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A Simple and Expedient Procedure for the Preparation of Gabapentin Lactam (2-aza-spiro[4,5]decan-3-one)

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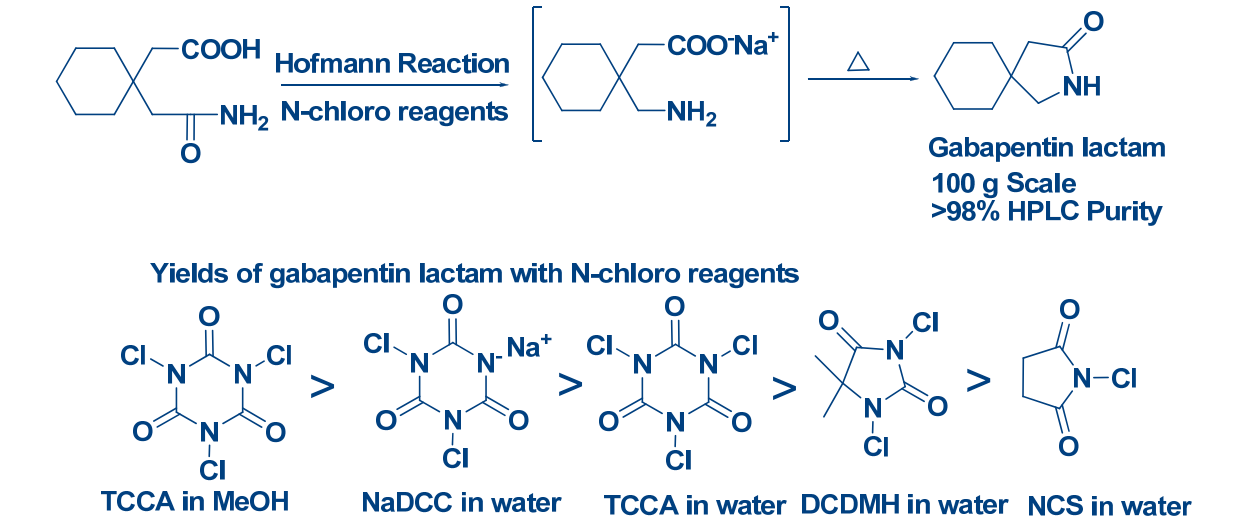

COOH
NH2
O
Hofmann Reaction
N-chloro reagents
COO-Na+
NH2
O
NH
Gabapentin lactam
100 g Scale
>98% HPLC Purity
Yields of gabapentin lactam with N-chloro reagents
TCCA in MeOH
NaDCC in water
TCCA in water
DCDMH in water
NCS in water

ABSTRACT

A novel process has been described on 100 g scale for the preparation of gabapentin lactam which is a penultimate intermediate for the preparation of gabapentin, comprising Hofmann reaction of 1,1-cyclohexanediacetic acid monoamide using chlorinating agents such as trichloroisocyanuric acid, sodium dichloroisocyanurate, 1,3-dichloro-5,5-dimethylhydantoin and N-chlorosuccinimide, which have not been employed so far for making this molecule. Reactions done in aqueous alkali on the 1,1-cyclohexanediacetic acid mono amide led to a solution of gabapentin sodium salt which on heating led to the formation of the gabapentin lactam in good yield.

KEYWORDS Hofmann reaction, gabapentin, gabapentin lactam, trichloroisocyanuric acid, sodium dichloroisocyanurate, 1,3-dichloro-5,5-dimethyl hydantoin, N-chlorosuccinimide.

INTRODUCTION

Gabapentin **1** is a therapeutically important drug in the treatment of certain forms of epilepsy, faintness attacks, cranial traumas, hypokinesia and which additionally brings about an improvement on certain cerebral functions.[1] Extensive and wide spread applications of gabapentin have given it a "blockbuster' status. There are several processes available for the synthesis of **1** among which one using gabapentin lactam **4** as a precursor is widely employed.[2] Lactam **4** by itself has interesting and potentially useful biological activities, eg. it is a K+ channel activator and is neuroprotective,[3] neurotrophic[4] and enhances new bone formation in vitro.[5] Lactam **4** is also useful for the preparation of N-substituted spirolactams.[2b] The first synthesis of **4** was reported by Sircar in 1928 by the Hofmann reaction of the 1,1-cyclohexanediacetic acid monoamide **2** with alkaline sodium hypobromite at 55 °C for 2 h.[6] The reaction mixture was then acidified with HCl and evaporated to dryness. The residue was washed with ether to remove free organic acids and extracted with acetone. The acetone extract was evaporated to dryness. The residue was neutralized with alkali and extracted into ether. Evaporation of ether afforded gabapentin lactam **4** in only 46% yield. This process is not useful for commercial production of **4**

because of the number of steps and the low yield of the desired product, making the process expensive and unviable for commercial production of gabapentin **1** for which **4** is the crucial precursor. Later some commercial processes for the preparation of gabapentin lactam **4** have been reported. Geibel et al. disclosed the synthesis of lactam **4** from cyclohexanone in three steps[7] - conversion of cyclohexanone into ethyl cyclohexylidene acetate, followed by addition of nitromethane to form ethyl 1-nitromethylcyclohexane acetate and finally catalytic reduction of the nitro ethyl derivative. In this process hazardous nitromethane and costly Wittig reagents are used. In addition explosive and inflammable hydrogen gas and pyrophoric catalyst such as 10% Pd-C are also employed. Steiner et al. disclosed a synthesis of **4** from cyclohexanone in four steps[8] - conversion of cyclohexanone into diethyl cyclohexylidene malonate, addition of sodium cyanide to form diethyl 1-cyanocyclohexyl malonate, hydrolysis of diethyl 1-cyanocyclohexyl malonate to 1-cyanocyclohexyl malonic acid and finally catalytic hydrogenation of the cyclohexyl malonic acid at elevated temperature resulting in decarboxylative lactamization. In this process the disadvantages are handling of highly poisonous sodium cyanide and use of rhodium or pyrophoric Raney nickel as catalyst in the final step. Recently we have reported a chemo-enzymatic process for making **4** from cyclohexanone.[9] This method again requires the use of highly poisonous sodium cyanide, explosive & inflammable hydrogen gas and use of Raney nickel as catalyst. Alternatively **4** has been made from monoamide **2** using sodium hypobromite.[10] This process requires expensive and corrosive bromine for the preparation of sodium hypobromite. Parsons and co-workers reported a new approach for the preparation of **4** on a small scale,[11] wherein 1-cyclohexene-1-carboxaldehyde was condensed with benzoyl hydrazine to form the corresponding hydrazone. This hydrazone was reduced with dimethylamine-borane/methane sulfonic acid to get the hydrazine which was then N-acylated with trichloroacetyl chloride to give the corresponding hydrazide. This was subjected to 5-exo-trig halogen atom transfer radical cyclization mediated by copper (I) chloride and TMEDA (tetramethylethylenediamine) to form trichlorospirolactam. Treatment of this trichlorospirolactam with wet Raney nickel gave **4**. This procedure suffers from a few obvious draw backs such as number of chemical steps and scale up

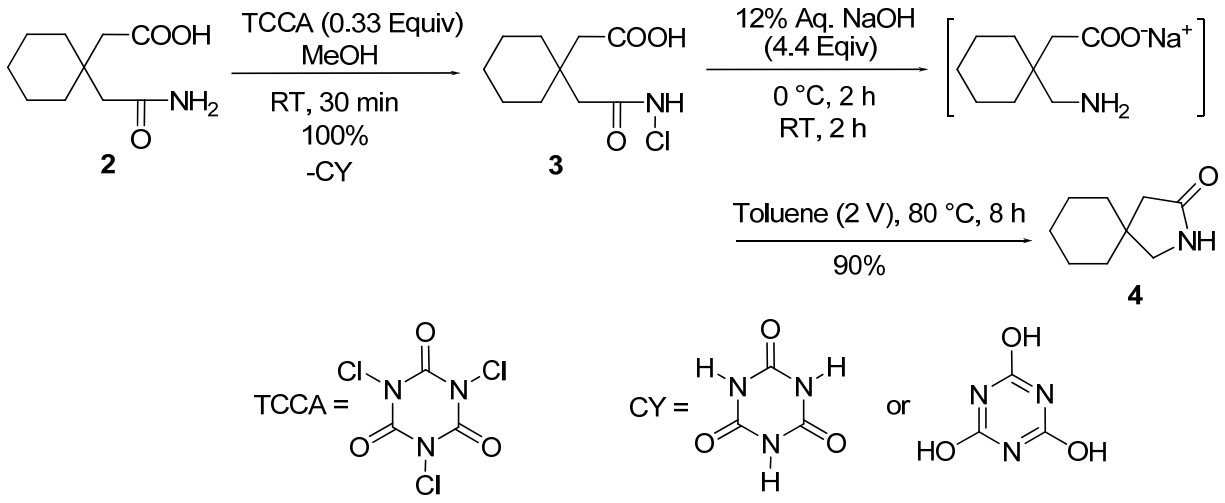
problems including chromatography. Hu and co-workers reported a transition metal catalyzed C-H insertion reaction catalyzed by $Rh_2(cap)_4$ to prepare N-tert-butyl gabapentin lactam.[12] This procedure is handicapped by the use of expensive $Rh_2(cap)_4$. Each of the above procedures suffers therefore from various limitations. We hence felt that there was a genuine need for synthesizing **4** in higher yields and of high purity at a low cost, which are commercial requirements so that the process can be used directly for the production of gabapentin on large scale. In the present work chlorinating agents such as trichloroisocyanuric acid, sodium dichloroisocyanurate, 1,3-dichloro-5,5-dimethylhydantoin and N-chlorosuccinimide are reported for Hofmann reaction of 1,1-cyclohexanediacetic acid monoamide to get lactam **4** in good yields.

RESULTS AND DISCUSSION

1,1-Cyclohexanediacetic acid monoamide **2** was prepared in high yield from commercially available 1,1-cyclohexanediacetic acid by following the literature procedure.[13] The use of chloro derivatives in place of bromo derivatives in the Hofmann Reaction will make it economical from a cost perspective at the production level.

As part of our work, initial experiments for the Hofmann reaction were performed using trichloroisocyanuric acid (TCCA). TCCA has been widely applied in organic synthesis.[14] It has been used for the Hofmann reaction in methanol in order to get methyl carbamates[15] but has not been utilized for the synthesis of gabapentin. The advantages involved in the use of trichloroisocyanuric acid are i) it is a solid having high melting point 246-247 °C, which can be handled easily ii) it is an inexpensive and easily available reactant, iii) it can be used in the molar ratio of 0.33 to 1 of reagent to substrate iv) the byproduct cyanuric acid can be recycled to make the starting material TCCA and this process can be repeated for a number of times. In addition to this, a significant advantage in using TCCA is that it can be stored at room temperature for many days unlike 10-15% sodium hypochlorite solution which has to be prepared freshly before starting the reaction and has to be stored below 5 °C. Also since the volumes of the reaction using TCCA are less compared to the common process using 10-15% sodium

hypochlorite process (~3 volumes less), batch throughputs can be usefully increased. Encouraged by the above potential advantages, N-chlorination of 1,1-cyclohexanediacetic acid monoamide **2** was performed on its methanol solution with TCCA as described in the experimental section. The byproduct cyanuric acid precipitated as solid. After disappearance of starting material **2**, as confirmed by TLC analysis, the reaction mixture was filtered to remove the byproduct cyanuric acid which was obtained quantitatively. The methanolic filtrate was evaporated to dryness using a rotary evaporator at 50 °C under vacuum to get N-chloro cyclohexanediacetic acid monoamide **3** as a solid in quantitative yield. This hitherto unknown N-chloroamide, **3** was characterized completely by NMR and mass spectral analysis. In ^{1}H-NMR (300 MHz, DMSO-d6) a peak at 12.00 ppm showed the presence of –COOH group. Proton resonating at 9.96 ppm showed the presence of –NH-Cl pattern. Protons resonating at 2.43 and 2.39 ppm showed the presence of two methylene groups as singlets. Multiplet seen in the region 1.52 – 1.27 ppm represents the cyclohexyl group. In ^{13}C-NMR (75 MHz, DMSO-d6) carbonyl carbons of acid and amide groups were seen at 172.9 & 169.3 ppm respectively. Methylene carbons which are attached to carboxylic acid and amide groups were seen at 40.7 & 40.3 ppm respectively. The signal of the quaternary carbon atom in the cyclohexyl group was seen at 35.1 ppm. The other five carbons of cyclohexyl group were seen at 35.0, 25.5 and 20.9 ppm. The structure of the compound was further confirmed by high resolution mass spectral analysis which showed the molecular ion peak at m/z 256 (M+Na). Thus the compound was unambiguously established to be N-chloro-1,1-cyclohexanediacetic acid monoamide **3**. This was subjected to the Hofmann Reaction by adding it portion wise to aqueous sodium hydroxide solution at 0 – 5 °C over a period of 1 h. The resulting reaction mass was processed as described in the experimental section. The solution containing the sodium salt of gabapentin was subjected to cyclization under the experimental conditions to give lactam **4** which was extracted by toluene. Evaporation of toluene at reduced pressure afforded **4** in 90% yield with HPLC purity >99% (Scheme 1).

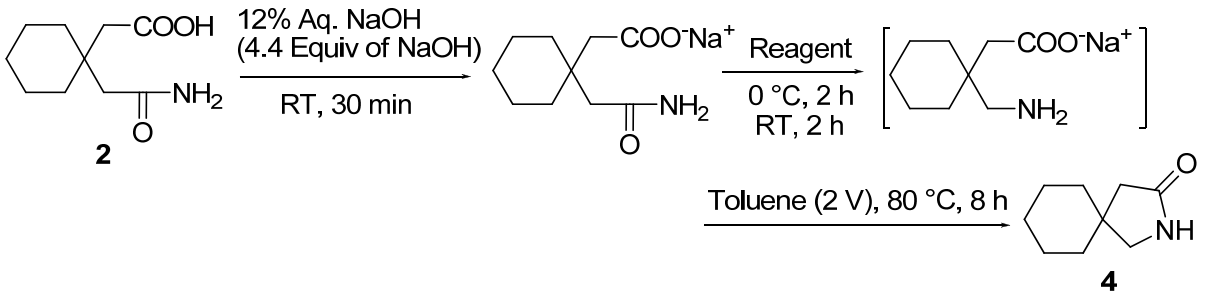


Scheme 1 Hofmann reaction using TCCA

Although the above process gave lactam **4** in 90% yield it has a few limitations for use in production level such as, i) one isolation step involved (N-chlorination) including complete distillation of solvent and ii) obligatory use of methanol for keeping the monoamide in solution for N-chlorination. In order to overcome the above drawbacks, reactions were planned for using TCCA in water which is a green solvent and executed successfully. Accordingly, a solution of the sodium salt of 1,1-cyclohexanediacetic acid monoamide, prepared by adding the monoamide **2** to excess 12% sodium hydroxide solution (4.4 equivalent of NaOH with respect to **2**; this excess NaOH is required for sodium salt formation of monoamide, Hofmann rearrangement including the liberated CO_2 quenching to Na_2CO_3) was added dropwise to a suspension of TCCA in water (1.5 V of water with respect to **2**) over a period of 1 h at 0-5 °C and the Hofmann reaction conducted under well defined conditions as described in the experimental section. Lactam **4** was obtained by evaporation of the toluene solution in vacuo in 75% yield with HPLC purity >98%. Cyanuric acid was recovered significantly from the TCCA reaction as described in the experimental section. To the best of our knowledge, trichloroisocyanuric acid has not been employed as chlorinating agent for making lactam **4** by Hofmann reaction. The generality of the method was extended to other chlorinating agents such as sodium dichloroisocyanurate (NaDCC), 1,3-dichloro-5,5-dimethylhydantoin (DCDMH) and N-chlorosuccinimide (NCS).

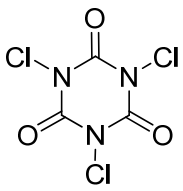
Sodium dichloroisocyanurate (NaDCC) is used widely for treating potable water, waste water, water in swimming pools and many other industrial water systems.[16] Benjamin Staskun reported the use of NaDCC for the Hofmann degradation of 4-chlorobenzamide to 4-chloroaniline[17] and also Pallavicini et al. have reported for N-chlorination.[18] Unlike trichloroisocyanuric acid, it is highly soluble in water (25 g in 100 mL water). We have examined its synthetic utility for making gabapentin lactam for the first time under conditions given in the experimental section and were gratified to find that it proceeded very well to afford **4** in 85% yield with HPLC purity >99%. Obviously the homogenous nature of reaction mass using the solution of the sodium dichloroisocyanurate compared to the non-homogeneity in the case of trichloroisocyanuric acid is the reason for the superior performance of the former reagent. Cyanuric acid was recovered significantly from the sodium dichloroisocyanurate reaction as described in the experimental section. These chloroisocyanuric acids are very interesting from the perspective of green chemistry,[19] as these are alternative reagents to generate organic compounds without using hazardous chlorine gas every time as these reagents can be prepared in bulk and can be stored at room temperature for long time and used on call.[20] They also have advantages from the atom economy point of view, as they can transfer majority of their mass to the substrate, for example trichloroisocyanuric acid can transfer up to 46% of its mass. They are not expensive and can be regenerated from recovered cyanuric acid.

We have also examined the synthetic utility of 1,3-dichloro-5-5-dimethyl hydantoin (DCDMH) for the Hofmann reaction in water. The reagent has been extensively used as a bleaching agent for industrial and domestic water.[21] Recently Zou et al. have reported the use of DCDMH for selective preparation of α-mono and α,α-dichloro ketones.[22] We have undertaken to study its synthetic utility for Hofmann reaction in the present work. Following the standard procedure for gabapentin lactam **4**, using DCDMH, **4** was obtained in only 55% yield with HPLC purity >99%. N-Chlorosuccinimide (NCS) has been widely used as electrophilic chlorinating agent in organic synthesis.[23] NCS in water was used for the synthesis of pregabalin.[24] In our hands, use of NCS for the Hofmann reaction of **2** afforded **4** in 46% yield (Scheme 2).

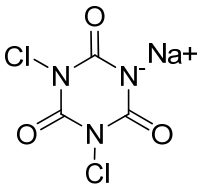


Reagent (Equiv)	Gabalactam (**4**) yield (%)
TCCA (0.33)	75
NaDCC (0.55)	85
DCDMH (0.55)	55
NCS (1.1)	46

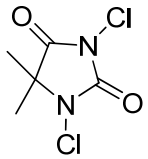
TCCA (Trichloroisocyanuric acid) =



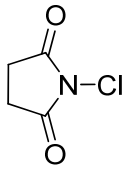
NaDCC (Sodium dichloroisocyanurate) =



DCDMH (1,3-Dichloro-5,5-dimethyl hydantoin) =



NCS (N-chloro succinimide) =



Scheme 2 Hofmann reaction using TCCA, NaDCC, DCDMH and NCS in water

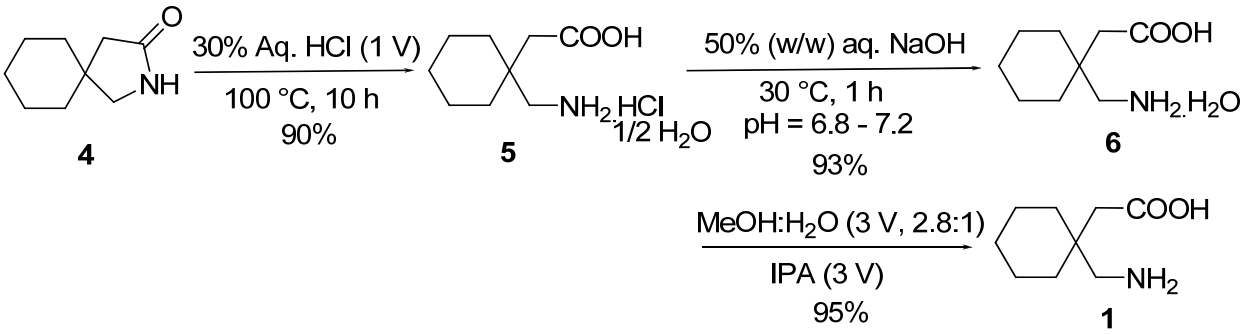
The quality of gabapentin lactam **4** is critical for the purity of derived gabapentin. HPLC data of lactam **4** obtained from these processes are listed in Table 1. Typical minor unknown impurities seen are at 0.74, 0.84 and 0.94 RRT and pleasingly, the levels are near nonsignificant. To the best of our knowledge there is no report available thus far in the literature for the use of TCCA, NaDCC, DCDMH and NCS to make gabapentin lactam in water and with high purity.

Table 1. HPLC purity of gabapentin lactam (**4**)

Entry	Source	HPLC Purity (%)	Single Impurity (RRT, %)		Unknown
			0.74	0.84	0.94
1	Example 1 (via N-chloro derivative)	99.75	0.04	0.02	0.09
2	Example 2	98.40	0.05	0.02	ND*
3	Example 3	99.50	0.07	ND*	ND*
4	Example 4	99.43	0.08	0.03	ND*
5	Example 5	98.00	0.22	0.13	ND*

*ND: Not detected

Gabapentin lactam **4** obtained from monoamide **2** and trichloroisocyanuric acid in methanol through the N-chloroamide **3** was converted to gabapentin **1** by following the procedure reported by us in a patent[25] (Scheme 3, Table 2). **1** was obtained in 79.5% overall yield from **4**, with more than 99.5% purity and a single unknown impurity <0.05%, matching well with samples obtained by a commercial process using NaOBr for the Hofmann Reaction and was superior to **1** made using NaOCl for the conversion of **4**.[26]



4 **5** **6** **1**

Scheme 3 Gabapentin lactam (**4**) to gabapentin (**1**)

Table 2. HPLC purity of gabapentin (**1**) obtained from gabapentin lactam (**4**)

Entry	Source	HPLC Purity (%)	Single Unknown Impurity (%, RRT)
1	**1** obtained from example 1 gabapentin lactam	99.46	0.0244 (3.7 RRT) 0.0094 (0.85 RRT) 0.0107 (0.89 RRT)

CONCLUSIONS

In conclusion, we have developed novel methodologies for the preparation of gabapentin lactam (**4**) in good yield using chlorinating agents such as trichloroisocyanuric acid, sodium dichloroisocyanurate, 1,3-dichloro-5,5-dimethylhydantoin and N-chlorosuccinimide. Recoverability of the precursors, recycling and use of water as solvent make these routes particularly attractive from an environmental point of view. The potential of these reagents for Hofmann Reaction in water with other amides is under study.

EXPERIMENTAL SECTION

General Information: Reactions were monitored by TLC on silica plates using Iodine chamber for visualization. ^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ solvent on 300 MHz NMR spectrometer using TMS as internal reference. Chemical shifts δ and coupling constants J are given in ppm (parts per million) and Hz (hertz) respectively. Chemical shifts are reported relative to residual solvent as an internal standard for ^{1}H and ^{13}C ($CDCl_3$ δ 7.26 ppm for ^{1}H and δ 77.0 ppm for ^{13}C). The following abbreviations are used to designate signal multiplicity: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, and br = broad. HPLC analyses were performed with Atlantis T-13 column (150 x 4.6 x 3u). Mobile phase:50:50/0.05% formic acid in water:methanol. Column temperature was programmed at 40 °C, with detector wavelength 210 nm. Flow rate was 0.6 mL/min and injection volume was 20 μL. Purity is given as area%. Melting points were recorded on a Veego melting point apparatus and are uncorrected. FT-IR spectrum was recorded using a FTLA 2000 spectrometer. TCCA,

NaDCC, DCDMH, NCS, sodium hydroxide, sulphuric acid, hydrochloric acid, toluene, methanol and isopropyl alcohol were of commercial grade and used as such. All compounds are characterized by ^{1}H NMR and ^{13}C NMR. All known compounds data are in consistent with the given literature reports.

Experimental Procedures

Example 1: Preparation of gabapentin lactam **4** using N-chloroamide **3**

(a) Preparation of N-chloroamide **3** from monoamide **2** in methanol: A suspension of monoamide **2** (100 g, 0.5025 mol) in methanol (6 V, 600 mL) was heated to 45 - 50 °C and stirred for 0.5 h, when a clear solution resulted. The solution was cooled to 20 - 25 °C, and then treated with TCCA (38.47 g, 0.166 mol) in three portions over a period of 45 min under stirring. Reaction mass became turbid during the course of the addition and was stirred for 1 h until TLC showed the disappearance of the starting material **2**. The reaction mixture was then filtered off. The solid obtained was cyanuric acid which was recovered quantitatively. The filtrate was evaporated in vacuo to dryness using a rotovap at 50 °C to get **3** in quantitative yield as a solid. The product was completely characterized by IR, NMR and mass spectral analysis. Melting point: 109 – 111 °C ; IR (ν, cm^{-1}): 3186, 2932, 2854, 1702, 1663, 1453, 1397, 1322, 1242, 1191, 1075, 968, 797, 678, 628; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 12.00 (s, 1H, -COO<u>H</u>), 9.96 (s, 1H, -CON<u>H</u>Cl), 2.43 (s, 2H, -C<u>H</u>$_2$COOH), 2.39 (s, 2H, -C<u>H</u>$_2$CONHCl), 1.52-1.27 (unresolved multiplet, 10 H, cyclohexyl group); ^{13}C NMR ($CDCl_3$, 75 MHz), δ 172.9 (-<u>C</u>OOH), 169.3 (-<u>C</u>ONHCl), 40.7 (-<u>C</u>H$_2$COOH), 40.3 (-<u>C</u>H$_2$CONHCl), 35.1, 35.0, 25.5, 20.9 ppm (cyclohexyl group); HRMS $[M+Na]^+$ for $C_{10}H_{16}ClNO_3Na$ calcd, 256.0711; found, 256.07.

Cyanuric acid which was filtered off was washed with methanol to remove impurities (recovery 100%) and converted to the trichloro derivative by a known procedure[27] and reused for a fresh reaction.

(b) Preparation of **4** from **3**: 750 g of 12% sodium hydroxide solution [4.5 equivalents of NaOH with respect to **2** in (a)] was cooled to 0 - 5 °C and treated with **3** (117.3 g, 0.5025 mol) by adding in three portions over a period of 1 h at the same temperature. Reaction was continued at 0 - 5 °C for more 2 h.

Then temperature of the reaction mass was increased to 15 - 20 °C under continued stirring for two more hours. The temperature was now raised to 50 °C and toluene (2 V, 200 mL) charged in one lot. Then the reaction mass temperature was raised to 80 °C and maintained for 8 h. After 8 h of stirring at 80 °C, the temperature was decreased to 50 °C and the toluene layer separated. The aqueous layer was extracted with further amounts of toluene (1 V, 100 mL) and the toluene layer separated. The combined toluene layers were washed with 30% brine (100 mL). The toluene solution was evaporated to dryness completely using a rotary evaporator under reduced pressure to get gabapentin lactam **4** (69.2 g, 90%) as a solid with HPLC purity >99%. The product was identical to standard lactam **4**.[10] Melting point: 89 – 90 °C (reported: 90 – 91 °C); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.05 (bs, 1H, -NH), 3.15 (s, 2H, -C<u>H</u>$_2$-NH-), 2.18 (s, 2H, -C<u>H</u>$_2$CO-), 1.67-1.31 (unresolved m, 10H, cyclohexyl group), ^{13}C NMR ($CDCl_3$, 75 MHz), δ 178.4 (-NH<u>C</u>O-), 53.8 (-<u>C</u>H$_2$NH), 43.3 (-<u>C</u>H$_2$CO-), 39.2, 36.7, 25.6, 22.8 (cyclohexyl group).

Example 2

Preparation of **4** from **2** using TCCA in water:

Monoamide **2** (100 g, 0.5025 mol) and 12% NaOH solution (750 g, 4.4 equivalents of NaOH with respect to **2**) were stirred together for 30 min at 25-30 °C. The resulting solution was added to a stirred mixture of TCCA (38.47, 0.165 mol) and 150 mL water (1.5 V) at 0 - 5 °C during 1 h. Then the reaction mixture was stirred for another 2 h at 0 – 5 °C. The temperature of the reaction mixture was slowly raised to 15 - 20 °C and maintained for 2 h. Then the reaction mass temperature was increased to 50 °C and toluene (2 V, 200 mL) was charged. The temperature was further raised to 80 °C and maintained for 8 h. The reaction mass was cooled to 50 °C and the toluene layer separated from the aqueous layer. Further work up as in example 1 gave **4** (57.6 g, 75%) with HPLC purity >98%.

The aqueous solution having a pH of 14 was acidified to pH 2 with 70% H_2SO_4. The precipitated cyanuric acid was washed with methanol to remove impurities (recovery 80%) and converted to the TCCA by a known procedure[27] and reused.

Example 3

Preparation of **4** using NaDCC:

To a solution of NaDCC (60.8 g, 0.276 mol) in 150 mL water (150 mL, 1.5 V with respect to **2**) at 0 - 5 °C was added a solution of **2** (100 g, 0.5025 mol) in 12% NaOH (750 g) at 0 – 5 °C. The reaction was conducted further as in example 2 to yield **4** (65.3 g, 85%) with HPLC purity of 99%.

The aqueous alkaline layer was acidified to pH 2 and the precipitated cyanuric acid filtered off and washed with methanol. The recovered cyanuric cid (80%) was converted to the NaDCC by a known procedure[27] and reused.

Example 4

Preparation of **4** using DCDMH:

Hofmann Reaction was conducted on monoamide **2** (100 g) dissolved in 12% sodium hydroxide (750 g) and DCDMH (54.4 g) in water (150 mL) as usual. The solution was heated as before in toluene. **4** was isolated as in example 2 to yield **4** (42.3 g, 55%) with HPLC purity >99%.

Recovery of byproduct dimethylhydantoin was not done because of its high solubility in methanol unlike cyanuric acid.

Example 5

Preparation of **4** using NCS:

Monoamide **2** (100 g in 750 g of 12% sodium hydroxide) was reacted with NCS (73.51 g) in water (150 mL) as usual and the solution processed as earlier in toluene. Evaporation of toluene layer gave **4** (35.7 g, 46%) with HPLC purity >98%.

Recovery of byproduct succinimide was not done because of its high solubility in methanol unlike cyanuric acid.

ACKNOWLEDGMENTS

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SUPPORTING INFORMATION

The Supporting Information is available free of charge on the ACS Publications website at DOI:

Characterization (^{1}H, ^{13}C NMR and HRMS) for compounds **3** & **4** and HPLC chromatograms for compounds **4** & **1** (PDF).

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