https://dx.doi.org/10.4314/jpb.v14i2.23
Vol. 14 no. 2, pp. 279-282 (September 2017)
http://ajol.info/index.php/jpb

Journal of
PHARMACY AND
BIORESOURCES

Synthesis and characterization of two new carboxamides: N-prop-2-ynylacrylamide and N-(prop-2-ynyl)but-2-enamide

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Received 5th June 2017; Accepted 12th July 2017

Abstract
The Schotten-Baumann method is a well-known veritable tool for amide synthesis. Since quite a number of amide compounds have been shown to possess biological activities especially CNS activity a simple method for synthesizing new amides that are potential biologically active molecules was explored using the Schotten-Baumann method. The two compounds, N-prop-2-ynylacrylamide and N-prop-2-ynylbut-2-enamide were synthesized in good yields (42% and 56% respectively) by treating propargylamine with acryloyl chloride and crotonyl chloride respectively. The synthesized compounds were fully characterized by elemental analysis, NMR (^{1}H and ^{13}C), and mass spectral techniques. These demonstrated that the Schotten-Baumann method could be used to synthesized potentially useful carboxamides in good yields.

Keywords: N-Prop-2-ynylacrylamide; N-Prop-2-ynylbut-2-enamide, Schotten-Baumann method; Carboxamides

INTRODUCTION

There are several different routes to the syntheses of amides. Usually a carboxylic acid is converted to a more reactive intermediate, e.g. the acid chloride, which is then allowed to react with an amine [1]. Amides are found in a large array of biologically important compounds [2]. The favourable properties of amides, such as high polarity, stability and conformational diversity, make it one of the most popular and reliable functional groups in all branches of organic chemistry [3]. The peculiar characteristics and ubiquitous nature of the amide bond has stimulated a great deal of research concerning the electronic effects that are responsible for their conformational preferences and unusual stabilities [4]. A recent survey among leading pharmaceutical companies conducted by the ACS Green Chemistry Institute identified "amide formation avoiding poor atom economy reagents" as a key challenge in synthetic chemistry. This finding was hardly surprising, considering that roughly one out of twelve reactions in the synthesis of drug candidates is estimated to be the formation of an amide bond. In fact, a study carried out in 1999 showed that about 25% of known pharmaceuticals contained at least one amide bond [5].

Acylation of amines by carboxylic acid halides represent the best method for preparing amides. The yields are usually in the 80-90% range, and purification of the product is rarely difficult. Ammonia,

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ISSN 0189-8442

ammonium salts, and primary or secondary amines are the usual the amidating agents [6]. One equivalent of the amine is usually lost as hydrogen chloride salt (*equation 2*) while with primary amines a second acyl group may be introduced (*equation 3*) as equilibrium could set up with poor acylating agents or with weakly nucleophilic amines. Usually the hydrochloric acid produced is trapped to obtain a reasonable yield of the amide. The Schotten-Baumann procedure uses aqueous alkali other methods involve refluxing with one equivalent of the amine in aromatic solvents, or reacting with dialkylamino-trimethylsilane to form the volatile trimethylchlorosilane. The latter method has advantages especially in the preparation of sterically hindered amides like acetic acid *t*-butylamide [7,8).

$RCOCl + NH_3 \rightarrow RCONH_2 + HCl$ … (1)
$RCOCl + 2R'NH_2 \rightarrow RCONHR' + R'NH_2 . HCl$ …(2)
$RCOCl + R'NH_2 \rightarrow RCONHR' + HCl$ …(3)

In peptide syntheses, over-reactivity of acyl chloride is often encountered. Even the reactivity of the chlorides is still too high. This renders them sensitive to nucleophiles that are less reactive than amines, *e.g.* water in the reaction medium. Unless anhydrous conditions are maintained, acylation of an amine with a carboxylic acid chloride is always accompanied with hydrolysis of the latter:

$R\text{-}CO\text{-}Cl + H\text{-}OH \rightarrow R\text{-}COOH + H\text{-}Cl$ …(4)

Even more disturbing is the possibility of intramolecular attack on the acid chloride group by a weak but favourable placed nucleophile within the molecule.

EXPERIMENTAL

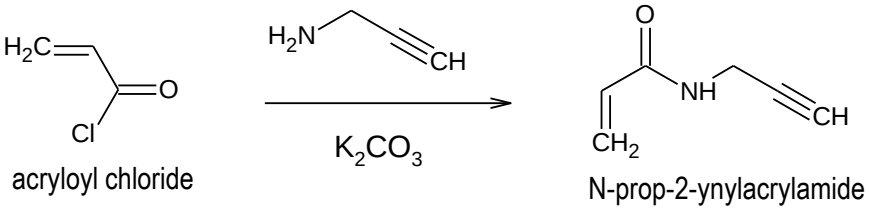
The Schotten-Baumann was used in this study. The reaction was first described in 1883 by German chemists Carl Schotten and Eugen Baumann [9].

Procedure. A solution of 0.03M propargylamine in tetrahydrofuran was added to aqueous potassium carbonate in a 1 litre three-necked round bottomed flask. The flask was immersed in an ice bath on a magnetic stirrer, equipped with a magnetic bar, an air condenser (carrying a drying tube to exclude moisture), an addition funnel with a stopper and a thermometer immersed in the solution. A 0.033M solution of acid chloride (acryloyl chloride) for the synthesis of N-prop-2-ynylacrylamide and 0.033M solution of crotonyl chloride for the synthesis of N-prop-2-ynylbut-2-enamide) was added drop wise over 50 minutes. The mixture was allowed to stir overnight and warm to ambient temperature. The mixture was transferred to a separatory funnel and extracted with chloroform. The extracts were combined, and washed with water, 10% aqueous HCl, saturated aqueous $NaHCO_3$, and water successively. The washed extract was dried over magnesium sulphate and the solvent was removed under vacuum. The resulting residue was purified by recrystallization from methanol.

RESULTS AND DISCUSSION

N-prop-2-ynylacrylamide
Molecular formula: C_6H_7NO (FW = 109.13)
Yield (%): 42%
m.p.: 45-46ºC
^{1}H-NMR ($CDCl_3$), δ (ppm): 2.2(), 3.98 (-CH_2-, s), (=CH, d), 6.2 (-CH_2=, t), 7.9 (1 NH, br s).
^{13}C-NMR ($CDCl_3$), δ (ppm): 29(-CH_2-), 72(=CH_2), 79(=CH), 128(≡CH), 131(≡C-), 167(C=O)

(2E)-N-Prop-2-ynylbut-2-enamide
Molecular C_7H_9NO (FW = 123.15)
Yield (%): 56%
m.p. (ºC): 55ºC
^{1}H-NMR ($CDCl_3$), δ (ppm): 2.2 (-CH_3, d), 3.98 (-CH_2-, s), 4.1 (=CH-, t), 6.2 (≡CH, s), 7.9 (1 NH, br s).
^{13}C-NMR ($CDCl_3$), δ: 27(CH_3), 29(CH_2), 68(=CH-), 71(=CH-), 124(≡CH), 140(≡C-), 168(C=O)



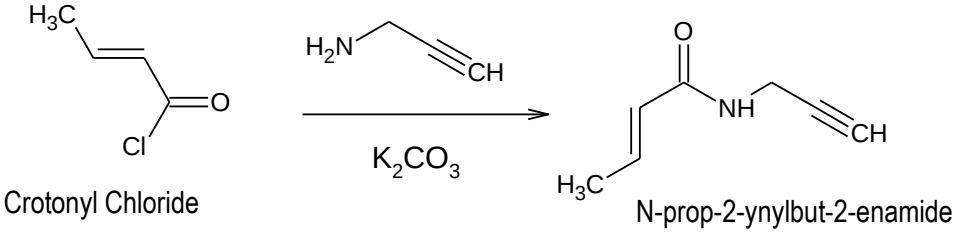
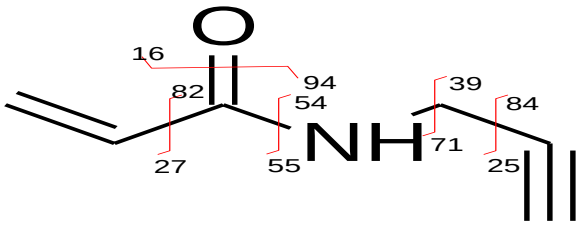


Table 1: Mass spectral data for N-prop-2-ynylacrylamide

EI (20 eV)		EI (70 eV)		CI-MS (NH_3)	
m/z (Rel. int., %)	Ion	m/z (Rel. int., %)	Ion	m/z (Rel. int., %)	Ion
109 (3.9)	[M]+	109 (8.3)	$[M]^+$	110 (100)	M-13[CH]
68 (2.6)	M±39[$HC{\equiv}CCH_2^+$]	80 (97.3)	M-29[CHO]	69 (6.6)	M-54[CH_2CHCO]
80 (100)	M-29 [CHO]	97 (5.4)	M-13[CH]	80 (40)	M-43[CONH]
96 (3.0)	M-13 [CH]	71 (10.9)	M-38[$HC{\equiv}CCH_2^+$]	94 (2.2)	M-13[CH]
55 (21.0)	55[CH_2CHCO]	43 (100)	43[CONH]	122 (3.1)	$[M]^+$



N-(prop-2-yn-1-yl)prop-2-enamide

Table 2: CHN Analysis data of N-(prop-2-ynyl)acrylamide

CHN Analysis	Carbon	Hydrogen	Nitrogen
(% Calculated)	66.04	6.47	12.84
% Found	65.45	6.46	12.53

Table 3: Mass spectra data of N-(prop-2-ynyl)but-2-enamide

EI (20 eV)		EI (70 eV)		CI-MS (NH_3)	
m/z (Rel. int., %)	Ion	m/z (Rel. int., %)	Ion	m/z (Rel. int., %)	Ion
122/123 (12.4/12.3)	[M]+	123 (28.9)	$[M]^+$	124(100)	$[M]^+$
69 (100)	M-55[$HC{\equiv}CCH_2NH$	39 (68.6)	M-86[$C_3H_5CO_2H$]	39 (68.6)	M-86[$C_3H_5CO_2H$]
80 (30.1)	M-43[CONH]	80(36.5)	M-43[CONH]	80(36.5)	M-43[CONH]
94 (70.8)	M-29[CHO]	94(69.5)	M29[CHO]	94(69.5)	M29[CHO]
55 (8.21)	M-69[C_3H_5CO]	69 (100)	M-55	69 (100)	M-55
		55 (17.6)	[HC≡CCH2NH]	55 (17.6)	[HC≡CCH2NH]

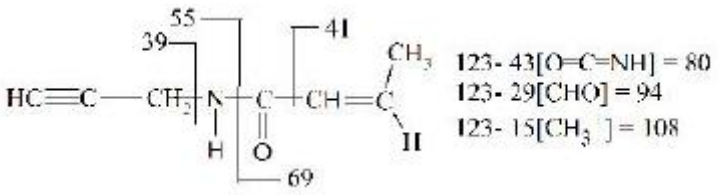


Table 4: CHN Analysis of N-(prop-2-ynyl)but-2-enamide

CHN Analysis	Carbon	Hydrogen	Nitrogen
(% Calculated)	68.27	7.37	11.37
% Found	67.78	7.32	11.19

The yield of the two products obtained signifies that the Schotten-Bauman method is a relatively efficient method for the synthesis of carboxamides. However, the difference observed in the % yield of the two carboxamides might be due to the stereo-electronic difference between hydrogen and methyl groups in acryloyl chloride and in crotonyl chloride respectively.

The two compounds also exhibit low melting points between 42 and 50 degrees Celsius, which signifies relatively low physical stability of the compounds. From the CHN analysis result obtained, it was clearly observed that the calculated percentages for both compounds were all within acceptable limits to that found experimentally which implies that the elemental composition of each of the compounds is confirmed. This also signifies that the intended compounds have been likely synthesized. The NMR data and the mass spectral data, as presented in Tables 2 and 3 above have confirmed clearly that the two compounds were successfully synthesized.

Conclusion. In this study, the synthesis of the N-prop-2-ynylacrylamide and N-prop-2-ynylbut-2-enamide have been successfully demonstrated for the first time using the Schotten-Bauman's method.

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