in Acetonitrile at Room Temperature**

| RCOOH | R'SH | Time | Yield (RCOSR') |
|---|---|---|---|
| Benzoic | *n*-BuSH | 4h | 95 % |
| Benzoic | *t*-BuSH | 15 | 95 |
| Benzoic | PhSH | 3 | 98 |
| *trnas*-Cinnamic | *n*-BuSH | 1 | 92 |
| *trans*-Cinnamic | *s*-BuSH | 12 | 87 |
| *trnas*-Cinnamic | *t*-BuSH | 24 | 94 |
| *trans*-Cinnamic | PhSH | 12 | 97 |
| Stearic | *n*-BuSH | 12 | 84 |
| Stearic | *s*-BuSH | 24 | 80 |
| Diphenylacetic | *n*-BuSH | 24 | 36 |
| Diphenylacetic | PhSH | 24 | 46 |
| Pivalic | *n*-BuSH | 24 | 44 |

*Reaction of Carboxylic Acids with FTNB and DMAP in the Presence of Two Competing Nucleophiles.* Selective reaction of reactive carboxylic acid derivatives such as active esters or mixed anhydrides with competing nucleophiles, *i.e.* alcohls, amines, and thiols, is often difficult to achieve in organic synthesis. Such selective conversion is of considerable interest in the functional group manipulation of complex molecules.

In order to study the possibility of differentiation of competing nucleophiles in the esterification reaction, several experiments were carried out using *trans*-cinnamic acid and benzoic acid in the presence of equimolar amounts of two competing nucleophiles as shown in Table 4.

When *trans*-cinnamic acid was treated with an equimolar mixture of ethanol and *n*-butyl mercaptan in a similar manner as adopted in the previous esterification, *n*-butyl thiol ester was exclusively obtained in 86% yield. However, using an equimolar mixture of ethanol and *t*-butyl mercaptan, the selectivity was lost. When benzoic acid or *trans*-cinnamic acid was treated with an equimolar mixture of ethanol and *sec*-butylamine, the corresponding amine was exclusively obtained. However, the selectivity was considerably decreased in the reaction of benzoic acid with an equimolar mixture of ethanol and aniline. Using *n*-butyl mercaptan and sec-butylamine, the thiol ester formation was a major course of the reaction.

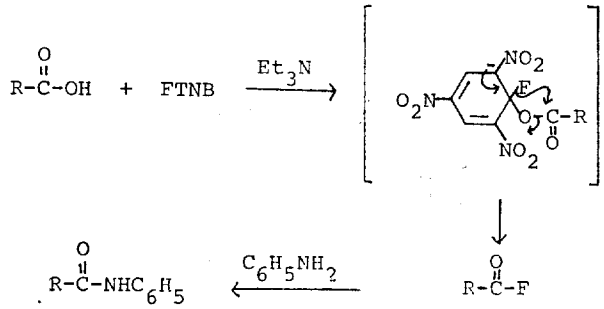
In conclusion, when two competing nucleophiles have the same degree of steric hindrance, it is possible to selectively convert simple carboxylic acids to thiol esters or amides in the presence of alcohols. Furthermore, it seems that the selectivity very much depends on the structure of both carboxylic acids and nucleophiles, although relative reactivity of nucleophiles within a limited series was observed as thiol> amine>alcohol.

*Preparation of 2,4,6-Trinitrophenyl Esters.* Kotake *et al.*[13] have previously reported that treatment of carboxylic acids with FTNB in the presence of 1 equiv of triethylamine, followed by the addition of aniline results in the carboxanilides in good yields. They speculated that the reaction proceeds

**TABLE 4: Reaction of Carboxylic Acids with FTNB and DMAP in the Presence of Two Competing Nucleophiles**

| Acid | Nucleophiles | Time, h | Products | Isolated Yields |
|---|---|---|---|---|
| *trans*-PhCH=CH-COOH | *n*-BuSH | 24 | *trans*-PhCH=CH-CO-S-*n*-Bu | 86 % |
| | EtOH | | *trans*-PhCH=CH-COOEt | 0 |
| *trans*-PhCH=CH-COOH | *t*-BuSH | 15 | *trans*-PhCH=CH-CO-S-*t*-Bu | 43 |
| | EtOH | | *trans*-PhCH=CH-COOEt | 50 |
| *trans*-PhCH=CH-COOH | *sec*-BuNH$_2$ | 24 | *trans*-PhCH=CH-CO-NH-sec-Bu | 94 |
| | EtOH | | *trans*-PhCH=CH-COOEt | 0 |
| *trans*-PhCH=CH-COOH | *n*-BuSH | 4 | *trans*-PhCH=CH-CO-S-*n*-Bu | 70 |
| | *sec*-BuNH$_2$ | | *trans*-PhCH=CH-CO-NH-*sec*-Bu | 20 |
| PhCOOH | PhNH$_2$ | 20 | PhCONHPh | 60 |
| | EtOH | | PhCOOEt | 30 |
| PhCOOH | *sec*-BuNH$_2$ | 24 | PhCONH-*sec*-Bu | 94 |
| | EtOH | | PhCOOEt | 0 |

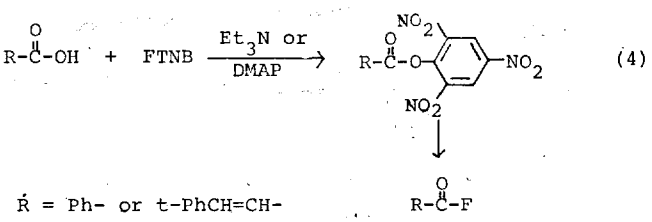
*via* the intermediacy of acyl fluoride, which was identified by isolation, by the initial formation of anionic sigma complex followed by intramolecular rearrangement as shown in Scheme 1. However, on the basis of our observation during esterification reactions, we speculate that the reaction proceeds *via* the intermediacy of 2,4,6-trinitrophenyl ester by initial formation of compound I from which the 2,4,6-trinitrophenyl group is transformed to carboxylic acids.



**Scheme 1.**

In order to clarify this discrepancy, we attempted to prepare 2,4,6-trinitrophenyl ester using triethylamine. When the reaction of *trans*-cinnamic acid and FTNB with triethylamine was carefully monitered by tlc, we have observed that the reaction mixture was consisted two products at the beginning. As the reaction proceeded, the more polar product was converted into the less polar product, which was cinnamyl fluoride (eq. 4). However, treatment of *trans*-cinnamic acid with FTNB in the presence of 0.3 equiv of triethylamine at room temperature for 3 hrs gave exclusively 2, 4,6-trinitrophenyl ester, which was rather unstable and decomposed to some extent during isolation through silica gel column chromatography. The reaction did not proceed to completion at low base concentrations (0.05 equiv and 0.1 equiv) and small increments of base did not significantly increase the reaction rate. Furthermore, using 1 equiv of triethylamine, the preparation of 2,4,6-trinitrophenyl ester was also accomplished by stopping the reaction after 3 mins. The isolated trinitrophenyl esters were fully characterized by comparison with authentic samples.

DMAP proved to react in a similar manner, although the formation of acyl fluoride was somewhat faster due to more facile nucleophilic attack of fluoride ion in 4-dimethylaminopyridinium fluoride.



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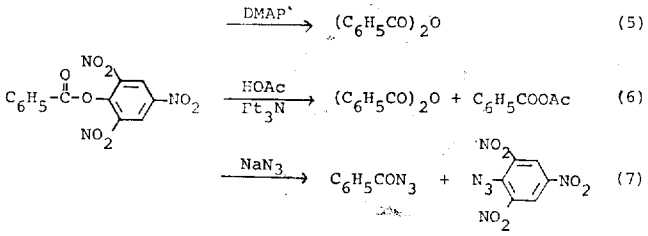
These results clearly demonstrate that the reaction proceeds *via* the intermediacy of 2,4,6-trinitrophenyl ester, followed by nucleophilic attack by fluoride ion. Our finding has useful synthetic applications for the selective conversion of carboxylic acids into either 2,4,6-trinitrophenyl esters or acyl fluorides.

**TABLE 5: Preparation of 2,4,6-Trinitrophenyl Esters**

| Acid | Base | Time | Yield |
|---|---|---|---|
| trans-Cinnamic | 0.3 Equiv $Et_3N$ | 3 h | 76 % |
| trans-Cinnamic | 0.3 Equiv DMAP | 24 h | 80 |
| trans-Cinnamic | 1 Equiv DMAP | 3 min | 85 |
| trans-Cinnamic | 1 Equiv DMAP | 2 h | 85[a] |
| Benzoic | 0.3 equiv $Et_3N$ | 3 h | 86 |
| Benzoic | 1 Equiv $Et_3N$ | 3 min | 70 |
| Benzoic | 1 Equiv $Et_3N$ | 3 h | 82[b] |

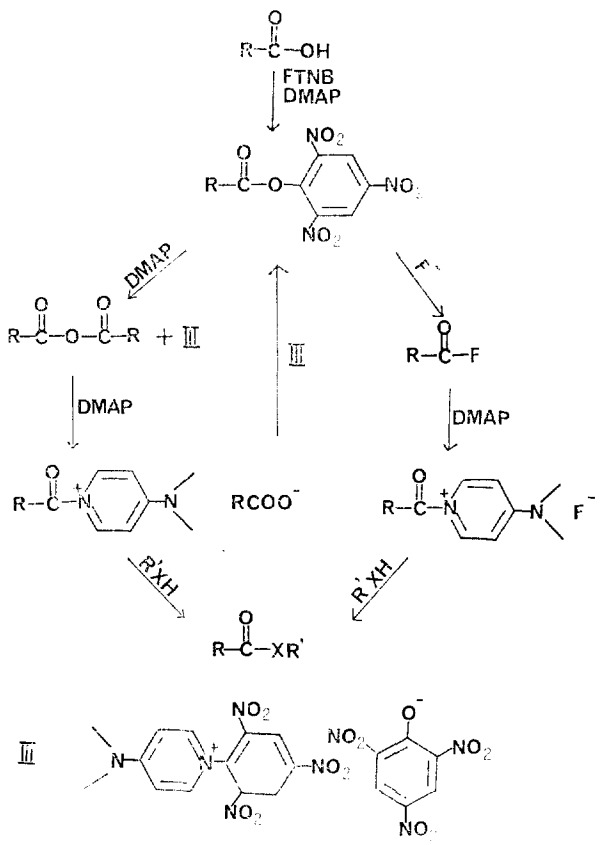
[a] The isolated yield of trans-Cinnamoyl fluoride; [b] The isolated yield of benzoyl fluoride.

*Reaction of 2,4,6-Trinitrophenyl Esters with Several Nucleophiles.* Since there are two reactive electrophilic centres in the nitrophenyl esters, the reaction of nitrophenyl esters with nucleophiles is of importance in mechanistic and synthetic aspects. It has been reported that a number of nitrophenyl esters of carboxylic acids underwent simultaneous aryl- and acyl-oxygen fission with benzenethioate ion and exclusive acyl-oxygen fission with piperidine.[14] Generally, it is believed that the orientation of the attack depends mainly on the relative hardness and softness of the carbonyl carbon and the aryl carbon respectively.



Treatment of 2,4,6-trinitrophenyl benzoate with 1 equiv of DMAP in acetonitrile at room temperature for 3hrs afforded benzoic anhydride (eq. 5), resulting from the attack by DMAP at the aromatic ring and subsequent attack by carboxylate ion at the carbonyl centre. The use of triethylamine as a nucleophile proved to behave in a same way according to tlc, although tlc indicated still the presence of a small amount of starting material even after prolonged stirring. Attempts to separate benzoic anhydride by silica gel column chromatography were unsuccessful due to similar $R_f$ values and partial decomposition of two products.

Unlike aryl-oxygen fission by DMAP and triethylamine, aryl- and acyl-oxygen fission were concurrently occurred for carboxylate ion and azide ion, (eq. 6 and 7). Treatment of 2,4,6-trinitrophenyl benzoate with an equimolar mixture of acetic acid and triethylamine at room temperature for 4 hrs afforded a mixture of benzoic-acetic anhydride and benzoic anhydride in a ratio of 7:3, thus demonstrating that acyl-oxygen fission for carboxylate ion is the major course of the reaction. The ratio of products was determined by NMR analysis. Treatment of 2,4,6-trinitrophenyl benzoate with 3 equiv of sodium azide in acetonitrile at room temperature for 4 hrs afforded 1-aza-2,4,6-trinitrobenzene in 40 % yield and benzoyl azide in 33 % yield after separation by silica gel column chromatography. 1-Aza-2,4,6-trinitro-



**Scheme 2.**

benzene was identical with the product obtained from the reaction of FTNB with sodium azide. The reaction of 2,4,6-trinitrophenyl benzoate with potassium cyanide was not clean and turned to dark brown. Attempts to identify the products were unsuccessful.

*Reaction Mechanism of Esterification.* Possible mechanisms which appear to be consistent with our experimental data are depicted in Scheme 2 for the esterification of carboxylic acids. The intermediacy of 2,4,6-trinitrophenyl esters can be reasonably explained by our earlier results. The transformation from 2,4,6-trinitrophenyl esters to N-acylpyridinium salts, apparently reactive interemidiate to react with nucleophiles, seems to proceed by two reaction pathways.

A pathway for the formation of N-acylpyridinium salts could involve the formation of acid anhydrides followed by nucleophilic attack of DMAP. The N-acylpyridinium salts could then react with nucleophiles, *i.e.* alcohols or thiols, to form the esters. Under the present reaction conditions, the carboxylate ion produced in this reaction appears to be recycled to raise the yield of overall reaction due to the fact that 2,4,6-trinitrophenylpyridinium picrate (III) could transfer 2,4,6-trinitrophenyl group to the carboxylic acids or the carboxylate ions like previous compound I.

Another pathway could involve acyl fluorides generated from 2,4,6-trinitrophenyl esters by nucleophilic attack of fluoride ion at the carbonyl center, followed by attack of DMAP to form N-acylpyridinium salts. Since reaction of 2,4,6-trinitrophenyl esters with DMAP or fluoride ion seems to be very fast and it is rather difficult to isolate and to identify the possible intermediates, *i.e.* acid anhydrides and acyl fluorides. Attempts to determine the exact course of the reaction were unsuccessful. Under the present reaction conditions, it is reasonable to assume that two reaction pathways could competitively take place, although they could depend on the structure of carboxylic acids.

A more detailed definition of how individual steps occur and a determination of relative rates of competitive reactions seem to be interesting prospects for future investigations.

## Experimental Section

Melting points were obtained on Electrothermal apparatus. and are uncorrected. Proton NMR spectra were taken on Varian T-60A Spectrometer in $CDCl_3$ or $CCl_4$ relative to tetramethylsilane as internal standard. Infrared spectra were taken on Perkin-Elmer 267 Spectrometer. GLC analysis were performed on Varian 2800 Gas Chromatograph Instrument using 10 ft, 10 % silicone SE-30 column. Analytical thin layer chromatography was performed on silica gel coated glass plates (Merck F-254). Silica gel (Activity III, ICN 04526) was used for column chromatography.

Acetonitrile was freshly distilled over calcium hydride under nitrogen. Toluene was distilled over sodium under nitrogen and methylene chloride was distilled over phosphorous pentoxide under nitrogen. 1-Fluoro-2,4,6-trinitrobenzene was readily prepared by the reported procedure.[2] Other commercially available reagents were used without further purification. The products obtained were readily available materials in many cases. If not, identification was effected through alternate preparation by the known procedure.

Since the reactions performed are all similar in many respects, the typical reaction will be described as specific examples.

*Preparation of Benzyl Benzoate.* To a mixture of benzoic acid (122 mg, 1.0 mmol) and FTNB (254 mg, 1.1 mmol) in acetonitrile (5 m*l*) were added DMAP (256 mg, 2.1 mmol) and benzyl alcohol (120 mg, 1.1 mmol). After stirring at room temperature for 3 hrs, ethyl ether (10 m*l*) was added to the reaction mixture and the precipitated salts were filtered off. The resulting solution was evaporated and the residue was purified by filtration through a short column of silica gel employing methylene chloride as an eluant. The desired product (198 mg, 94%) was the only compound on solvent removal. The product was found to be identical with an authentic compound in all respects. NMR $\delta$ 5.32 (*s*, 2H), 7.2-8.1 (*m*, 10H); IR(neat) 1720 $cm^{-1}$.

*Preparation of 12-Dodecanolide.* To a reaction mixture of FTNB (107) mg, 0.46 mmol) and DMAP (60 mg, 0.48 mmol) in acetonitrile (4 m*l*) at room temperature was added a solution of 12-hydroxydodecanoic acid (100 mg, 0.46 mmol) in acetonitrile (50 m*l*). The resulting solution was refluxed at 80°C for 25 hrs under nitrogen. The solvent was evaporated and the residue was subjected to silica gel column chromatography using methylene chloride-hexane (1:1) as an eluant to give 12-dodecanolide (23mg, 25 %) and a major byproduct (22 mg). The desired product was found to be identical with an authentic sample in all respects (NMR, IR, GLC, and $R_f$ values in a variety

of solvent systems) GLC analysis was carried out on 10ft, 10 % silicone SE-30 column at 110°C. NMR $\delta$ 4.10 (*t*, 2H), 2.34 (*t*, 2H), 1.2-1.8 (*b*, 18H); IR(KBr) 1735 $cm^{-1}$.

*Preparation of S-n-Butyl Benzothioate.* To a mixed solution of benzoic acid (123 mg, 1.0 mmol) and FTNB (235 mg, 1.0 mmol) in acetonitrile (5 m*l*) at room temperature was added DMAP (249 mg, 2.0 mmol). After stirring for 10 mins, *n*-butanethiol (98 mg, 1.1 mmol) was added to the reaction mixture and the resulting mixture was stirred at room temperature for 4 hrs. After diethyl ether (10 m*l*) was added to the reaction mixture, the precipitated salts were filtered off, the solution was evaporated, and then the residue was purified through a column of silica gel employing methylene chloride as an eluant. The desired thiol ester (184 mg, 95 %) was obtained after solvent removal. The product was found to be identical with an authentic sample in all respects. NMR $\delta$ 0.7-2.0 (*m*, 7H), 3.05 (*t*, *J* 7Hz, 2H), 7.2-8.1 (*m*, 5H); IR ( neat ) 1660 $cm^{-1}$.

*Reaction of trans-cinnamic Acid with FTNB and DMAP in the Presenve of n-Butanethiol and sec-Butylamine.* To mixture of *trans*-cinnamic acid (163 mg, 1.1 mmol), FTNB (234 mg, 1.0 mmol) and DMAP (256 mg, 2.1 mmol) in acetonitrile (5 m*l*) at room temperature was added the freshly prepared acetonitrile solution containing *n*-butanethiol (117 mg, 1.3 mmol) and *sec*-butylamine(95 mg, 1.3 mmol). The reaction mixture was stirred at room temperature for 4 hrs and evaporated to dryness under reduced pressure. The residue was subjected to silica gel column chromatography to give S-*n*-butyl *trans*-cinnamthioate (154 mg, 70 %) using methylene chloride as an eluant and sec-butyl *trans*-cinnamide (41 mg, 20 %) using ethyl acetate as an eluant in order. S-*n*-butyl *trans*-cinnamthioate: NMR $\delta$ 0.8-1.9 (*m*, 7H), 3.05 (*b.t.*, J=7 Hz, 2H), 6.50 (*d*, *J*=16 Hz, 1H), 7.1-7.5 (*m*, 5H), 7.60 (*d*, J=16 Hz, 1H): IR (neat) 1675 $cm^{-1}$. *sec*-Butyl *trans*-cinnamide: NMR $\delta$ 0.7-1.7(*m*, 8H), 3.7-4.2 (*m*, 1H), 6.55 (*d*, *J*=16 Hz, 1H), 7.1-7.5 (*m*, 5H), 7.60 (*d*, *J*=16 Hz, 1H): IR (KBr) 1630 $cm^{-1}$.

*Preparation of 2,4,6-Trinitrophenyl Benzoate.* To a solution of benzoic acid (304 mg, 2.5 mmol) and FTNB (578 mg, 2.5 mmol) in acetonitrile (5 m*l*) at room temperature was added triethylamine (265 mg, 2.6 mmol). The reaction mixture was stirred at room temperature for 3 min, evaporated and the residue was immediately passed through a short column of silica gel employing methylene chloride as an eluant to yield the pale yellow solid product (740 mg). The crude product was recrystallized from chloroform to give a pale yellow crystal (582 mg) in 70 % yield. mp 158-159 °C (*lit.*[14a] 162-163°); IR (KBr) 1765, 1620, 1545, 1345 $cm^{-1}$.

*Anal.* Calcd for $C_{13}H_7N_3O_8$: C, 46.86; H, 2.12; N, 12.61. Found: C, 46.52; H, 1.76; N, 12.57.

*Reaction of 2,4,6-Trinitrophenyl Benzoate with DMAP.* To a solution of 2,4,6-trinitrophenyl benzoate (102 mg, 0.31 mmol) in acetonitrile (5 m*l*) at room temperature was added DMAP (38 mg, 0.31 mmol). The reaction mixture was stirred at room temperature for 3 hrs, evaporated to dryness and the residue was immediately passed through a short column of silica gel employing methylene chloride as an eluant to yield benzoic anhydride (30 mg°) in 87 % yield. The product was identical with an authentic sample in all respects (mp, NMR, and IR).

*Reaction of 2,4,6-Trinitrophenyl Benzoate with Triethylamine and Acetic Acid.* To a solution of 2,4,6-trinitrophenyl benzoate (150 mg, 0.45 mmol) in acetonitrile (3 m*l*) at room temperature was added the freshly prepared acetonitrile solution containing acetic acid (30 mg, 0.5 mmol) and triethylamine (0.5 mmol). The resulting solution was stirred at room temperature for 4 hrs. The solvent was evaporated and the residue was passed through a short column of silica gel employing methylene chloride as an eluant to yield a mixture of benzoic-acetic anhydride and benzoic anhydride 47 mg) NMR $\delta$ 2.4 (*s*, 3H), 7.4-8.3 (*m*, 9H); IR (neat ) 1810, 1780, 1710 cm .

*Reaction of 2,4,5-Trinitrophenyl Benzoate with Sodium Azide.* To a solution of 2,4,6-trinitrophenyl benzoate (234 mg, 0.7 mmol) in acetonitrile (4 m*l*) at room temperature was added sodium azide (130 mg, 2.0 mmol). The resulting solution was stirred at room temperature for 4 hrs and the precipitate was filtered off. The filtrate was concentrated and the residue was chromatographed through the column of silica gel using methylene chloride-hexane (1:1) as an eluant. Benzoyl azide (34 mg, 33 %, $R_f$ 0.56) and 1-aza-2,4,6-trinitrobenzene (66 mg, 40 %, $R_f$ 0.35) were isolated. Benzoyl azide: NMR $\delta$ 7.4-8.2 (*m*); IR ($CHCl_3$) 2135, 1690 $cm^{-1}$. 1-Aza-2,4,6-trinitrobenzene: NMR $\delta$ 9.0(*s*); IR ($CHCl_3$) 2115, 1540, 1345 $cm^{-1}$.

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# The Facile Synthesis of Pentane-1, 5-diamines from Glutaraldehyde and Secondary Amines with Tetracarbonylhydridoferrate

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Ethanolic tetracarbonylhydridoferrate solution combined with glutaraldehyde is a very effective reducing agent for the selective transformation of two moles of secondary amines into pentane-1, 5-diamine derivatives. A variety of aliphatic secondary amines react with ferrate-glutaraldehyde at room temperature under carbon monoxide to give the corresponding N-substituted pentane-1, 5-diamines in reasonable yields.

## Introduction

Several workers have shown that tetracarbonylhydridoferrate acts as an efficient and highly selective reducing reagent with respect to various functional groups.[1~6] In the preceding paper, we reported that a large variety of both aliphatic and aromatic amines react with glutaraldehyde in the presence of tetracarbonylhydridoferrate at room temperature under carbon monoxide to give the corresponding N-alkyl- and N-arylpiperidines in good to excellent yields.[7] Recently, we received a private communication from Laine that catalytic reactions of pyridine with carbon monoxide and water in the presence of $Rh_6(CO)_{16}$ gave dipiperidinopentane-1, 5-diamine and its derivatives.[8] In this connection, the present study deals with the reaction of secondary amines and the ferrate-glutaraldehyde system under carbon monoxide atmosphere.

## Experimental

Potassium tetracarbonylhydridoferrate was prepared according to the method described in previous papers.[9,10] 11 mmol of the ferrate was used in each run. Pentacarbonyliron, secondary amines, aqueous glutaraldehyde (45 %), and the other compounds employed were all commercial products, which have been proved to be sufficiently pure by glpc.

A typical reaction procedure is as follows: to the ethanolic tetracarbonylhydridoferrate derived from pentacarbonyliron (11 mmol) and 1*M*-potassium hydroxide (33 mmol) solution in ethanol, added a secondary amine (22 mmol) using a syringe and then aqueous glutaraldehyde (11 mmol) was added dropwise for 5–10 min. The mixture was stirred vigorously for 24h at room temperature under carbon monoxide. The amount of carbon monoxide absorbed was determined volumetically. The reaction was readily monitored by glpc analysis of the secondary amine consumed. When most of the secondary amine was consumed, the reaction was stopped and potassium carbonate formed in the reaction was filtered off. The filtrate was concentrated to 3–5 m*l* on a rotary evaporator and/ or with Kugelrohr apparatus. The products were purified by careful vacuum distillation, and submitted to analysis.

The glpc analysis was made using internal standards; a column (0.3 cm$\phi$, 3m) packed with 10 % Versamid on Neopak 60–80 mesh was used. The measurements of the H-NMR and IR spectra were made on a JEOL Model 3H 60-NMR spec-