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# TRIFLUOROMETHANESULFONIC ACID-PROMOTED REACTION OF HEXAHYDRO-1,3,5-TRIAZINES WITH KETENE SILYL ACETALS. CONVENIENT SYNTHESIS OF ALKYL β-AMINOCARBOXYLATES

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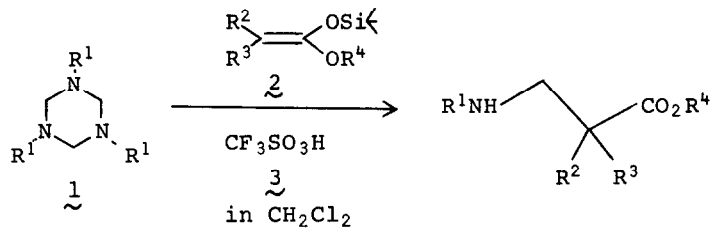
A new, convenient synthesis of alkyl β-aminocarboxylates has been achieved by a reaction of hexahydro-1,3,5-triazines with ketene silyl acetals in the presence of catalytic amount of trifluoromethanesulfonic acid.

β-Aminocarboxylates are important precursors for synthesizing mono-cyclic β-lactams in connection with naturally occurring sulfazecin and related monobactam antibiotics. In earlier paper from this laboratory,[1] a synthetic method for N-ureido-β-aminocarboxylates by a titanium tetrachloride-aided reaction of N-(chloromethyl)carbamates, derived from 1,3,5-trialkylhexahydro-1,3,5-triazines (1) and benzyloxycarbonyl chloride, with ketene silyl acetals (2) was reported. As a part of our continuing studies on the hexahydro-1,3,5-triazine chemistry, we now wish to report that in situ aminomethylation of carboxylates at the α-position is readily achieved by a new reaction of 1 with 2 in the presence of a catalytic amount of trifluoromethanesulfonic acid (3). Of foremost importance, this reaction provides an efficient method for direct introduction of the secondary aminomethyl group $RNHCH_2$ into carboxylates at the α-position. In contrast to

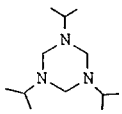
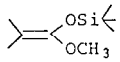
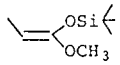
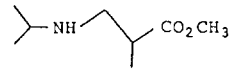
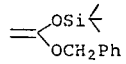
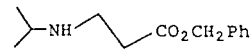
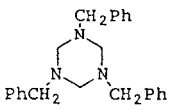
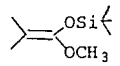
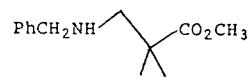
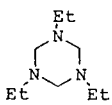
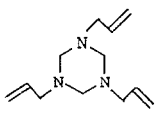
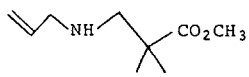
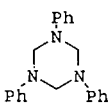
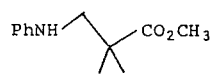
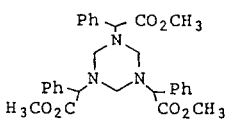
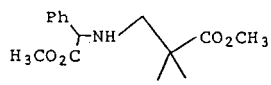
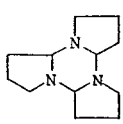
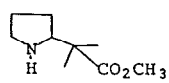
this method, the previously known methods[2] have been limited only to the introduction of the tertiary aminomethyl group $R'RNCH_2$ into carbonyl compounds at the α-position.




A typical experiment (entry 4 in Table 1) is as follows. To a solution of 1,3,5-tribenzylhexahydro-1,3,5-triazine (2 mmol) and dimethylketene methyl trimethylsilyl acetal (6 mmol) in 10 ml of dichloromethane, 3 (0.3 mmol) was added dropwise on cool. The mixture was stirred for 3 hr at room temperature. The solution was washed with 10% potassium bicarbonate solution and dried over anhydrous magnesium sulfate. After removal of the solvent the resulting oily residue was submitted to distillation under reduced pressure to give methyl 2,2-dimethyl-3-(benzylamino)propionate in 82% yield. A liquid: bp 101-102°C(0.15 mmHg); IR (film) 1735(ester C=O) and 3355 $cm^{-1}$(NH); $^1H$ NMR ($CDCl_3$) δ=1.20[6H, s, $C(CH_3)_2$], 1.53(1H, br s, NH), 2.63(2H, s, $NCH_2$), 3.63(3H, s, $OCH_3$), 3.77(2H, s, $C_6H_5CH_2$), 7.27(5H, s, $C_6H_5$); $^{13}C$ NMR ($CDCl_3$) δ=23.6(q), 43.5(s), 51.4(t), 54.3(q), 58.0(t), 126.7(d), 127.9(d), 128.1(d), 140.8(s), and 177.5(s). In preliminary examination for catalyst, trimethylsilyl and di-n-butylboryl triflates were also effective for the above reaction under the same condition, resulting in 85% and 83% yield of the product, respectively, which turn out to be comparable to that displayed by 3. In the initial stage of the reaction 3 may be transformed into trimethylsilyl triflate which functions as a catalyst.

This reaction was extended to the use of a number of derivatives of 1 and 2

Table 1. PRODUCTION OF ALKYL N-ALKYL-β-AMINOCARBOXYLATES

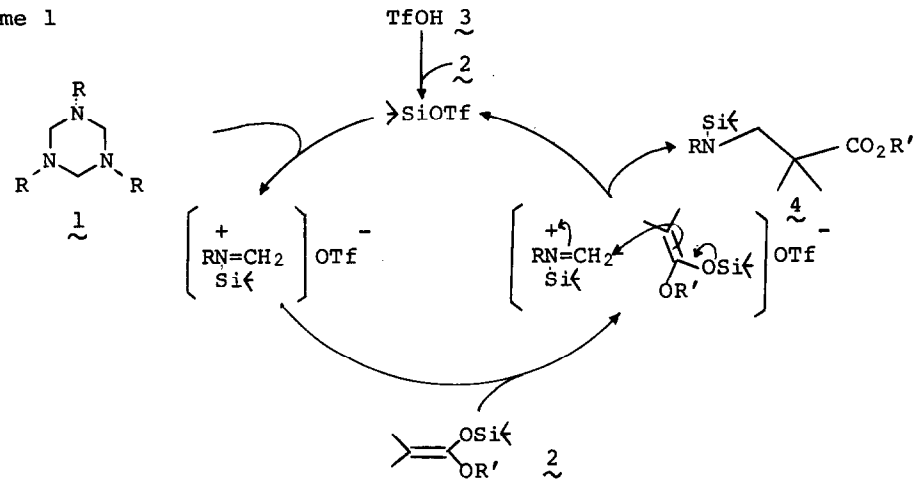
| Entry | Hexahydro-1,3,5-triazine (1) | Ketene silyl acetal (2) | Reaction[a] Temp., hr | Product[b] | Yield[c] (%) |
|---|---|---|---|---|---|
| 1 |  |  | r.t. 5 |  | 83 |
| 2 | 〃 |  | r.t. 1.5 |  | 87 |
| 3 | 〃 |  | r.t. 1.5 |  | 41 |
| 4 |  |  | r.t. 3 |  | 83 |
| 5 |  | 〃 | r.t. 1 |  | 58 |
| 6 |  | 〃 | r.t. overnight |  | 76 |
| 7 |  | 〃 | r.t. 2 |  | 67 |
| 8 |  | 〃 | r.t. 2 |  | 69 |
| 9 |  | 〃 | r.t. overnight |  | 20 |

a) Triazine(1) : Ketene silyl acetal(2) = 1/3(molar proportion), $CF_3SO_3H$: 5 mol%, Solvent: $CH_2Cl_2$. b) All products gave satisfactory elemental analyses and their spectral data were consistent with the proposal structures. c) Based on the product isolated.

and the results are summarized in Table 1. It can be seen from the Table that the in situ N-alkylaminomethylation of carboxylates at the α-position proceeds smoothly at room temperature in fair yield of the products. N-(α-Methoxycarbonyl) benzyl-substituted β-aminocarboxylates (entry 8), which may be converted into a β-lactam, structurally related to nocardicin A, was also produced in considerable yield. The reaction of tetracyclic hexahydro-1,3,5-triazine is exemplified by the use of trimer of 1-pyrroline (entry 9), in which an alicyclic β-aminocarboxylate is afforded, but in somewhat lower yield.

Scheme 1 illustrates the mechanistic rationale for the present reaction. Trimethylsilyl triflate, first formed from 3, enters the catalytic cycle which is initiated by the formation of silylated methylene iminium salt by the reaction with 1 and this intermediate attacks 2 as an electrophile to give 4, along with simultaneous regeneration of trimethylsilyl triflate.

Scheme 1

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2) a) F.F. Blicke, Org. Reactions, 1, 303(1942); b) A. Hosomi, S. Iijima, and H. Sakurai, Tetrahedron Lett., 23, 547(1982) and references cited therein.

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