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A New Procedure for Preparation of Carboxylic Acid Hydrazides

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Abstract: The standard method for preparing carboxylic acid hydrazides is hydrazinolysis of esters in alcoholic solutions. However, when applied to α,*β*-unsaturated esters, the main product typically is the pyrazolidinone resulting from an undesired Michael-type cyclization. Other alternative methodologies reported for direct preparation of hydrazides from acids are inefficient. We developed an efficient and general process, involving preforming activated esters and/or amides followed by reaction with hydrazine, for the preparation of hydrazides including those of α,*β*-unsaturated acids. This process gives the desired hydrazides in excellent yield and purity under mild conditions.

Compounds **A** and **B** are potential fibrinogen receptor antagonists under development (Scheme 1).[1] A key intermediate common to both compounds is *E*-3-(*N*-*t*-butoxycarbonyl-4-piperidinyl)propenoic acid hydrazide (**1**). To prepare multikilogram drug quantities for further study, we were in need of an efficient and high-yielding method for preparing this α,*β*-unsaturated hydrazide from the corresponding acid **2** (Scheme 1). Though this seemed to be straightforward initially, the transformation turned out to be quite complex. While acyl hydrazides are important building blocks in many syntheses,[2,3] there are no efficient and general procedures for preparing hydrazides, especially α,*β*-unsaturated hydrazides, from the corresponding acids. Most reported procedures are low yielding and require chromatographic purification that is not suitable for large-scale preparations. Several literature approaches were investigated without satisfactory results. The most promising lead came from a traditional carbodiimide-based coupling of acids and hydrazine. Our careful investigation resulted in an efficient, high-yielding procedure, involving preforming activated esters and/or amides followed by reaction with hydrazine, for preparing acyl hydrazides from the corresponding acids. This coupling procedure is rapid, convenient, proceeds under mild conditions, and is suitable for large-scale preparations. We have studied a variety of conjugated and unconjugated unsaturated acids as well as saturated acids bearing ester and carbamate moieties for a general application of this method. This paper will discuss the scope and generality of this method.

Hydrazinolysis of esters is the conventional method for preparing acyl hydrazides.[4,5] However, when this method was applied to the α,*β*-unsaturated ester **4**, the predominant product was the pyrazolidinone **3**, the result of hydrazinolysis and an undesired subsequent intramolecular Michael-type addition (Scheme 2).[6]

Alternatively, acyl hydrazides may be prepared by condensing carboxylic acids with hydrazine in the presence of coupling agents. Unfortunately, most of these methods provide low yields and complicated product isolations.[7−10] Krysin reported good yields using bis(trimethylsilyl)acetamide as a condensing agent, but this method requires strictly anhydrous conditions.[11] We evaluated the use of acid chloride[12] and mixed anhydride[13] approaches to preparing the desired hydrazide but observed incomplete reactions, poor yields, and a large number of impurities.

To prepare the desired hydrazide, we turned our attention to a commonly used carbodiimide-based coupling reaction such as using 1-hydroxybenzotriazole (HOBt) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC) as coupling reagents.[7,8] Our initial investigation showed that the order of reagent addition affected the outcome of the reaction, which prompted us to examine this variable in detail (equation 1). In a typical peptide coupling procedure wherein all reagents were added sequentially as described in method I,[7] we observed low conversion and poor yield. Modifying the addition sequence to add hydrazine last gave slightly better results (method II).

1 → **2** (1)

Method I: (1) 4-methylmorpholine; (2) HOBt; (3) N_2H_4; (4) EDC <30%

Method II: (1) 4-methylmorpholine; (2) HOBt; (3) EDC; (4) N_2H_4 30−70%, inconsistent

Method III: (1) HOBt; (2) DCC, 5 min, filter into N_2H_4 60%

Attempts to drive the reaction to completion in either method I or II by using excess coupling agent, different

† Chemical Development.
‡ Analytical Development.

(1) Hoekstra, W.; Lawson, E.; Maryanoff, B. PCT Int. Appl. WO 0006570, 2000.
(2) Khodairy, A. *Synth. Commun.* **2001**, *31*, 2697−2712.
(3) Wasfy, A.; El-Shenawy, A.; Nassar, S. *Heterocycl. Commun.* **2001**, *7*, 493−500.
(4) Carter, D.; Vranken, D. *J. Org. Chem.* **1999**, *64*, 8537.
(5) Mazaleyrat, J.; Wakselman, M.; Formaggio, F.; Crisma, M.; Toniolo, C. *Tetrahedron Lett.* **1999**, *40*, 6245.
(6) Harada, R.; Kondo, H. *J. Org. Chem.* **1968**, *41*, 2521.
(7) Patterson, J.; Ollmann, I.; Cravatt, B.; Boger, D.; Wong, C.; Lerner, R. *J. Am. Chem. Soc.*, **1996**, *118*, 5938.
(8) Jansen, R.; Schummer, D.; Irschik, H.; Hoefle, G. *Liebigs Ann. Chem.* **1990**, *10*, 975−88.
(9) Pavlov, A.; Berdnikova, T.; Olsufyeva, E.; Miroshnikova, O.; Filipposyanz S.; Preeobrazzhenskaya, M. *J. Antibiot.* **1996**, *49*, 194.
(10) Miyasaka, T.; Hibino, S. *J. Chem. Soc., Perkin Trans. 1* **1986**, 479.
(11) Krysin, E.; Karel'skii, V.; Antonov, A.; Rostovskaya, G. *Chem. Nat. Compd.* **1979**, *15*, 601.
(12) Plehnert, R.; Schroeter, J.; Tschierske, C. *J. Mater. Chem.* **1998**, *8*, 2611.
(13) Monge, A.; Palop, J.; Goni, T.; Fernandez-Alvarez, E. *J. Heterocycl. Chem.* **1986**, *23*, 141.

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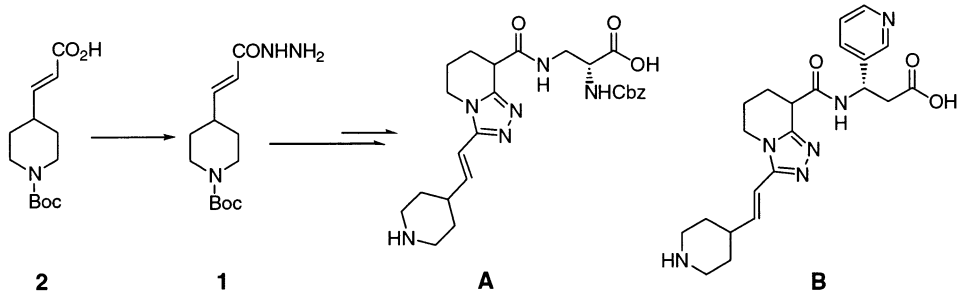
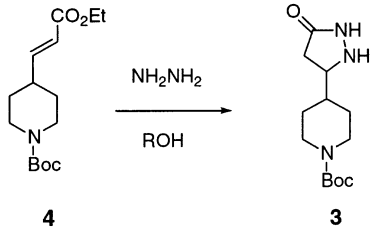
SCHEME 1

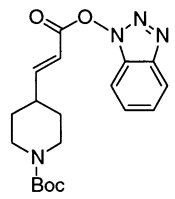


SCHEME 2

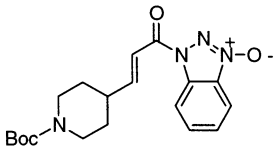


bases, and longer reaction times did not improve the yield and/or purity of the product. Instead, we found, in addition to the desired product, a multitude of undesired byproducts (Scheme 3). Under the reaction conditions, acid, EDC, hydrazine, and hydrazide react with each other to form **5**−**9**.[14,15] We also detected the saturated hydrazide **10** and acid **11**, the products of double-bond reductions by diimide, a contaminant in the commercial hydrazine.[16,17] These impurities were each formed in the range of 3−15% and were very difficult to remove from the desired product. Folkers reported that Cbz-L-Pro-$NHNH_2$ could be prepared in 89% yield by treating Cbz-L-ProOH with HOBt and 1,3-dicyclohexylcarbodiimide (DCC) and waiting for 5 min before filtering the mixture into a hydrazine solution.[18] However, when we applied this method to our α,β-unsaturated acid **2**, we observed only 60% conversion (method III, eq 1). It is clear from these observations that the seemingly "simple" conversion of α,β-unsaturated acids to hydrazides is a rather complex and a poorly understood reaction.

To minimize these side reactions, it is important to avoid the coexistence of acid **2** and hydrazide **1** or hydrazine and EDC in the reaction mixture. A stepwise reaction in which the acid is first converted to an activated intermediate followed by reaction with hydrazine would satisfy these requirements and preclude most of the side reactions. To that effect, treatment of **2** with HOBt and EDC in acetonitrile resulted in a heavy suspension in 2 h. Analysis of the reaction mixture by HPLC revealed the formation of two isomeric intermediates **12** and **13**. These two compounds showed different solubilities in acetonitrile, and the less soluble compound **13** was easily isolated. Compounds **12** and **13** were identified by NMR and MS as the ester and the amide, respectively.[19,20] The structure of amide **13** was further confirmed by the observation of a long-range (three bonds) heteronuclear correlation between the α-proton of the acyl group and one nitrogen of the benzotriazole moiety in a gradient-enhanced HMBC NMR experiment. The activated ester **12** forms initially and then slowly rearranges to the amide **13**. The intermediate formation is complete within 2 h, resulting in a 1:2 mixture of **12** and **13**.[21] Both **12** and **13** are equally reactive toward hydrazine, and their conversion to the desired hydrazide is instantaneous.



12



13

The order of the reagent addition is critical to the success of the reaction as shown in Scheme 4. To suppress the reduction of the double bond, cyclohexene[17] was added to the hydrazine solution to consume any formed diimide. Among the solvents investigated, we found that CH_2Cl_2, DMF, and CH_3CN are the most suitable for this reaction.

The preformation of the intermediates and a reverse mode of addition effectively drives the reaction to completion, suppresses the formation of side products, and affords the desired hydrazide in a nearly quantitative yield with 98% purity. This procedure enabled us to successfully prepare multikilogram quantities of hydrazide **1** without chromatographic purification.

To explore the generality of this procedure, we applied it to a variety of functionalized carboxylic acids as shown in Table 1. The stepwise hydrazide formation procedure was compared to a standard coupling condition that represents the best scenario of methods II and III. While DCC and EDC give comparable results, EDC is safer and the byproducts are easier to remove from the product; thus, EDC was used in all entries. In addition to expanding the study to other alkenoic acids, we investigated alkynoic acids, since hydrazinolysis of alkynoic esters is also complicated by formation of pyrazolones **14**.

(14) Side products were identified by LC/MS and mostly confirmed by comparison to authenic samples.

(15) Pottorf, R.; Szeto, P. *Encyclopedia of Reagents for Organic Synthesis*; Wiley and Sons: New York, 1995; Vol. 4, p 2430.

(16) Corey, E. J.; Mock, W.; Pasto, D. *Tetrahedron Lett.* **1961**, 347

(17) Maryanoff, B.; Greco, M.; Zhang, H.; Andrade-Gordon, P.; Kauffman, J.; Nicolaou, K.; Liu, A.; Brung, P. *J. Am. Chem. Soc.* **1995**, *117*, 1225.

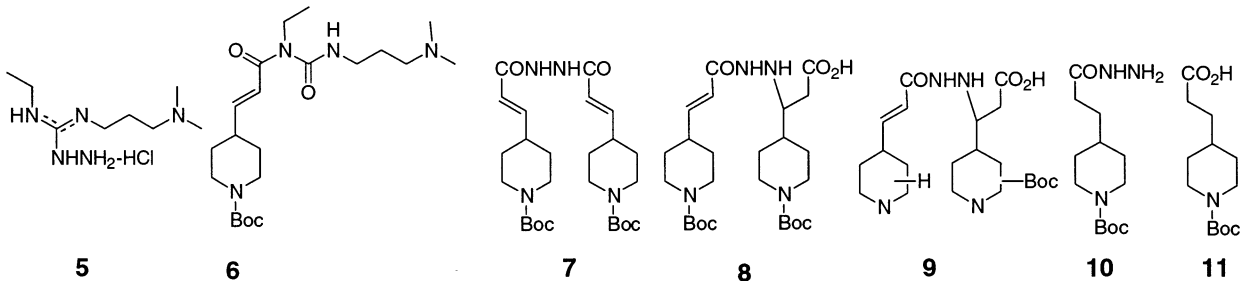
(18) Folkers, K.; Bowers, C.; Lutz, W.; Friebel, K.; Kubiak, T.; Schircks, B.; Rampold, G. *Anorg. Chem. Org. Chem.* **1982**, *37*, 1075.

(19) Okawara, T.; Ikeda, N.; Yamasaki, T.; Forukawa. M. *Chem. Pharm. Bull.* **1988**, *36*, 36628.

(20) Meldal, M. *Acta Chem. Scand.* **1986**, *B 40*, 242.

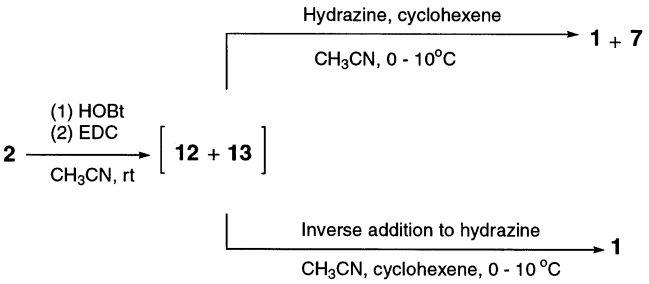
(21) Prolonged stirring resulted in complete conversion to the amide.

SCHEME 3

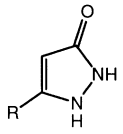


5 **6** **7** **8** **9** **10** **11**

SCHEME 4



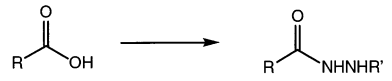
We included acids bearing ester and carbamate moieties, since entry into this class of hydrazides may not be easily accomplished via hydrazinolysis. Finally, the method was applied to enantiomeric carboxylic acids with stereocenters at the potentially racemizable α-positions. We also extended the methodology to include phenylhydrazine.



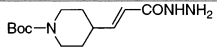
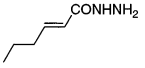
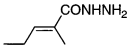
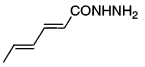
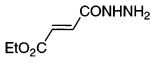
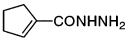
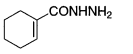
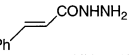
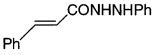
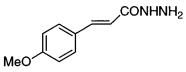
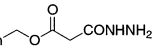
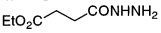
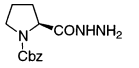
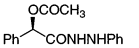
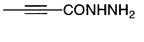
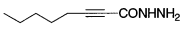
14

The results in Table 1 demonstrate the superiority of the stepwise procedure. The mild conditions tolerate the presence of a variety of functional groups. The rate of the activated intermediate formation in all entries was determined by HPLC analysis and found to be substrate dependent. For most alkenoic acids (entries 1−10), the formation of activated intermediates requires about 2 h to reach completion. One exception is entry 5, which requires only 15 min for the intermediate formation. The slow intermediate formation suggests that for this group of acids, it is necessary to preform the activated ester/amide before reaction with hydrazine for the success of hydrazide preparation. Most saturated and nonconjugated acids (entries 11−16) require only 10−20 min for the intermediate formation. The activated esters/amides in this group are too labile to be analyzed by HPLC directly. One exception, however, is 2-phenylpropanoic acid (entries 14 and 15) where the intermediates of this acid form in 2 h and can be analyzed by HPLC directly. High yields and purities were achieved with our new procedure, while the standard coupling procedure gave poor results. For some acids in this group, method III (eq 1) will result in fare yields if enough time is allowed before reaction with hydrazine. This observation explains the good yield employing coupling method III (eq 1) on a

TABLE 1. Preparation of Hydrazides: Comparison between the New Procedure and Standard Coupling Procedure



1, 15-31

Entry	Product		Yield (%)[a] Standard Coupling Procedure[b]	New Procedure[b]
1		**1**	60	98[c]
2		**15**	62	98
3		**16**	38	97
4		**17**	39	95
5		**18**	89	97
6		**19**	45	95
7		**20**	46	98
8		**21**	49	97[c]
9		**22**	55	96[c]
10		**23**	49	94[c]
11		**24**	34	96
12		**25**	72	93
13		**26**	73	97
14		**27**	55	98
15	 acid: 98% ee	**28**	50	97 98%ee[d]
16	 acid: 98% ee	**29**	75	98 98%ee[d]
17		**30**	90	91
18		**31**	93	98

[a] Yields calculated by HPLC analysis with internal and external standards unless otherwise indicated. [b] As described in the general procedures. [c] Isolated yield. [d] Determined by enantiomeric HPLC analysis.

saturated acid as reported by Folkers and the poor yield when it was applied to α,β-unsaturated acid **2** in our initial evaluation. Interestingly, alkynoic acids (entries 17 and 18) form the activated intermediates rapidly within 5 min, and the intermediates are stable to analysis by HPLC. Both the standard coupling procedure and our new procedure work equally well for alkynoic acids. Esters and carbamates are unaffected under our reaction conditions (entries 1, 5, 11−13, and 16). The reaction conditions do not cause any measurable racemization as demonstrated by entries 15 and 16. The procedure is not limited to hydrazine: reactions with phenylhydrazine under our conditions are clearly superior to those performed using standard coupling procedure (entries 9, 15, and 16).

In conclusion, our investigation led to a clear understanding of the poorly studied reaction of acid and hydrazine. We isolated the intermediates, studied a variety of acids, and observed the structure−reaction rate relationship in different classes of substrates. An efficient, convenient, and practical procedure was developed for preparing carboxylic acid hydrazides from the corresponding acids in excellent yield and purity. This procedure is particularly effective in the preparation of α,β-unsaturated carboxylic acid hydrazides. The mild reaction conditions tolerate the presence of such groups as ester and carbamate, cause no racemization, and are applicable to substituted hydrazines such as phenyl hydrazine.

Experimental Section

^{1}H and ^{13}C NMR spectra were recorded at 300 and 75.45 MHz, respectively. Accurate mass measurements were obtained under electrospray ionization conditions. Most reagents were commercially available reagent-grade chemicals and used without further purification.

General Procedures: Standard Coupling Procedure. The acid (40 mmol) was dissolved or suspended in CH_3CN (80 mL) at room temperature. NMM (48 mmol), HOBt (48 mmol), and EDC (48 mmol) were added sequentially followed by hydrazine (80 mmol) 5 min later. The mixture was stirred at room temperature overnight. The yield was determined by HPLC analysis compared to product standard. The yields obtained with this procedure were similar to those obtained with method III. Method III was not used here due to the insolubility of the activated intermediates in some entries.

New Procedure. The acid (40 mmol) was dissolved or suspended in CH_3CN (80 mL) at room temperature. HOBt (48 mmol) was added in one portion followed by EDC (48 mmol). The mixture was stirred at room temperature, and the reaction progress was monitored by HPLC until all of the acid was converted to the activated ester/amide mixture. The resulting mixture was then slowly added to a solution of hydrazine (80 mmol) and cyclohexene (1 mL) in CH_3CN (40 mL) while the temperature was maintained at 0−10 °C. The reaction was usually complete upon the completion of addition. Water (40 mL) was added. The aqueous CH_3CN mixture was extracted with EtOAc followed by a carbonate wash of the organic layer to remove HOBt. Removal of the solvents under reduced pressure yielded the hydrazide. Water-insoluble hydrazides were easily isolated by filtration after diluting the reaction mixture with water. Highly water-soluble hydrazides were isolated as *p*-toluenesulfonic acid or oxalic acid salts without extraction. DCC worked equally well. DMF and methylene chloride can also be used as solvents for this reaction.

Representative Spectroscopic Data for Compounds 1 and 13−31. *E*-3-(*N*-*t*-Butoxycarbonyl-4-piperidinyl)propenoic Acid Hydrazide (1, as Tosylate): white solid; mp 161−163 °C; ^{1}H NMR (DMSO-d_6) δ 1.19 (m, 2H), 1.39 (s, 9H), 1.67 (m, 2H), 2.30 (s, 3H), 2.35 (m, 1H), 2.76 (m, 2H), 3.94 (m, 2H), 5.93 (d, J = 15.6 Hz, 1H), 6.83 (dd, J = 15.7, 6.4 Hz, 1H), 7.10 (d, J = 7.6 Hz, 2H), 7.50 (d, J = 7.6 Hz, 2H); ^{13}C NMR (DMSO-d_6) δ 21.13, 28.43, 32.25, 37.96, 78.97, 118.81, 125.84, 128.43, 138.05, 145.91, 150.41, 154.18, 164.74. Anal. Calcd for $C_{20}H_{31}N_3O_6S$: C, 54.40; H, 7.08; N, 9.52; S, 7.26. Found: C, 54.23; H, 7.09; N, 9.47; S, 7.47.

***tert*-Butyl 4-[3-Oxo-3-(3-oxybenzotriazol-1-yl)propenyl]-piperidine-1-carboxylate (13):** white solid; mp 144−146 °C; ^{1}H NMR (acetic acid-d_4) δ 1.48 (m, 2H), 1.48 (s, 9H), 1.88 (dd, J = 13.3, 2.5 Hz, 2H), 2.60 (m, 1H), 2.91 (m, 2H), 4.20 (d, J = 11.3 Hz, 2H), 7.08 (dd, J = 15.5, 1.4 Hz, 1H), 7.42 (dd, J = 15.6, 6.7 Hz, 1H), 7.68 (ddd, J = 8.4, 7.2, 0.8 Hz, 1H), 7.88 (ddd, J = 8.4, 7.2, 1.0 Hz, 1H), 8.10 (d, J = 8.4 Hz, 1H), 8.47 (d, J = 8.4 Hz, 1H); ^{13}C NMR (acetic acid-d_4) δ 28.5, 31.0, 39.8, 44.2, 81.3, 116.2, 117.0, 118.4, 128.4, 133.6, 133.8, 134.2, 158.5, 162.6. Anal. Calcd for $C_{19}H_{24}N_4O_4$: C, 61.28; H, 6.50; N, 15.04. Found: C, 61.11; H, 6.62; N, 15.11.

5-Pentyl-1,2-dihydro-pyrazol-3-one (14): yellow solid; mp 194−195 °C; ^{1}H NMR (DMSO-d_6) δ 0.86 (t, J = 6.8 Hz, 3H), 1.27 (m, 4H), 1.52 (m, 2H), 2.42 (t, J = 7.5 Hz, 2H), 5.22 (s, 1H), 10.27 (br s, 2H); ^{13}C NMR (DMSO-d_6) δ 14.23, 22.15, 25.93, 28.66, 31.14, 68.24, 149.00, 161.21. Anal. Calcd for $C_8H_{14}N_2O$: C, 62.31; H, 9.15; N, 18.17. Found: C, 62.07; H, 8.93; N, 18.18.

3-Phenylacrylic Acid *N*′-Phenylhydrazide (22). The activated ester/amide mixture was added slowly to phenylhydrazine (2 equiv) in CH_3CN at room temperature. The resulting suspension was stirred at room temperature for 30 min and then diluted with water. The product precipitated and was collected by filtration and dried. Data were identical with those of commercial compounds.

Benzyl Hydrazinocarbonyl Acetate (24, as Oxalate). Upon reaction completion, the mixture was filtered and the filtrate was evaporated to dryness under reduced pressure. The residue was suspended in ethyl acetate and filtered to remove any insoluble solid. Oxalic acid (1 molar equiv) in ethyl acetate was added to the clear filtrate, and the salt of the product precipitated and was isolated by filtration. White solid; mp 106−107 °C; purity, 98.5%; ^{1}H NMR (DMSO-d_6) δ 3.25 (s, 2H), 5.10 (s, 2H), 7.40 (m, 5H), 8.05−8.50 (br s, 5H); ^{13}C NMR (DMSO-d_6) δ 66.33, 127.27, 128.20, 128.39, 128.76, 136.19, 163.05, 164.84, 167.61; HRMS calcd for $C_{10}H_{12}N_2O_3$, 209.0926; found, 209.0931.

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Supporting Information Available: Experimental details. This material is available free of charge via the Internet at http://pubs.acs.org.

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