Communications to the Editor

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A CONVENIENT METHOD FOR THE SYNTHESIS OF αβ-UNSATURATED CARBOXYLIC ACID AMIDES UTILIZING A NEW HETERO-BIFUNCTIONAL REAGENT, DMPATT

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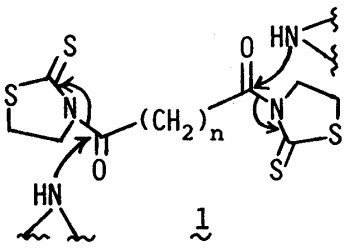
As a new extention of monitored aminolysis of 3-acyl-1,3-thiazolidine-2-thione (ATT), a convenient procedure for the synthesis of αβ-unsaturated carboxylic acid amides has been developed using a new hetero-bifunctional reagent, 3-dimethylphosphonoacetyl-1,3-thiazolidine-2-thione (DMPATT). DMPATT was effectively used as the bridging reagent between amino (or imino) compounds and aldehydes (or ketone) to afford various olefinic amides in good yields.

KEYWORDS ——— thiazolidine-2-thione; hetero-bifunctional reagent; αβ-unsaturated amide; Wittig reaction; feruloyltryptamine

Our recent research interests have been focused on the development of new reactions using functional five-membered heterocycles, particularly 1,3-thiazolidine-2-thione and 1,3-oxazolidine-2-thione derivatives.[1] As a series of studies, we previously reported a homo-bifunctional reagent 1 and a hetero-bifunctional reagent 2.[2] The former 1 was successfully used for the macrocyclic diamide and / or tetramide synthesis[2a] and the bridging reaction[2b] between NH_2 groups of amino acids. The latter 2 was employed to crosslink between the SH group of a cysteine derivative and the ω-NH_2 group of a lysine derivative.[2b]



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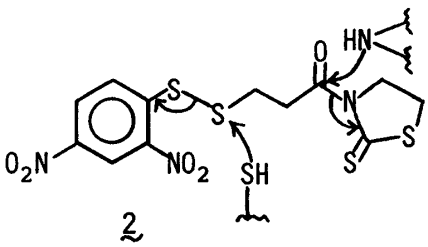

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Now, we wish to report a new hetero-bifunctional reagent, 3-dimethylphosphonoacetyl-1,3-thiazolidine-2-thione (DMPATT) (5), which should be conveniently available for the preparation of αβ-unsaturated calboxylic acid amides 9 using amino (or imino) compounds 6 and aldehydes (or ketone) 8 (see Chart 1).

In recent years, biologically active natural products containing the αβ-unsaturated carboxylic acid amide system have been found.[3] We are attempting a total synthesis of

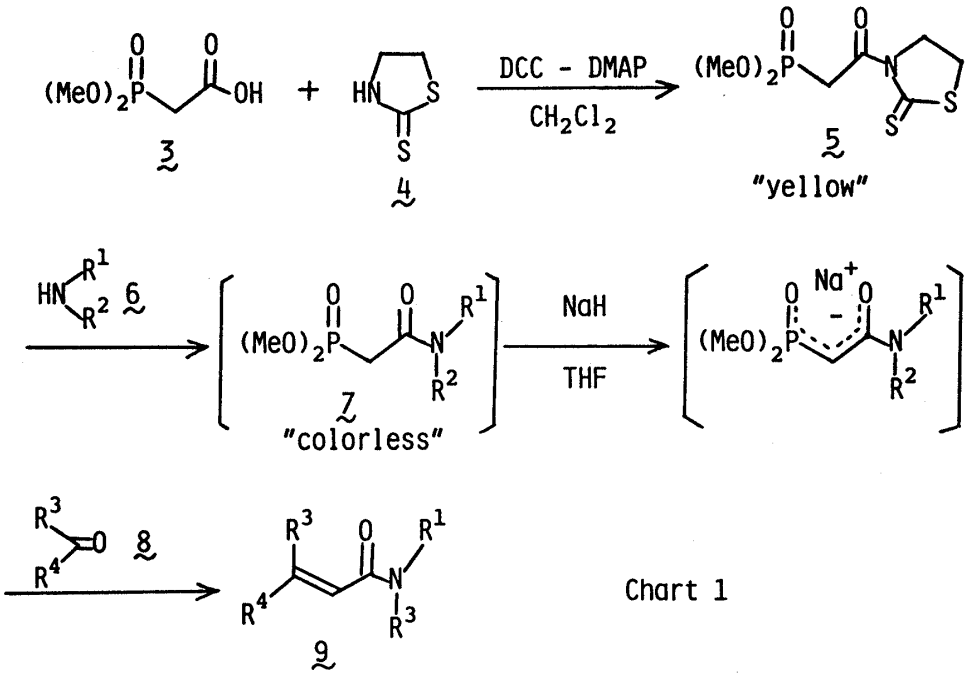


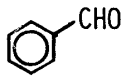
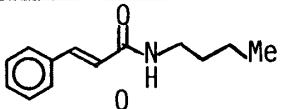
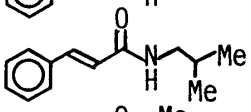
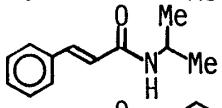
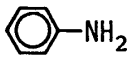
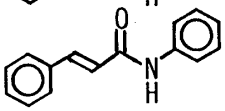
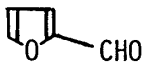
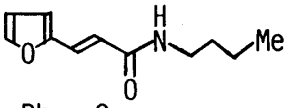
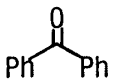
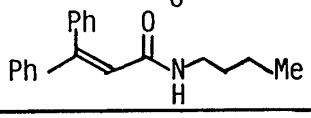
Chart 1

virginiamycin M2, a macrolactam antiobiotic, which possesses an αβ-unsaturated carboxylic acid amide system in the molecule.[4] There have been a few reports on the preparation of αβ-unsaturated carboxylic acid amides using the Wittig reaction.[5] However, the methods are not practically convenient. Hence, we designed a practically useful procedure using DMPATT (5) (see Chart 1). In this reaction course, we can recognize the end point of preparation of the key-intermediate dimethyl *N*-alkyl (or *N*, *N*-dialkyl) carbamoylmethylphosphonate (7) by the disappearance of the yellow color of DMPATT (5). Thus, we can easily judge suitable timing to carry out the following Wittig reaction.

A typical example of the preparation of αβ-unsaturated carboxylic acid amides 9 is as follows. To a solution of dimethylphosphonoacetic acid (3) (168 mg, 1 mmol), 1,3-thiazolidine-2-thione (4) (125 mg, 1.05 mmol), and catalytic 4-*N*, *N*-dimethylaminopyridine (DMAP) in CH_2Cl_2 (1.5 ml), was added a solution of *N*, *N*'-dicyclohexylcarbodiimide (DCC) (227 mg, 1.1 mmol) in CH_2Cl_2 (1.5 ml) under ice-cooling. After being stirred at room temperature for 3h, the reaction mixture became a yellow suspension,[6] to which was added *n*-butylamine (0.11 ml, 1.1 mmol) with stirring (the yellow color of the reaction mixture disappeared instantly). The colorless suspension was further stirred at room temperature for 5 min and the precipitate (*N*, *N*'-dicyclohexylurea) was filtered off. After evaporation of the filtrate *in vacuo*, a solution of the residue in anhydrous THF (2 ml) was added dropwise to a suspension of 60% NaH (the type coated with mineral oil) (200 mg, 5 mmol) in anhydrous THF (2 ml) under ice-cooling. After stirring the mixture for 10 min under similar conditions, benzaldehyde (0.11 ml, 1.1 mmol) was added and the mixture was stirred at room temperature for 12 h. The reaction mixture was treated as usual to afford *N*-cinnamoylbutylamine (9) (140 mg, 69% yield) as colorless needles (mp 78 - 79°C).

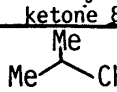
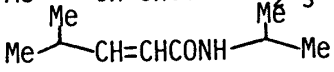
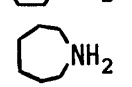
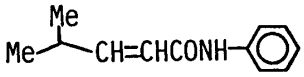
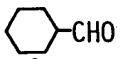
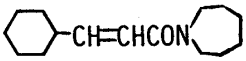
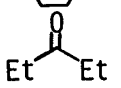
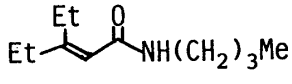
All other results are summarized in Tables 1 and 2. The structurers of products 9 were

Table 1. Synthesis of αβ-Unsaturated Carboxylic Acid Amide 9 Employing Aromatic Aldehyde or Ketone 8 [a]

Entry	Amine 6	Aldehyde or ketone 8	Product 9	Yield (%)[b]
1	*n*-BuNH$_2$			69
2	*iso*-BuNH$_2$	"		65
3	*iso*-PrNH$_2$	"		63
4		"		54
5	*n*-BuNH$_2$			63
6	"			69

a) Wittig reactions were carried out using 5 mol eq of NaH. b) Isolated yield.

Table 2. Synthesis of αβ-Unsaturated Carboxylic Acid Amide 9 Employing Aliphatic Aldehyde or Ketone 8 [a]

Entry	Amine 6	Aldehyde or ketone 8	Product 9	Yield[b] (%)	Product composition (*E* : *Z*)[c]
1	*n*-BuNH$_2$			75	(71 : 29)
2	*iso*-PrNH$_2$	"		72	(74 : 26)
3		"		60	(59 : 41)
4				38	(82 : 18)
5	*n*-BuNH$_2$			53	

a) Wittig reactions were carried out using 2.1 mol eq of NaH. b) Total yield of two geometric isomers. c) Product composition ratio was determined by the isolated yield of each corresponding isomer.

confirmed on the basis of their spectroscopic data (IR, ^{1}H-NMR, and Mass) and elemental analyses.

In this procedure, the Wittig reaction employing aromatic aldehyde exclusively yielded the corresponding *E*-olefinic amide (Table 1). On the other hand, a similar reaction employing aliphatic aldehyde afforded a considerable amount of *Z*-olefinic amide as the minor product. (Table 2). We also realized that DMPATT (5) is highly reactive not only toward all aliphatic amino

compounds (reaction time: less than 3 sec) but also toward a weak nucleophile, aniline (reaction time: within 20 min).

Subsequently, this method was applied to the simple synthesis of *N*-ferulyltryptamine (11), a very minor constituent isolated from the ground kernels of *Zea mays* (see Chart 2).[7]

Thus, DMPATT (5) proved to be practically useful as a hetero-bifunctional reagent for the construction of αβ-unsaturated carboxylic acid amides.

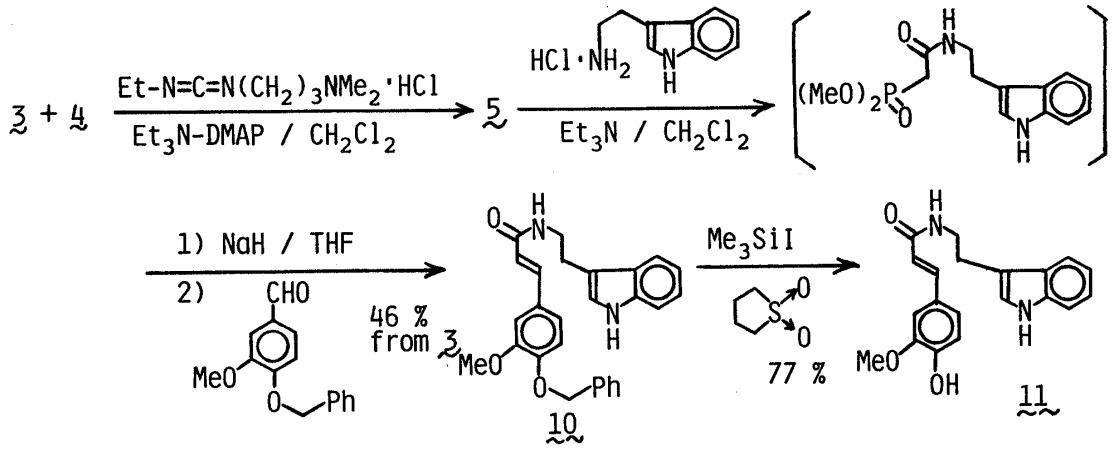


Chart 2

REFERENCES AND NOTES

1) a) Y. Nagao and E. Fujita, *Heterocycles*, 17, 537 (1982); b) Y. Nagao, T. Ikeda, M. Yagi, E. Fujita, and M. Shiro, *J. Am. Chem. Soc.*, 104, 2079 (1982); c) Y. Nagao, T. Miyasaka, Y. Hagiwara, and E. Fujita, *J. Chem. Soc., Perkin Trans. 1*, 1984, 183.

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6) Because DMPATT (5) is strongly reactive, this compound is usually employed without isolation. Characterization of DMPATT: yellow oil; IR($CHCl_3$) 1695 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ: 3.37 (2H, t, *J*=7.6 Hz), 3.83 (6H, d, *J*=11.2 Hz). 4.25 (2H, d, *J*=20.0 Hz), and 4.63 (2H, t, *J*=7.6 Hz); M^+ *m/e*=269.

7) A. Ehmann, *Phytochemistry*, 13, 1979 (1974).

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