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Trimethylsilyldiazomethane in the preparation of diazoketones via mixed anhydride and coupling reagent methods: a new approach to the Arndt–Eistert synthesis

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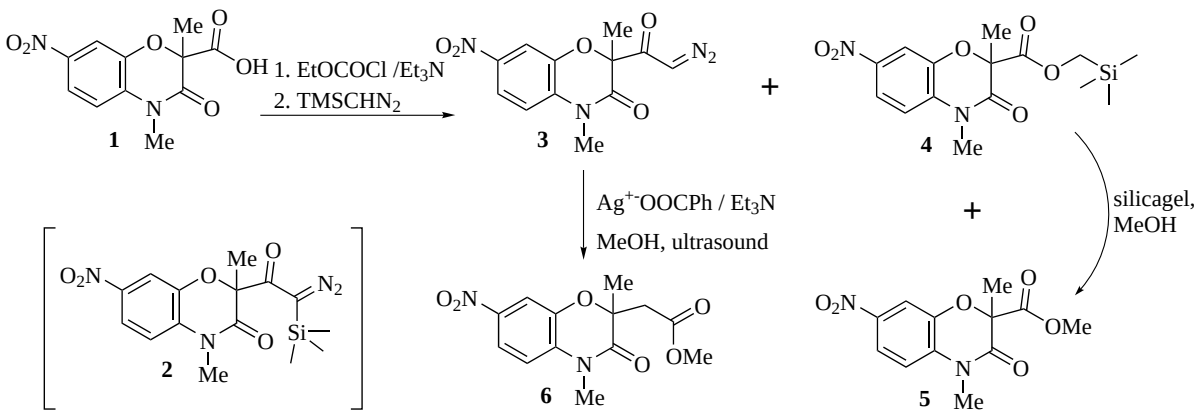
Abstract—Reaction of trimethylsilyldiazomethane with a mixed anhydride derived from a carboxylic acid by the action of ethyl chloroformate, yields the corresponding diazoketone in high yield. Subsequent Wolff rearrangement of the diazoketone leads to the homologated ester. Reaction of trimethylsilyldiazomethane with carboxylic acid–dicyclohexylcarbodiimide mixtures leads to the formation of diazoketone and trimethylsilylmethyl ester in equimolar ratio via an acid anhydride intermediate. The *N*-hydroxysuccinimide ester of the acid does not react with trimethylsilyldiazomethane or with its more reactive lithiated derivative.

The Arndt–Eistert synthesis consists of conversion of activated carboxylic acids to diazoketones by the action of diazomethane, followed by Wolff rearrangement.[1] It is a well known procedure for the synthesis of homologated acids and their derivatives such as esters or amides. The method has became widely used in recent years for the synthesis of β-peptides and β-amino acid derivatives from appropriately protected α-amino acids.[2] Solid-phase synthesis of β-peptides by this procedure has been described.[3]

Diazomethane is applicable in many organic reactions, but since it is highly toxic, labile and explosive,[4] much effort has been put into finding a less hazardous substitute. Trimethylsilyldiazomethane ($TMSCHN_2$) has been successfully used by Aoyama and his co-workers in numerous reactions previously dominated by diazomethane.[5]

The application of $TMSCHN_2$ in the classical Arndt–Eistert reaction starting from acyl chlorides is efficient in practice.[6] However, in the case of the amino acid



Scheme 1. †,‡

Keywords: trimethylsilyldiazomethane; Arndt–Eistert synthesis; mixed anhydrides; diazoketones; Wolff rearrangement; dicyclohexylcarbodiimide; *N*-hydroxysuccinimide.

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Table 1. Synthesis of diazoketones via mixed anhydride/$TMSCHN_2$

Starting acid	Yield (%) of pure diazoketone (eluent)	Literature yield (%) (procedure)
1	81 (EtOAc/hex = 3/2)	
$PhCH_2CH_2COOH$	64 (EtOAc/hex = 2/3)	78 (phenylpropanoyl chloride/CH_2N_2)[14]
PhCOOH	31 (Et_2O/petroleum ether = 3/4)	85 (benzoyl chloride/CH_2N_2)[15] 7 (benzoic acid/ClCOOEt, CH_2N_2)[8]
Boc-Phe-OH	78 (EtOAC/hex = 1/2)	76 (Boc-Phe-OH/ClCOOEt, CH_2N_2)[2b]

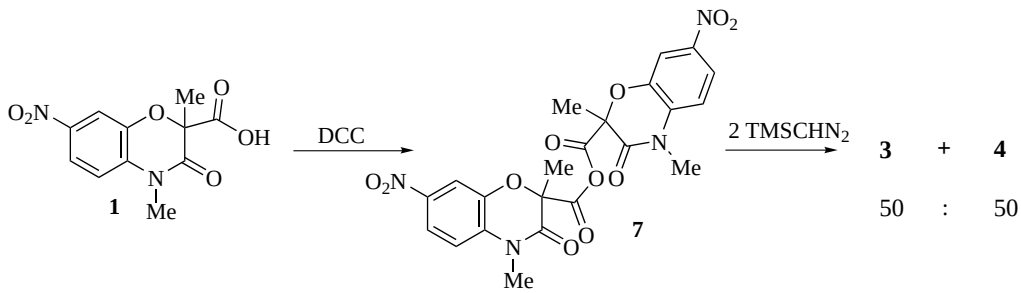
chemistry, other methods for acid activation, such as mixed anhydrides and the use of coupling reagents, are preferred.

In the course of our research, an extension to the side chain at 2-position of 3-oxo-3,4-dihydro-2*H*-1,4-benzoxazine-2-carboxylic acid derivative **1** was needed. The acid is readily available from 2-amino-5-nitro-phenol by the method published by Kikelj.[7] Various further substitution possibilities make the benzoxazine a useful template for designing peptidomimetics. Conversion of the acid **1** to its acyl chloride with thionyl chloride or oxalyl chloride did not give satisfactory results.

As an alternative, the mixed anhydride was prepared with $ClCOOEt/Et_3N$ and allowed to react with $TMSCHN_2$ in a manner analogous to the method of Tarbell and Price (Scheme 1[†‡]).[2,8] Using 2 equiv. of $TMSCHN_2$, the reaction gave the corresponding diazoketone **3** in high yield.[9] No anticipated trimethylsilyldiazoketone intermediate **2** could be detected in the reaction mixture by IR spectroscopy or mass spectrometry. In addition to the diazoketone, trimethylsilylmethyl ester **4** and methyl ester **5** by-products were formed.[10–12] These could be detected by ^1H NMR and did not exceed 10% under optimal reaction conditions. Ultrasound promoted Ag^+/base catalysed Wolff rearrangement of the diazoketone **3** in methanol proceeded smoothly to give the homologated methyl ester **6**.[13] Ester by-products from the first step did not interfere with subsequent rearrangement and could be separated from the end product **6** by silica gel column chromatography. Using methanol as a solvent, some transesterification of the trimethylsilylmethyl ester **4** to the methyl ester **5** occurred during the chromatographic separation.

To establish the generality of the mixed anhydride/$TMSCHN_2$ procedure for the synthesis of diazoketones, the method has been applied to three other carboxylic acids: hydrocinnamic acid as a simple aliphatic acid, benzoic acid as an aromatic acid and Boc-phenylalanine as a protected amino acid, respectively. The results are shown in Table 1.

The yields of diazoketones are completely comparable with classical procedures except in the synthesis of diazoacetophenone, where benzoyl chloride as a starting material is preferred. In the synthesis of diazoacetophenone we obtained a complex mixture of products, which were not fully characterized, but could be separated from the diazoketone with column chromatography.



Scheme 2. §

† All reagents and solvents were freshly distilled prior to use in accordance with standard procedures, and reactions were carried out under argon atmosphere. Commercially available $TMSCHN_2$ from Aldrich® (2.0 M solution in hexanes) was used. ClCOOEt (6.2 mmol) in anhydrous THF (5 ml) was added to the solution of carboxylic acid **1** (6.0 mmol) and Et_3N (6.2 mmol) in THF (30 ml) at −15°C and the mixture was stirred for 30 minutes at −5°C. The precipitated $Et_3NH^+Cl^-$ was filtered off. Acetonitrile (20 ml) and $TMSCHN_2$ (12.0 mmol) were added to the filtrate and the mixture was stirred for 24 h at +4°C. After that, diethyl ether (80 ml) was added and the mixture was extracted with 10 % aq. citric acid, sat. aq. $NaHCO_3$ and sat. aq. NaCl (60 ml each). The organic layer was dried over Na_2SO_4 and the solvents evaporated to give 5.5 mmol of crude diazoketone **3** which could be purified by silica gel column chromatography using EtOAc/hexane = 3/2 as an eluent or could be used in the next step without purification.

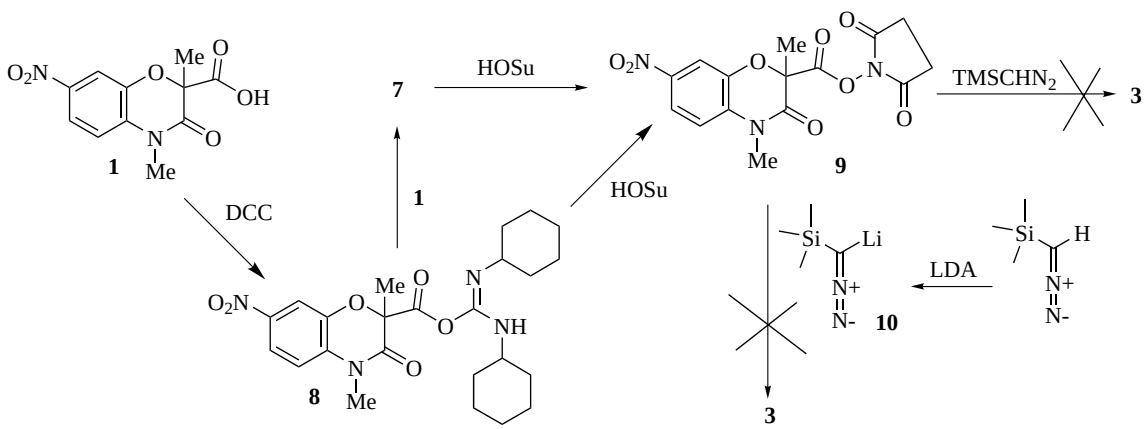
‡ The crude diazoketone **3** (5.0 mmol) was suspended in anhydrous MeOH (50 ml) and a solution of silver benzoate (1.0 mmol) in Et_3N (20 mmol) was gradually added while the mixture was sonicated in an ultrasound bath. The reaction was completed in 30 min at room temperature (monitored by N_2 liberation and TLC). Methanol was evaporated and the residue was dissolved in EtOAc (60 ml), extracted with sat. aq. $NaHCO_3$, 10 % aq. citric acid and sat. aq. NaCl (40 ml each) and dried over Na_2SO_4. Evaporation of the solvent followed by silica gel column chromatography (CH_2Cl_2/MeOH = 90/1 for the products **4** and **5**, then CH_2Cl_2/MeOH = 30/1 for **6**) afforded trimethylsilylmethyl ester **4** (0.2 mmol), methyl ester **5** (0.3 mmol) and homologated methyl ester **6** (4.2 mmol, 77% overall yield from **1**).

Besides the mixed anhydride activation of the carboxylic acid we tested other activation methods. The reaction of diazomethane with carboxylic acids and dicyclohexylcarbodiimide (DCC) mixtures has been described.[16] The procedure is useful for the preparation of diazoketones where acid chlorides are not available, but the yields are limited to 50% because the activated acids forms have proved to be symmetric anhydrides. Unlike peptide bond formation, regenerated free acids react with diazomethane to give corresponding methyl esters. Similarly, in our case, the addition of $TMSCHN_2$ to the mixture of the acid **1** and DCC resulted in formation of diazoketone **3** and trimethylsilylmethyl ester **4** in approx. 50:50 ratio (Scheme 2[§]), as detected by ^1H NMR.[17] This was the expected result and proved that the acid–DCC product was anhydride **7**. It also proved that $TMSCHN_2$ strongly resembles diazomethane in its nucleophilic (diazoketone formation) as well as basic and electrophilic (ester formation) properties.

To improve the yield of the diazoketone formed, we assumed that addition of an auxiliary nucleophile such as *N*-hydroxysuccinimide (HOSu) to the reaction mixture prior to the addition of $TMSCHN_2$, might prevent the anhydride formation. This assumption was based on direct comparison with the use of coupling reagents in peptide bond formation.[18] HOSu would react with *O*-acyl isourea **8** or the anhydride **7**, leading to active ester acylating agent **9** (Scheme 3[¶]).[19] From the reaction of **9** with $TMSCHN_2$ no free acid would be formed that could protonate $TMSCHN_2$ and give rise to **4**. The active ester **9** was in fact formed, however it did not react with $TMSCHN_2$ and remained the only major product in the reaction mixture even under stronger reaction conditions (excess of $TMSCHN_2$ and/or raising the temperature to the boiling point).

It is known that conversion of $TMSCHN_2$ to its lithiated derivative $TMSC(Li)N_2$ **10** improves its nucleophilic properties and enables some reactions which cannot take place with $TMSCHN_2$ to proceed.[5,20] Therefore, we isolated HOSu-ester **9** and allowed it to react with $TMSC(Li)N_2$, prepared according to the procedure of Aoyama.[21] However, the reaction did not take place. On the other hand, reactions of active esters with diazomethane have also been claimed to be unsuccessful.[2b]

In conclusion, we have demonstrated that the mixed anhydride activation of carboxylic acid can be successfully used for the Arndt–Eistert synthesis in most cases where diazomethane is replaced by $TMSCHN_2$. Until now, similar attempts have not been efficient and therefore mixed anhydrides were claimed not to be reactive enough to give diazoketones with $TMSCHN_2$.[5c] Substitution of diazomethane with $TMSCHN_2$ in β-peptide synthesis or in SPOS has yet to be determined but it would, no doubt, be of great advantage. Not surprisingly, $TMSCHN_2$ also behaves similarly to diazomethane in reactions with carboxylic acid–DCC mixtures.



Scheme 3. ¶

[§] DCC (2.0 mmol) was dissolved in THF (15 ml) and the acid **1** was added in four portions (0.5 mmol each) over 60 min at −15°C. The mixture was stirred for 60 min after the last addition, then $TMSCHN_2$ was added (3.0 mmol) and the resulting mixture was stirred for 24 h at +4°C. Two spots on TLC, corresponding to standards for **3** and **4**, respectively, indicated the formation of two products. After filtration of the precipitated dicyclohexylurea and evaporation of the solvent, ^1H NMR spectra confirmed the formation of diazoketone **3** and trimethylsilylmethyl ester **4** in approximately 50:50 ratio.[17] By chromatographic separation (see above) some additional methyl ester **5** was formed from **4**.

[¶] $TMSCHN_2$ (2.0 mmol) was added dropwise to a solution of LDA (2.0 mmol; 2.0 M solution in heptanes from Aldrich®) in THF (15 ml) at −78°C. The mixture was stirred at −78°C for 30 min to give lithiated derivative **10**, then a solution of **9** (1.0 mmol) in THF (5 ml) was added. After stirring for 72 h at +4°C no diazoketone **3** was formed.

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9. Compound **3**: ^1H NMR (DMSO, 300 MHz): δ 1.73 (s, 3H, 2-CH_3), 3.38 (s, 3H, N-CH_3), 6.48 (s, 1H, CH-N_2), 7.40 (d, 1H, $J=8.66$ Hz, Ar-H_5), 7.89–8.02 (m, 2H, Ar-H_8, H_6) ppm; ^{13}C NMR (DMSO, 75 MHz): δ 21.87 (2-CH_3), 30.17 (N-CH_3), 55.50 (CH-N_2), 84.90 (C_2), 113.29 (Ar-C_8), 116.90 (Ar-C_5), 120.14 (Ar-C_6), 135.84 (Ar-C_7), 143.50 (N-Ar), 143.57 (O-Ar), 163.64 (-CON-), 190.47 (-CO-) ppm; HRMS (70 eV, EI): calcd for $C_{12}H_{10}N_4O_5$: 290.0651, found: 290.0662.
10. Ester by-products could be explained by incomplete activation of the carboxylic group and/or by the catalytic amount of water present, though excess of $TMSCHN_2$ or variations in reaction conditions (redistillation of THF, lower temperature, use of other solvents e.g. ether, acetonitrile,…) did not significantly improve the purity or the yield of the diazoketone **3**. Another explanation might be formation of a small amount of symmetric anhydride **7**. For the mechanism of methyl ester formation, see: Hashimoto, N.; Aoyama, T.; Shioiri, T. *Chem. Pharm. Bull.* **1981**, *29*, 1475–1478
11. Compound **4**: ^1H NMR ($CDCl_3$, 300 MHz): δ −0.06 (s, 9H, $Si(CH_3)_3$), 1.92 (s, 3H, 2-CH_3), 3.46 (s, 3H, N-CH_3), 3.78–3.88 (2d, $J=17.71$ Hz, CH_2), 7.05 (d, 1H, $J=9.04$ Hz, Ar-H_5), 7.96 (d, 1H, $J=2.63$ Hz, Ar-H_8), 7.80–8.02 (dd, 1H, $J=9.04$, 2.64 Hz, Ar-H_6) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ −3.03 ($Si(CH_3)_3$), 21.63 (2-CH_3), 29.80 (N-CH_3), 60.82 (CH_2), 81.76 (C_2), 113.52 (Ar-C_8), 114.71 (Ar-C_5), 119.35 (Ar-C_6), 135.28 (Ar-C_7), 143.98 (N-Ar), 144.08 (O-Ar), 163.64 (-CON-), 168.73 (-COO-) ppm; HRMS (70 eV, EI): calcd for $C_{15}H_{20}N_2O_6Si$: 352.1091, found 352.1103.
12. Compound **5**: ^1H NMR (DMSO, 300 MHz): δ 1.79 (s, 3H, 2-CH_3), 3.39 (s, 3H, N-CH_3), 3.65 (s, 3H, O-CH_3), 7.41 (d, 1H, $J=9.04$ Hz, Ar-H_5), 7.85 (d, 1H, $J=2.64$ Hz, Ar-H_8), 7.99–8.03 (dd, 1H, $J=9.05$, 2.64 Hz, Ar-H_6) ppm; ^{13}C NMR (DMSO, 75 MHz): δ 21.64 (2-CH_3), 30.28 (N-CH_3), 54.32 (O-CH_3), 81.58 (C_2), 112.85 (Ar-C_8), 116.95 (Ar-C_5), 119.97 (Ar-C_6), 135.72 (Ar-C_7), 143.57 (N-Ar), 143.71 (O-Ar), 163.06 (-CON-), 168.70 (-COO-) ppm; HRMS (70 eV, EI): calcd for $C_{12}H_{12}N_2O_6$: 280.0695, found 280.0706.
13. Compound **6**: ^1H NMR ($CDCl_3$, 300 MHz): δ 1.54 (s, 3H, 2-CH_3), 2.86 (d, 1H, $J=16.58$ Hz, CH_2), 3.34 (d, 1H, $J=16.58$ Hz, CH_2), 3.46 (s, 3H, N-CH_3), 3.68 (s, 3H, O-CH_3), 7.03 (d, 1H, $J=9.04$ Hz, Ar-H_5), 7.81 (d, 1H, $J=2.64$ Hz, Ar-H_8), 7.94–7.98 (dd, 1H, $J=9.04$, 2.63 Hz, Ar-H_6) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 23.63 (2-CH_3), 29.40 (N-CH_3), 42.89 (CH_2), 52.38 (O-CH_3), 79.20 (C_2), 113.35 (Ar-C_8), 114.27 (Ar-C_5), 118.77 (Ar-C_6), 135.02 (Ar-C_7), 142.78 (N-Ar), 143.93 (O-Ar), 167.85 (-CON-), 170.04 (-COO-) ppm; HRMS (70 eV, EI): calcd for $C_{13}H_{14}N_2O_6$: 294.0852, found 294.0862.
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17. Based on comparison of the integrals, not shaded by dicyclohexylurea: 5.67 singlet for **3** and −0.06 singlet for **4** ($CDCl_3$, 300 MHz).
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19. Compound **9**: mp 174–176°C; ^1H NMR (DMSO, 300 MHz): δ 1.99 (s, 3H, 2-CH_3), 2.74 (s, 4H, 2 CH_2), 3.45 (s, 3H, N-CH_3), 7.52 (d, 1H, $J=8.66$ Hz, Ar-H_5), 7.95 (d, 1H, $J=2.64$ Hz, Ar-H_8), 8.05–8.09 (dd, 1H, $J=9.04$, 2.64 Hz, Ar-H_6) ppm; HRMS (70 eV, EI): calcd for $C_{15}H_{13}N_3O_8$: 363.0702, found 363.0715; EA: anal. calcd for $C_{15}H_{13}N_3O_8$: C, 49.59; H, 3.61; N, 11.57. Found: C, 49.50; H, 3.87; N, 11.44.
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