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A Convenient Synthesis of Carboxanilides from Silyl Carboxylates and Weakly Nucleophilic Anilines Using *p*-Trifluoromethylbenzoic Anhydride and a Catalytic Amount of Active Titanium(IV) Salt

Mitsutomo MIYASHITA, Isamu SHIINA, and Teruaki MUKAIYAMA
Department of Applied Chemistry, Faculty of Science,
Science University of Tokyo, Kagurazaka, Shinjuku-ku, Tokyo 162

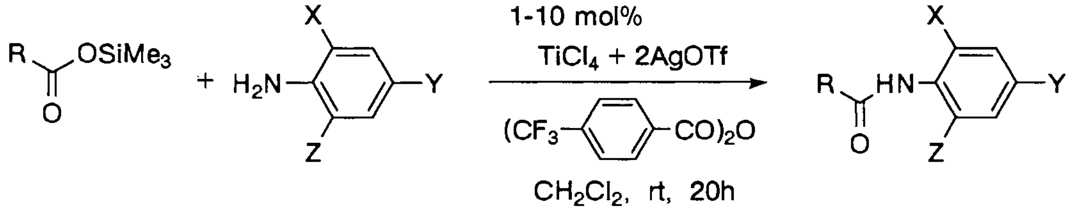
Various carboxanilides are prepared in excellent yields from nearly equimolar amounts of silyl carboxylates and the corresponding *weakly nucleophilic anilines* under mild conditions by using *p*-trifluoromethylbenzoic anhydride and a catalytic amount of active titanium(IV) salt.

Carboxamides are generally prepared by the acylation of amines with acyl halides or carboxylic anhydrides under basic or acidic conditions. Further, many coupling reagents between carboxylic acids and amines have been developed for the effective synthesis of carboxamides.[1] However, in the acylation of *weakly nucleophilic amines* such as nitroanilines and trihaloanilines, drastic reaction conditions have been required to complete the acylation. For example, the acylation of *o*-nitroaniline with excess of acetyl chloride and pyridine was carried out in dibutyl ether at 70 °C to give the corresponding carboxanilide in 88% yield,[2] while treatment of *o*-nitroaniline with 3-phenylpropionyl chloride in the presence of triethylamine at rt for 90 h in dichloromethane afforded the desired carboxanilide in 14% yield.

Recently, two efficient methods for the preparation of carboxanilides derived from *weakly nucleophilic anilines* were reported; that is, transamination of *S*-*t*-butyl carbothioates with *o*-nitroaniline in the presence of more than stoichiometric amounts of silver(I) trifluoroacetate,[3] and acylation of *o*-nitroaniline with acyltrimethylsilylpolyphosphates, prepared from trimethylsilyl carboxylates and phosphorus pentoxide, by heating at 80 °C within several hours.[4] It is still desired to develop further efficient and convenient methods for the synthesis of carboxanilides from simple carboxylic acid derivatives and *weakly nucleophilic anilines.* Now we report a facile method for the preparation of carboxanilides from nearly equimolar amounts of silyl carboxylates and *weakly nucleophilic anilines* under mild conditions by the use of *p*-trifluoromethylbenzoic anhydride and a catalytic amount of active titanium(IV) salt.

First, acylation of *o*-nitroaniline with 3-methylbutanoic anhydride was examined by using a catalytic amount of titanium(IV) salt generated in situ from 1 mol of $TiCl_4$ and 2 mol of AgOTf. This reaction proceeded at rt in dichloromethane to give the corresponding carboxanilide in 77% yield. Next, in order to develop a facile method, the reaction of silyl carboxylates with the *o*-nitroaniline was tried according to the mixed anhydride method recently developed in our laboratory.[5] In the presence of *p*-trifluoromethylbenzoic anhydride and the active titanium(IV) catalyst, the acylation of *o*-nitroaniline with a nearly equimolar amount of trimethylsilyl 3-methylbutanoate proceeded smoothly at rt in dichloromethane to give the desired carboxanilide in 99% yield. It was observed that the reaction was completed at rt, and a by-product formed from *p*-trifluoromethylbenzoic anhydride was not obtained at all. Several examples of the present acylation of *weakly nucleophilic anilines* are listed in Table 1. In every case, the reaction proceeds smoothly at rt to give the corresponding carboxanilides derived from *weakly nucleophilic anilines* such as 2,4-dinitroaniline and 2,4,6-trichloroaniline in excellent yields.

Table 1. Yields of Substituted Anilides Derived from *Weakly Nucleophilic Anilines*[a)]



R	X = NO_2 Y = Z = H	X = Y = NO_2 Z = H	X = NO_2 Y = Cl Z = H	X = Cl Y = NO_2 Z = H	X = Y = Z = Cl
Me	95[b)]	93	99	95	89
^{i}Pr	97	97	99	98	96
^{i}Bu	99	95	99	98	96
^{t}Bu	97	97	99	97	98
Ph$(CH_2)_2$	92	99	97	99	95
o-Me-C_6H_4	95[c)]	97	98	95	99

a) Isolated yield. 10 mo% of catalyst was used.
b) One mol% of catalyst was used. The reaction time was 50 h.
c) Ten mol% of $TiCl_4$ and 30 mol% of AgOTf were used as a catalyst.

A typical experimental procedure is described for the reaction of trimethylsilyl 2,2-dimethylpropionate and *o*-nitroaniline in the presence of a catalytic amount of active titanium(IV) salt generated from $TiCl_4$ and AgOTf; to a suspension of AgOTf (0.05 mmol) and $TiCl_4$ (0.025 mmol) in dichloromethane (2.0 ml), were added successively a mixture of *p*-trifluoromethylbenzoic anhydride (0.275 mmol) and trimethylsilyl 2,2-dimethylpropionate (0.275 mmol) in dichloromethane (1.0 ml) and a solution of *o*-nitroaniline (0.25 mmol) in dichloromethane (1.0 ml). The reaction mixture was kept stirring for an additional 20 h at rt, and then quenched with aq. sat. $NaHCO_3$. After the usual work up, the crude product was purified by preparative TLC on silica gel to afford 2,2-dimethyl-2'-nitropropananilide (97% yield) with excellent chemoselectivity (>200 / 1).

Thus, a facile method for the preparation of carboxanilides derived from *weakly nucleophilic anilines* was successfully developed. Further application of the present acylation method is now in progress.

References

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