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A convenient synthesis of tetrazole, precursors of α-dialkylated α-amino acids, by reaction of trimethylsilyl azide with α-dialkylated β-ketoesters

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Abstract—The Schmidt rearrangement using trimethylsilyl azide with various α-dialkylated β-keto esters affords a convenient synthesis of tetrazole, precursors of α-dialkylated α-amino acids.

1. Introduction

Recently, several papers and reviews have been published concerning the important role that α,α-disubstituted amino acids can play in the design of peptides with enhanced properties.[1] Georg et al.[2] have demonstrated that the Schmidt rearrangement of optically active α,α-disubstituted β-keto esters is a convenient method to generate α,α-disubstituted amino acids in high yields and excellent purity.

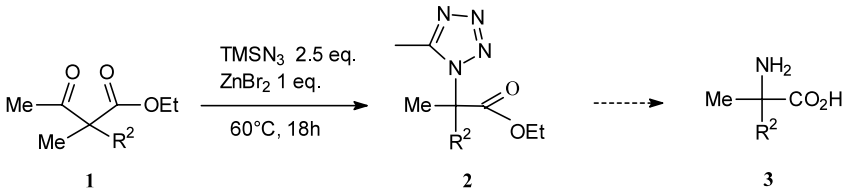
Sodium azide and methanesulfonic acid are the usual reagents for such Schmidt rearrangements,[3] but they generate in situ free hydrazoic acid, which can be highly dangerous.

That is the reason why we tried to develop a new method for the Schmidt rearrangement, using trimethylsilyl azide (TMSA) with various α-dialkylated β-keto esters, to afford a convenient synthesis of tetrazole, precursors of α-dialkylated α-amino acids, with better safety.

2. Results and discussion

It has been shown that silyl azides react with aldehydes and ketones, but no example is described in the literature with β-keto esters.

The reaction of TMSA with various aldehydes were found to be a procedure for the synthesis of *gem*- and 1,3-diazides, tetrazoles, and nitriles, whose formation was determined by controlling the quantities of TMSA, the nature of catalyst, and the reaction conditions.[4] With ketones, TMSA gave 1:1- or 1:2-adducts, which reacted with Lewis acid to afford tetrazoles.[5]



1 2 3

Scheme 1. Schmidt rearrangement with TMSA.

Keywords: Schmidt rearrangement; β-keto ester; trimethylsilyl azide; tetrazole; amino acids.
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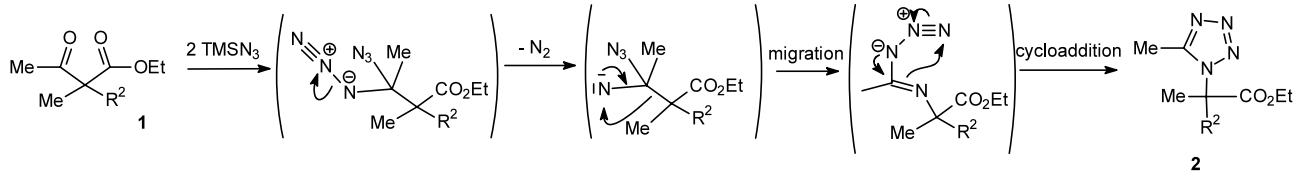

Table 1. Optimization of the conditions for Schmidt rearrangement of α-dialkylated β-keto ester

Entry	TMSA (equiv.)	Co-reagent	Solvent	Temp. (°C)	Time	Isolated yield of **2** (%)
1	1.1	NaN_3, 5% mol.	–	20	24 h	0
2	2.1	$ZnBr_2$, 1 equiv.	$CHCl_3$	Reflux	24 h	5
3	2.5	$ZnBr_2$, 1 equiv.	CH_2Cl_2	Reflux	18 h	30
					3 days	70
4	2.5	$ZnBr_2$, 1 equiv.	–	65	24 h	90

At first we chose compound **1a** (R^2 = Et) as substrate (Scheme 1) to optimize the conditions for the Schmidt rearrangement of α-dialkylated β-keto ester. α-Dialkylated β-keto ester **1a** was treated with TMSA under various conditions and the results are summarized in the Table 1. The most satisfactory results were obtained with 2.5 equiv. of TMSA for 1 equiv. of $ZnBr_2$, at 60°C for 18 h without any solvent. In this case, the reaction is highly regioselective and provides **2a** as the only compound, isolated in 90% yield (Table 1).

From the mechanistic point of view, we assume that the tetrazole formation takes place via a β-diazidoester shown below, reported also by Yamamoto et al.[6] and Nishiyama et al.[7]

Various α-dialkylated β-keto esters (**1a–d**) were treated with TMSA and $ZnBr_2$ under the same conditions, the results are listed in Table 2. The tetrazoles **2** were obtained in good yields.[8]

The next step of this synthesis is the transformation of the tetrazole **2a** in dialkylated aminoacids or esters. $AlLiH_4$ at 60°C, one the most useful reagent for this reaction[2] cannot be used in our case, owing to the ester function. However, the transformation of the tetrazole moiety, by quaternization with methyliodide, was performed in 65% yield.[9,10] Basic hydrolysis of the tetrazolium ring **3**, described by by Duffin et al.,[11] using concentrated KOH afforded the α-azido acid **4** in 70% yield (Scheme 2). Reduction of the α-azido acid in classical ways should provide the corresponding amino acid.[12]

Table 2. Schmidt rearrangement using TMSA with various α-dialkylated β-keto esters

Entry	R^2	Yield (%)
2a	Et	90
2b	Bn	70
2c	*i*Bu	78
2d	Ph	40

3. Conclusion

In conclusion, we have developed a new simple method for the synthesis of tetrazole precursors of α-dialkylated α-amino acids, using trimethylsilyl azide with various α-dialkylated β-keto esters. Quaternization of the tetrazole heterocycle with methyliodide, followed by basic hydrolysis with concentrated KOH affords the α-azido acid, direct precursor of the α-amino acids.

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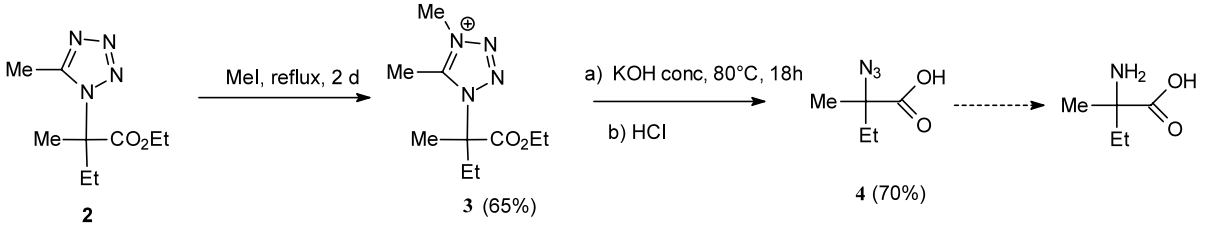

Scheme 2. Formation of the α-azido acid **4**.

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8. *General procedure for tetrazole synthesis (**2a**)*: Under N_2, to a 30 ml flask containing 442 μl of ethyl 2-ethyl 2-methyl acetoacetate (2.5 mmol) and 565 mg of $ZnBr_2$ (3.53 mmol), was added 830 μl of $TMSN_3$ (6.25 mmol). The reaction mixture was then stirred for 24 h at 65°C. At room temperature, the mixture was then treated with 40 ml of CH_2Cl_2 and 50 ml of aqueous ammonia (pH >9) and extracted three times with 20 ml of CH_2Cl_2. The organic layer was washed with satd aq. NaCl, and dried with $MgSO_4$. Removal of the solvent in vacuum yielded an oil, which was purified by column chromatography (Merck silica gel, 63–200 μm), hexane/AcOEt 100/0 to 50/50.
   *(±)-Ethyl 2-methyl 2-(5-methyltetrazol-1-yl)butyrate (**2a**).* ^{1}H NMR (200.13 MHz, $CDCl_3$): δ 4.23 (q, 2H, $^3J=7.5$ Hz, OCH_2CH_3), 2.46 (s, 3H, CH_3C=N), 2.36 [(qd, 2H, $^3J=7.2$ Hz, $^2J=1.4$ Hz, $CH_3CH_2C(CH_3)$], 1.87 (s, 3H, CH_3CEt), 1.24 (t, 3H, OCH_2CH_3), 0.84 [t, 3H, $^3J=7.2$ Hz, $CH_3CH_2C(CH_3)$]; ^{13}C NMR (50.32 MHz, $CDCl_3$): δ 170.2 (*C*=O), 155.55 (CH_3C=N), 67.59 (CH_3CEt), 62.53 (O CH_2CH_3), 30.32 ($CH_3CH_2CCH_3$), 22.5 (CH_3CH_2-CCH_3), 13.88 (CH_3CH_2O), 10.63 (CH_3C=N), 7.67 ($CH_3CH_2CCH_3$); IR (NaCl): 2980, 2930, 1750, 1525, 1455, 1400, 1260, 1245; HRMS FAB$^+$ (NBA): Calcd for $C_9H_{17}N_4O_2$ $[M+H]^+$ 213.1352, found: 213.1360. $R_f=0.4$ (60/40 hexane/AcOEt). 86% isolated yield.
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10. In a Schott tube (20 ml) containing 106 mg of β-tetrazoloester **2a** (0.5 mmol), 10 ml of ICH_3 (160 mmol) was added. The reaction mixture was then stirred for 2–3 days at 80°C in darkness. At room temperature, the mixture was concentrated under vacuum, and then filtered on 5 g of Merck silica gel (63–200 μm) with hexane/AcOEt (70/30). The tetrazolium moiety then was eluted with AcOEt/MeOH (90/10) to give **3** as a brown solid in 65% isolated yield.
    In a 50 ml flask containing 20 ml of a solution of KOH (50%) was added 800 mg of the tetrazolium compound **3** (2.25 mmol). The reaction mixture was stirred for 18 h at 80°C, then concentrated under vacuum, acidified with concentrated HCl and extracted three times with 30 ml of CH_2Cl_2. The organic layer was washed with a 10% solution of sodium thiosulfate, and dried on $MgSO_4$. Removal of solvent in vacuum yielded a yellow oil, in 70% isolated yield.
    *(±)-2-Azido 2-methyl butyric acid (**4**).* ^{1}H NMR (200.13 MHz, $CDCl_3$): δ 10.18 (1, 1H, O*H*), 1.84 (m, 2H, CH_3CH_2), 1.51 (s, 3H, $CH_3CH_2CCH_3$), 0.97 (t, 3H, $^3J=$ 7.2 Hz, CH_2CH_3); ^{13}C NMR (50.32 MHz, $CDCl_3$): δ 178.93 (*C*=O), 67.87 (CH_3CEt), 31.03 (CH_3CH_2), 21.9 ($EtCCH_3$), 8.38 (CH_3CH_2); IR (NaCl): 3500, 2950, 2910, 2140, 1725, 1280; HRMS FAB$^-$ (NBA): Calcd for $C_5H_8N_3O_2$ $[M-H]^-$: 142.0617, found: 142.0630.
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