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A GENERAL N-ALKYLATION PROCEDURE FOR ETHYL PYROGLUTAMATE

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Abstract: Despite several reported procedures for coupling alkyl halides and 5-oxoproline esters (pyroglutamate derivatives), no general method has been described. The reaction of pyroglutamate with sodium hydride, in anhydrous THF in the presence of the halide, provides this general and practical alkylation method. Alkylation under phase transfer conditions is a useful, but less general, alternative.

The N-alkylation of lactams is a well-established procedure, and the related N-alkylation of esters of pyroglutamate (such as 5-oxoproline ethyl ester, **1b**) has been reported several times. We found, however, that no general procedure gave good yields of product, especially with alkylating agents other than simple alkyl halides. In previous work, we found that the phase transfer techniques used for simple lactams,[1] did not always work or gave poor yields with **1**.[2] We found that this sluggish

1a R = Me
1b R = Et
1c R = Bn

2a R' = -$(CH_2)_3CO_2Et$
2b R' = *n*-C_6H_{13}
2c R' = Me

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reactivity could be overcome in some cases by the use of ultrasound with the phase transfer procedure.[2,3] As mentioned, the literature provides several examples for the N-alkylation of the ethyl and methyl esters of 5-oxoproline (**1b** and **1a**). One important method reacted **1a** with sodium hydride and DMF. This was followed by treatment with ethyl 4-bromobutyrate to give a 25% yield of **2a**.[4a] This derivative was isolated in a mixture with other products, however. Other ω-halo esters were coupled to 5-oxoproline esters with this procedure,[4b] and iodomethane was added directly to 5-oxoproline (80% yield) using two equivalents of sodium iodide.[4c] Sodium hydride in THF was used to couple **1a** to 1-bromohexane, giving **2b** in 29% yield,[5] and other long chain halides have been coupled under these conditions.[6] Allylic halides have been coupled directly to the acid (5-oxoproline) using sodium hydride in DMSO,[7] and both allylic and benzylic halides have been coupled to **1a** with sodium hydride in benzene.[8] Substituted alkyl halides have been coupled to 5-oxoproline derivatives, as well as other lactams, using sodium hydride in toluene.[9] Other bases have been used for this coupling. Sodium metal has been used to couple **1a** and bromomethane to give **2c**.[10] Bromomethane was coupled to **1b**, in an alutoclave using potassium carbonate, but this required heating up to 100°C for several hours to give **3a**.[11] Other bases have also been used.[12] Phase transfer techniques were shown to be effective in some cases, prior to our work.[10b] Diethyl sulfate was used to convert 5-oxoproline to the N-ethyl derivative (**3b**), but in poor yield,[13] and dimethyl sulfate was similarly used under phase transfer conditions to give **2c**.[10b] An interesting alkylation method converted **1c** to the N-trimethylsilyl derivative by reaction with chlorotrimethylsilane. Subsequent heating (to 130°C) with benzylic halides gave moderate to good yields of the corresponding N-substituted lactam.[14]

Our work demanded that both simple alkyl, allylic and benzylic halides be attached to the nitrogen of **1b**, but we also required that ester, ether, halide, dioxolane and other substituents be incorporated into the alkyl chain. When we attempted to extend our

phase transfer/ultrasound procedure to these type of halides, we found that diminished reactivity of the halide led to saponification of the ester in **1b** and, in some cases, ring opening of the lactam. The use of ultrasound, that had greatly enhanced the reactivity of allylic halides in our earlier work, did not alleviate these problems. We were therefore faced with the task of examining new alkylation techniques for **1b**. Rather than continue to invent a new alkylation procedure for each type of halide, which appeared to be necessary from our work and from examining the literature, we set out to find a general method. We can now report that the use of sodium hydride in THF, under rather specific reaction conditions, meets this goal and can be used as a general method for N-alkylation of **1b** which complements the use of phase transfer methods. Between these two methods, virtually any alkyl halide will react with **1b** to give the N-alkylated product.

We found that when **1b** was treated with sodium hydride in anhydrous THF, for less than five minutes, and then reacted with an alkyl halide, good to excellent yields of the N-alkylated product were obtained in virtually every case. The exception to this statement was reaction with secondary halides, which gave either no reaction, or poor yields. The key factor in this reaction was the presence of water. If scrupulously dry THF was not used, hydrolysis of the ester moiety occurred, and in some cases the lactam ring opened giving unwanted side products. Careful drying of the THF, as usually done in enolate anion reactions using THF, led to reproducible and good yields of the N-alkylated product. The sodium hydride used is commercially available as a slurry in mineral oil. The oil can be removed prior to reaction, but since isolation of the N-alkylated lactams required chromatographic separation, we used the sodium hydride/mineral oil slurry directly. The oil was easily separated during the chromatography on silica gel and this procedure led to higher yields of lactam.

In several cases, the phase transfer method (powdered NaOH, aqueous THF) gave excellent results and this technique was more amenable to large-scale reactions. The

phases transfer method was only effective, however, when the alkyl halide was reactive enough to supersede the saponification reaction at the ester. In some cases, as mentioned above, running the reaction in an ultrasonic bath led to good yields in the phase transfer reaction. The use of ultrasound in the NaH/THF reaction did not change the outcome of the reaction to any significant degree. A comparison of N-alkylation of **1b** with several halides is shown in the Table.

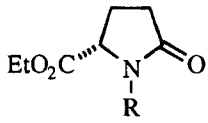

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Table. Comparison of alkylation procedures. Reactions with 1b.

R	Procedure	Product	% Yield
-Me	A	**3a**	92
	B		37
-Et	A	**3b**	84
	B		14
-Bn	A	**3c**	95
	B		65
$-CH_2CH=CH_2$	A	**3d**	94
	B		64
$-CH_2CH=CHBr$	A	**3e**	93
	B		62
$-CH_2C(Br)=CH_2$	C	**3f**	52
$-CH_2CH_2Br$	A	**3g**	42
	B		26
-CHMeEt	A	**3h**	0
	A+NaI		0
	B		34
$-CH_2CO_2Et$	A	**3i**	97
	C		52
$-CH_2CH_2CO_2Et$	A	**3j**	51
	B		35
$-CH_2CH_2CH_2CO_2Et$	A	**3k**	0
	A+NaI		41
	B		26

It is clear that the sodium hydride/THF procedure reported here is general for reactions of primary halides, and generally superior to the sodium hydride/DMF or DMSO procedure reported previously. Our modified method also gives better yields and appears to be more general than the sodium hydride/THF procedure previously reported by Zoretic[5] and Peck.[6] It is noted that Yates and Maclachlan[4a] mixed a small amount of sodium iodide with ethyl 4-bromobutanoate to improve the reaction. Although the reported yield was only 25%, this apparently represented an improvement over using the bromide directly. When we added 2 mole % of sodium iodide to the same reaction using our NaH/THF method, the yield of **3k** improved from 0% to 41%. This modification did not solve all reactivity problems, however, since with or without addition of NaI, 2-bromopropane gave 0% of N-substitution. Similarly, 2-bromocyclohexane failed to react with NaH/THF with or without NaI present. In conclusion, this NaH/anhydrous THF method satisfies our goal for a general N-alkylation procedure for 5-oxoproline esters (pyroglutamate derivatives) and is the method of choice in all of our work. The obvious limitation of this method is that secondary halides fail to react.

EXPERIMENTAL SECTION

All glassware was oven dried prior to use. Most reactions were conducted under an atmosphere of dry argon. Reaction progress was checked by TLC or GC/MS. Infrared spectra were taken on a Perkin-Elmer Spectrophotometer Model 283 and recorded in reciprocal centimeters. All ^{1}H and ^{13}C NMR spectra were recorded with an IBM WP-270 Spectrometer at 270 MHz or at 67.92 MHz as solution in $CDCl_3$ and reported in ppm downfield from tetramethylsilane, which was used as an internal reference. High resolution mass spectra were measured on an AEI MS-902 mass spectrometer and are accurate to ±5 ppm. All chemicals were purchased from Janssen.

The THF was distilled under an argon atmosphere from sodium metal and benzophenone immediately prior to use. General drying of product solutions was accomplished over anhydrous magnesium sulfate. Thin layer chromatography was performed with E. Merck AG Darmstadt silica 60F-254 sheets. Column chromatography was performed on silica gel 60 (70-230 mesh). We prepared ethyl pyroglutamate from *L*-glutamic acid by procedures we described earlier.[15]

A. General Procedure for N-Alkylation of 5-Oxoproline Ethyl Ester Using NaH as a Base.

Ethyl pyroglutamate[15] (**1b**) and 1.1 equivalents of the halide were dissolved in 50 mL of dry THF, under stirring. The reaction mixture was cooled to 0°C than NaH (powder, 60% mineral oil; 1.5 equiv.) was added in small portions. After stirring at 0°C for about 20-30 min, the mixture was allowed to warm to room temperature. The product was washed twice with saturated aqueous ammonium chloride solution and water, then the aqueous phases were extracted with diethyl ether. The combined organic phases were washed with brine, separated and dried ($MgSO_4$). Removal of solvents by rotary evaporation was followed by application of the resulting oil to a column with silica and elution with diethyl ether. The mineral oil was eluted with the solvent front and discarded. The pure product was isolated after evaporation of the solvent. Typical yields were 80-95%.

B. General Procedure for N-Alkylation of 5-Oxoproline Ethyl Ester in Phase Transfer Catalysis Conditions.

Ethyl pyroglutamate (**1b**), 1.2 equivalents of halide and 0.1 equivalents of tetrabutylammonium bromide were dissolved, with stirring, in 100 mL of dry THF. Pulverized KOH (1.2 eq) were immediately added to the mixture in small portions, with vigorous stirring. The reaction mixture was refluxed for about 2 hours, then allowed to cool to room temperature. Two washings with saturated aqueous ammonium chloride solution was followed by washing with water. The combined

aqueous solution was extracted twice with diethyl ether and the combined organic layers were washed with brine, separated and dried ($MgSO_4$). Removal of solvents by rotary evaporation was followed by application of the resulting oil to a column with silica and elution with diethyl ether. The pure product was isolated after evaporation of the solvent. Typical yields were 50-60%.

C. General Procedure for N-Alkylation of 5-Oxoproline Ethyl Ester Using LDA as a Base.

Ethyl pyroglutamate (**1b**) was dissolved in 25 mL of dry THF and in a separate flask, 1.1 equivalents of diisopropylamine was dissolved in 50 mL of dry THF and cooled to -20°C with stirring. A total of 1.1 equivalents of *n*-butyllithium (in hexanes) was added dropwise (under stirring under argon). After stirring an additional 10 min, the LDA solution was cooled to -78°C and the ethyl pyroglutamate solution was added dropwise. The reaction mixture was stirred at -78°C for 30 min, quenched with saturated aqueous ammonium chloride solution, and allowed to warm to room temperature.

The reaction mixture was partitioned between water and diethyl ether, the aqueous phase was extracted twice with diethyl ether the combined organic phases were washed with brine, separated and dried ($MgSO_4$). Removal of solvents by rotary evaporation was followed by application of the resulting oil to a column with silica and elution with diethyl ether. The mineral oil was eluted with the solvent front and discarded. The pure product was isolated after evaporation of the solvent. Typical yields were 30-40%.

1-Methyl-5-oxoproline Ethyl Ester, 3a. Reaction of 1.0 g (6.4 mmol) of **1b** and 1.0 g (7.0 mmol) of iodomethane using procedure A gave 1.0 g (5.8 mmol, 92%) of **3a**.[11] Similar reaction of 1.0 g (6.4 mmol) of **1b** and 1.1 g (7.7 mmol) of iodomethane using procedure B gave 0.4 g (2.3 mmol, 37%) of **3a**: R_f 0.27 (diethyl ether); ^1H NMR ($CDCl_3$): δ 1.31 (t, 3H), 2.38 (m, 4H), 2.86 (s, 3H), and 4.23 (m, 3H) ppm; ^{13}C NMR ($CDCl_3$): δ 14.2, 22.7, 28.9, 29.3, 61.6, 61.9, 171.8, and 175.3

ppm; IR (neat) 1700, 1748 cm^{-1}; MS (m/e, Rel. intensity) 171 (P), 142, 114, 98 (100), 80, 70, 55.

1-Ethyl-5-oxoproline Ethyl Ester, 3b. Reaction of 1.0 g (6.4 mmol) of **1b** and 1.1 g (7.0 mmol) of iodoethane using procedure A gave 1.0 g (5.3 mmol, 84%) of **3b**.[13] Similar reaction of 1.0 g (6.4 mmol) of **1b** and 1.2 g (7.7 mmol) of iodoethane using procedure B gave 0.16 g (0.86 mmol, 14%) of **3b**: R_f 0.33 (diethyl ether); ^1H NMR ($CDCl_3$): δ 1.19 (t, 3H), 1.24 (t, 3H), 2.46 (m, 5H), 3.50 q (2H), and 3.69 q (2H) ppm; MS (m/e, Rel. intensity) 185(P), 142, 112(100), 84, 68, 56; HRMS Calcd for $C_9H_{15}NO_3$: 185.1053. Found 185.1052.

1-Phenylmethyl-5-oxoproline Ethyl Ester, 3c. Reaction of 1.0 g (6.4 mmol) of **1b** and 1.2 g (7.0 mmol) of benzyl bromide using procedure A gave 1.5 g (3.2 mmol, 95%) of **3c**.[6] Similar reaction of 1.0 g (6.4 mmol) of **1b** and 1.3 g (7.7 mmol) of benzyl bromide using procedure B gave 1.03 g (0.86 mmol, 65%) of **3c**: R_f 0.47 (diethyl ether); ^1H NMR ($CDCl_3$): δ 1.26 (t, 3H), 2.06-2.54 (m, 4H), 4.08 (m, 3H), 5.05 (d, 2H), and 7.19-7.35 (m, 5H) ppm; ^{13}C NMR ($CDCl_3$): δ 13.9, 22.6, 29.3, 45.4, 58.7, 61.2, 127.6, 127.7, 128.1, 128.3, 128.4, 128.5, 173.3, and 174.9 ppm; IR (neat) 1695, 1721 cm^{-1}; MS (m/e, Rel. intensity) 247 (P), 174, 146, 91 (100), 65; HRMS Calcd for $C_{14}H_{17}NO_3$: 247.1208. Found 247.1204.

1-(2-Propen-1-yl)-5-oxoproline Ethyl Ester, 3d. Reaction of 1.003 g (6.4 mmol) of **1b** and 0.85 g (7.0 mmol) of allyl bromide using procedure A gave 1.18 g (6.0 mmol, 94%) of **3d**.[16,2] Similar reaction of 1.0 g (6.4 mmol) of **1b** and 0.92 g (7.7 mmol) of allyl bromide using procedure B gave 0.8 g (4.0 mmol, 64%) of **3d**: R_f 0.41 (Diethyl ether); ^1H NMR ($CDCl_3$): δ 1.29 (t, 3H), 2.08-2.51 (m, 4H), 3.71 q (2H), 4.19 (m, 3H), 5.17 (m, 2H), and 5.71 (m, 1H) ppm; ^{13}C NMR ($CDCl_3$): δ 14.0, 22.8, 29.4, 44.3, 58.0, 59.0, 61.3, 131.9, 173.3, and 175.0 ppm; IR (neat) 1700, 1748 cm^{-1}; MS (m/e, Rel. intensity) 197 (P), 124 (100), 96, 84, 68.

1-(3-Bromo-2-propenyl)-5-oxoproline Ethyl Ester, 3e. Reaction of 1.0 g (6.4 mmol) of **1b** and 1.4 g (7.0 mmol) of 1,3-dibromo-2-propene using procedure A gave 1.63 g (5.9 mmol, 93%) of **3e**. Similar reaction of 1.0 g (6.4 mmol) of **1b** and 1.4 g (7.0 mmol) of 1,3-dibromo-2-propene using procedure B gave 1.1 g (3.9 mmol, 62%) of **3e**: ^{1}H NMR ($CDCl_3$): δ 1.30 (t, 3H), 2.14 (m, 2H), 2.41 (m, 2H), 2.74 (d, 2H), 4.24 (q, 2H), 6.10 (m, 1H), 6.39 (m, 1H), and 6.87 (m, 1H) ppm; ^{13}C NMR ($CDCl_3$): δ 14.2, 22.9, 23.1, 29.2, 29.3, 41.1, 43.5, 59.2, 59.4, 61.6, 61.7, 109.8, 111.8, 129.0, 131.5, 172.2, 172.3, 174.6, and 174.8 ppm; IR (neat) 2962, 1718, 1616 cm^{-1}; HRMS Calcd for $C_{10}H_{14}O_3NBr$: 275.0157, found 275.0151; MS (m/e, Rel. intensity): 206, 204, 196 (100), 121, 119, 94, 68, 55.

1-(2-Bromo-2-propen-1-yl)-5-oxoproline Ethyl Ester, 3f. Reaction of 1.0 g (6.4 mmol) of **1b** and 1.4 g (7.0 mmol) of 1,2-dibromo-2-propene using procedure C gave 0.91g (3.3 mmol, 52 %) of **3f** as a mixture of *E* and *Z* isomers: R_f 0.35 (diethyl ether); ^{1}H NMR ($CDCl_3$): δ 1.30 (t, 3H), 2.23 (m, 2H), 2.45 (m, 2H), 3.71-4.72 (dd, 2H), 4.22 (m, 3H), and 5.61-5.79 (dd, 2H) ppm; ^{13}C NMR ($CDCl_3$): δ 14.1, 22.8, 29.2, 49.5, 58.4, 61.5, 120.1, 127.6, 172.4, and 175.2 ppm; IR (neat) 1719, 1260, 737 cm^{-1}; HRMS Calcd for $C_{10}H_{15N}O_3Br$: 276.0235, found 276.0236; MS (m/e, Rel. intensity): 204, 202 (100), 156, 128, 94, 82, 55.

1-(2-Bromoethyl)-5-oxoproline Ethyl Ester, 3g. Reaction of 5.0 g (31.9 mmol) of **1b** and 6.6 g (35.1 mmol) of 1,2-dibromoethane using procedure A gave 3.5 g (13.3 mmol, 42%) of **3g**. Similar reaction of 1.0 g (6.4 mmol) of **1b** and 1.44 g (7.6 mmol) of 1,2-dibromoethane using procedure B gave 0.43 g (1.65 mmol, 26%) of **3g**: R_f 0.44 (diethyl ether); ^{1}H NMR ($CDCl_3$): δ 1.30 (t, 3H), 1.86 (m, 2H), 2.21 (m, 2H), 2.43 (m, 2H), 3.74 (m, 1H), 3.56-4.38 (m, 2H), and 4.25 (q, 2H) ppm; ^{13}C NMR ($CDCl_3$): δ 14.3, 23.2, 29.0, 29.2, 44.1, 60.6, 61.7, 172.3, and 174.9 ppm; IR (neat) 2954, 1739, 1699 cm^{-1}; MS (m/e, Rel. intensity): 192, 190 (100), 164, 162, 109, 107, 84, 68, 55. No molecular ion could be detected.

The main by-product of this reaction was N-ethenyl-5-oxoproline ethyl ester.

1-(1-Methyl-1-ethyl)-5-oxoproline Ethyl Ester, 3h. Reaction of 1.0 g (6.4 mmol) of **1b** and 0.96 g (7.0 mmol) of 2-bromobutane using procedure A gave a 0% yield of **3h**. Similar reaction of 1.0 g (6.4 mmol) of **1b** and 1.0 g (7.3 mmol) of ethyl 2-bromobutane using procedure B gave 0.46 g (2.15 mmol, 34%) of **3h** R_f 0.38 (diethyl ether); ^1H NMR ($CDCl_3$): δ 0.90 (t, 3H), 1.23 (m, 6H), 1.61 (m, 2H), 2.12 (m, 2H), 2.38 (m, 2H), 3.68 (m, 3H), and 4.23-4.91 (m, 1H) ppm; ^{13}C NMR ($CDCl_3$): δ 9.4, 16.1, 19.1, 24.7, 28.5, 29.1, 55.6, 57.9, 73.7, 171.6, and 178.1 ppm; IR (neat) 1728, 1698 cm^{-1}; MS (m/e, Rel. intensity): 213 (P), 156, 128, 84 (100), 56. HRMS. Calcd for $C_{11}H_{19}O_3N$: 213.1367. Found: 213.1365.

1-(Carboethoxymethyl)-5-oxoproline Ethyl Ester, 3i. Reaction of 2.0 g (12.74 mmol) of **1b** and 2.3 g (13.8 mmol) of ethyl 2-bromoacetate using procedure A gave 3.0 g (12.3 mmol, 97%) of **3i**. Similar reaction of 5.0 g (31.85 mmol) of **1b** and 6.4 g (38.3 mmol) of ethyl 2-bromoacetate using procedure B gave 4.0 g (16.6 mmol, 52%) of **3i**: R_f 0.40 (diethyl ether); ^1H NMR ($CDCl_3$): δ 1.25-1.32 (m, 6H), 2.13 (m, 2H), 2.47 (m, 2H), 3.67-4.65 (dd, 2H), 4.15-4.26 (m, 4H), and 4.42 (m, 1H) ppm; ^{13}C NMR ($CDCl_3$): δ 13.9, 22.6, 28.8, 30.0, 42.8, 59.3, 61.1, 61.3, 168.5, 171.3, and 175.2 ppm; IR (neat) 2978, 1724, 1697 cm^{-1}; HRMS Calcd for $C_{11}H_{17}NO_5$: 243.1107, found 243.1113; MS (m/e, Rel. intensity): 243 (P), 197, 170 (100), 142, 98, 96, 68.

1-(2-Carboethoxyethyl)-5-oxoproline Ethyl Ester, 3j. Reaction of 6.0 g (38.2 mmol) of **1b** and 7.5 g (41.4 mmol) of ethyl 3-bromopropanoate using procedure A gave 5.0 g (19.4 mmol, 51%) of **3j**.[17] Similar reaction of 5.0 g (31.8 mmol) of **1b** and 6.9 g (38.1 mmol) of ethyl 3-bromopropanoate using procedure B gave 2.9 g (11.1 mmol, 35%) of **3j**: R_f 0.43 (diethyl ether); ^1H NMR ($CDCl_3$): δ 1.18-1.33 (m, 6H), 2.07 (m, 2H), 2.38 (m, 2H), 2.57 (m, 2H), 3.34-3.84 (m, 2H), 4.11 (q, 2H), 4.21 (q, 2H), and 4.35 (m, 1H) ppm; ^{13}C NMR ($CDCl_3$): δ 13.6, 17.7,

22.8, 28.8, 32.0, 37.6, 60.0, 60.1, 61.0, 171.3, 171.5, and 175.0 ppm; IR (neat) 2978, 1736, 1701 cm^{-1}; HRMS Calcd for $C_{12}H_{19}NO_5$: 257.1263, found 257.1258; MS (m/e, Rel. intensity): 257 (P), 212, 184, 170, 138 (100), 96, 55.

1-(3-Carboethoxypropyl)-5-oxoproline Ethyl Ester, **3k**. Reaction of 2.0 g (12.7 mmol) of **1b** and 2.7 g (13.8 mmol) of ethyl 4-bromobutanoate using procedure A gave a 0% yield of **3k**.[3a] Similar reaction of 4.6 g (29.3 mmol) of **1b** and 6.85 g (35.1 mmol) of ethyl 4-bromobutanoate using procedure B gave 2.2 g (8.3 mmol, 26%) of **3k** (using 0.34 g of 18-crown-6 as a phase transfer catalyst and DME as a solvent). Similar reaction of 2.7 g (17.2 mmol) of **1b**, 0.06 g (0.38 mmol) of NaI, and 3.7 g (19.0 mmol) of ethyl 4-bromobutanoate using procedure A gave 5.17 g (19.1 mmol, 41%) of **3k**: R_f 0.41 (diethyl ether); ^1H NMR ($CDCl_3$): δ 1.19-1.31 (m, 6H), 1.78 (m, 2H), 2.21 (m, 2H), 2.30 (m, 2H), 2.46 (m, 2H), 2.98-3.70 (m, 2H), 3.68 (m, 1H), 4.20 (q, 2H), and 4.22 (q, 2H) ppm; ^{13}C NMR ($CDCl_3$): δ 14.0, 18.2, 22.3, 23.0, 29.3, 31.4, 41.2, 59.7, 60.3, 61.5, 170.7, 172.8, and 175.5 ppm; IR (neat) 2978, 1731, 1689 cm^{-1}; MS (m/e, Rel. intensity): 271 (P), 225, 198, 152 (100), 124, 87, 69; HRMS Calcd for $C_{13}H_{21}NO_5$: 271.1417. Found 271.1420.

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