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## A convenient methodology for the synthesis of functionalized nitrogen mustards

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### ABSTRACT

A short protocol for the synthesis of functionalized bis(chloroethyl)amines (nitrogen mustards) has been described via the nucleophilic substitution of allylic bromides derived from Baylis-Hillman alcohols with diethanolamine followed by dichlorination.

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### KEYWORDS

Baylis hillman reaction;  
Bis(chloroethyl)amines;  
Nitrogen mustards;  
Chlorethamine drugs;  
Nucleophilic substitution.

### INTRODUCTION

Bis(chloroethyl) amine moiety is an excellent pharmacophore in nitrogen mustard based DNA alkylating anticancer agents<sup>[1]</sup>. The reaction mechanism of these molecules involves the formation of reactive aziridinium intermediate followed by a nucleophilic attack of the DNA to form mono and dialkylated DNA adducts resulting in the cellular toxicity (Figure 1)<sup>[2]</sup>.

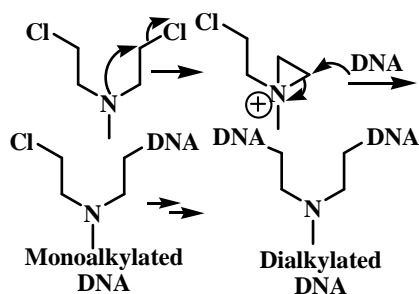


Figure 1: General mode of anti-cancer action of nitrogen mustards

There are several chloroethylamine based drugs that are in clinical use for the treatment of wide variety of cancers. Some of these include mechlorethamine (**1**) (used for Hodgkin's disease, chronic myelocytic/chronic lymphocytic leukemia (CLL), lymphosarcoma, and lung cancer), chlorambucil (**2**) (for CLL and malignant lymphomas including giant follicular lymphoma, lymphosarcoma, and Hodgkin's disease), melphalan **3** (for multiple myeloma, breast and ovarian cancer), cyclophosphamide (**4**) (for breast, ovarian, lymphomas, leukemia's, multiple myeloema, lung, and bone), ifosfamide (**5**) (for testicular, bone and lung cancers, soft tissue sarcoma,) etc. (Figure 2)<sup>[1]</sup>.

### EXPERIMENTAL

#### Preparation of diol (13a)

To a suspension of  $\text{Na}_2\text{CO}_3$  (2.12 g, 20.0 mmol) in  $\text{CH}_3\text{CN}$  (20.0 mL) was added diethanolamine (1.05 g, 10.0 mmol) and the bromide (**11a**) (2.55 g, 10.0

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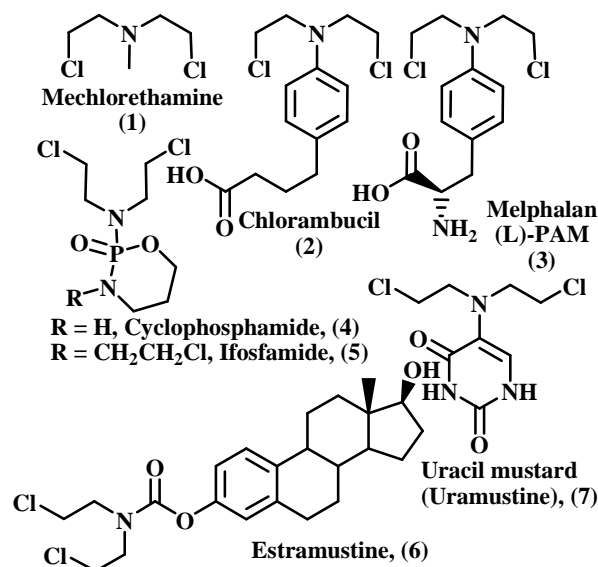


Figure 2: Anti-cancer nitrogen mustards in clinical use

mmol) and heated at 60°C for 3h. Upon complete consumption of the bromide, the reaction mixture was filtered and washed with dichloromethane. The filtrate was concentrated and purified by silica gel column chromatography (dichloromethane:methanol, 10:1) to obtain 2.0 g (72%) of the pure diol. (~5% of SN<sub>2</sub>' substitution product was also observed). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): δ 7.86 (s, 1H), 7.32-7.45 (m, 5H), 3.85 (s, 3H), 3.62 (s, 2H), 3.58 (t, J = 5.5 Hz, 4H), 2.55 (t, J = 5.5 Hz, 4H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>): δ 169.2, 142.6, 135.1, 131.1, 129.5, 129.0, 128.8, 59.6, 55.7, 52.6, 49.6; ESI-MS: 280 (M+H)<sup>+</sup>.

**Preparation of diol (13b)**

Procedure similar to that of (13a). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): δ 7.83 (s, 1H), 7.20-7.30 (m, 4H), 3.85 (s, 3H), 3.66 (t, J = 5.5 Hz, 4H), 3.60 (t, J = 5.5 Hz, 4H), 2.98 (br s, 2H), 2.56 (m, 4H), 2.4 (s, 3H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>): δ 169.4, 142.9, 139.3, 132.1, 130.1, 129.7, 129.5, 58.6, 55.6, 52.6, 49.6, 21.6; ESI-MS: 294 [(M+H)<sup>+</sup>, 100%]

**Preparation of diol (13c)**

Procedure similar to that of (13a). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): δ 7.74 (s, 1H), 7.30-7.36 (m, 4H), 3.81 (s, 3H), 3.56 (t, J = 5.5 Hz, 4H), 3.17 (br s, 2H), 2.52 (t, J = 5.5 Hz, 4H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>): 169.0, 141.2, 133.5, 131.0, 129.0, 59.6, 55.7, 52.6, 49.5; ESI-MS: 314 [(M+H)<sup>+</sup>, 100%]

**Preparation of diol (13d)**

Procedure similar to that of (13a). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): δ 7.59 (d, J = 8.5 Hz, 2H), 7.33 (d, J = 8.5 Hz, 2H), 6.38 (s, 1H), 5.45 (s, 1H), 5.11 (s, 1H), 3.45-3.63 (m, 4H), 2.63-2.91 (m, 4H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>): δ 168.1, 143.3, 140.7, 132.6, 130.2, 129.2, 118.8, 111.8, 64.3, 60.5, 53.0, 52.8; ESI-MS: 305 [(M+H)<sup>+</sup>, 100%]

**Preparation of diol (13e)**

Procedure similar to that of (13a). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): δ 6.22 (d, J = 1.0 Hz, 1H), 5.75 (d, J = 1.5 Hz, 1H), 3.74 (s, 3H), 3.58 (t, J = 6.0 Hz, 4H), 3.32 (m, 3H), 2.62 (t, J = 6.0 Hz, 4H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>): δ 167.8, 137.9, 128.4, 59.6, 55.7, 55.6, 52.3.

**Preparation of diol (13f)**

Procedure similar to that of (13a). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): 7.81 (s, 1H), 7.22-7.44 (m, 5H), 4.23 (t, J = 7.5 Hz, 2H), 3.62 (s, 2H), 3.58 (t, J = 7.5 Hz, 4H), 2.54 (t, J = 7.5 Hz, 4H), 1.64-1.76 (m, 2H), 1.16-1.48 (m, 26H), 0.87 (t, J = 7.5 Hz, 3H).

**Preparation of bis(chloroethyl) amine (14a)**

To a solution of the diol (13a) (1.39 g, 5.0 mmol) in 10.0 mL of CH<sub>2</sub>Cl<sub>2</sub> at 0°C was added excess thionyl chloride (7.1 mL, 100.0 mmol) over a period of 20 minutes and stirred for 2h. Upon completion (TLC), the reaction mixture was quenched by the addition of methanol (10mL) and concentrated in vacuo. The crude product thus obtained was purified by silica gel column chromatography (hexane: ethyl acetate, 4:1) to obtain 1.18 g (75%) of bis(chloroethyl) amine (14a). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): δ 7.85 (s, 1H), 7.28-7.54 (m, 5H), 3.87 (s, 3H), 3.62 (s, 2H), 3.49 (t, J = 7.0 Hz, 4H), 2.87 (t, J = 7.0 Hz, 4H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>): δ 169.0, 142.9, 135.2, 130.5, 130.0, 129.2, 128.8, 56.2, 52.4, 50.2, 41.8.

**Preparation of bis(chloroethyl) amine (14a)**

To a solution of the diol (13a) (1.39 g, 5.0 mmol) in 10.0 mL of CH<sub>2</sub>Cl<sub>2</sub> at 0°C was added excess thionyl chloride (7.1 mL, 100.0 mmol) over a period of 20 minutes and stirred for 2h. Upon completion (TLC), the reaction mixture was quenched by the addition of methanol (10mL) and concentrated in vacuo. The crude

product thus obtained was purified by silica gel column chromatography (hexane: ethyl acetate, 4:1) to obtain 1.18g (75%) of bis(chloroethyl) amine (**14a**).  $^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.85 (s, 1H), 7.28-7.54 (m, 5H), 3.87 (s, 3H), 3.62 (s, 2H), 3.49 (t,  $J = 7.0$  Hz, 4H), 2.87 (t,  $J = 7.0$  Hz, 4H);  $^{13}\text{C NMR}$  (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  169.0, 142.9, 135.2, 130.5, 130.0, 129.2, 128.8, 56.2, 52.4, 50.2, 41.8.

#### Preparation of bis(chloroethyl) amine (14b)

Procedure similar to that of (**14a**).  $^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.84 (s, 1H), 7.47 (d,  $J = 8.0$  Hz, 2H), 7.23 (d,  $J = 8.0$  Hz, 2H), 3.85 (s, 3H), 3.63 (s, 2H), 3.50 (t,  $J = 7.0$  Hz, 4H), 2.88 (t,  $J = 7.2$  Hz, 4H), 2.40 (s, 3H);  $^{13}\text{C NMR}$  (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  169.2, 143.3, 139.6, 132.3, 130.3, 129.5, 129.4, 56.2, 52.4, 50.4, 41.9, 21.6.

#### Preparation of bis(chloroethyl) amine (14c)

Procedure similar to that of (**14a**).  $^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.80 (s, 1H), 7.55 (d,  $J = 8.5$  Hz, 2H), 7.39 (d,  $J = 8.5$  Hz, 2H), 3.85 (s, 3H), 3.59 (s, 2H), 3.51 (t,  $J = 7.0$  Hz, 4H), 2.87 (t,  $J = 7.0$  Hz, 4H);  $^{13}\text{C NMR}$  (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  168.8, 142.1, 135.5, 133.5, 131.7, 130.6, 129.1, 56.0, 52.6, 50.4, 41.8.

#### Preparation of bis(chloroethyl) amine (14d)

Procedure similar to that of (**14a**).  $^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.82 (s, 1H), 7.72 (m, 4H), 3.88 (s, 3H), 3.58 (s, 2H), 3.51 (t,  $J = 6.5$  Hz, 4H), 2.87 (t,  $J = 6.5$  Hz, 4H);  $^{13}\text{C NMR}$  (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  168.4, 140.9, 139.6, 132.9, 132.5, 130.7, 118.7, 112.8, 55.9, 52.7, 50.4, 41.7. ESI-MS: 337 [(M-CN+Na) $^+$ , 100%].

#### Preparation of bis(chloroethyl) amine (14e)

Procedure similar to that of (**14a**).  $^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  6.22 (d,  $J = 1.5$  Hz, 1H), 5.84 (d,  $J = 1.5$  Hz, 1H), 3.75 (s, 3H), 3.50 (t,  $J = 7.0$  Hz, 4H), 3.42 (s, 2H), 2.91 (t,  $J = 7.0$  Hz, 4H);  $^{13}\text{C NMR}$  (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  167.3, 138.2, 126.8, 56.6, 55.7, 52.1, 42.0.

#### Preparation of bis(chloroethyl) amine (14f)

Procedure similar to that of (**14a**).  $^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ ): 7.71 (s, 1H), 7.24-7.42 (m, 5H), 4.12 (t,  $J = 7.0$  Hz, 2H), 3.52 (s, 2H), 3.35 (t,  $J = 7.0$  Hz, 4H), 2.75 (t,  $J = 7.0$  Hz, 4H) 1.61-1.64 (m, 2H), 1.10-1.38 (m, 26H), 0.78 (t,  $J = 7.5$  Hz, 3H);  $^{13}\text{C NMR}$  (125

MHz,  $\text{CDCl}_3$ ):  $\delta$  168.6, 142.8, 135.3, 130.7, 130.0, 129.2, 128.7, 65.6, 56.2, 50.3, 41.8, 32.2, 29.96, 29.95, 29.93, 29.87, 29.82, 29.6, 29.5, 29.0, 26.3, 22.9, 14.4.

#### Preparation of hydrochloride (15a)

To a solution of the bis(chloroethyl) amine (**14a**) (1.0 g, 3.16 mmol) in ether (10 mL), was added 4.0 mL of HCl (1M solution in ether) and stirred for an hour. The resulting solid was filtered and dried in vacuo to obtain the hydrochloride salt (**15a**) in 90% yield (1.0 g).  $^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  8.30 (s, 1H), 7.39-7.54 (m, 5H), 4.39 (s, 2H), 3.97 (s, 3H), 3.86 (m, 4H), 3.38 (m, 4H);  $^{13}\text{C NMR}$  (125 MHz,  $\text{CDCl}_3$ ): 166.9, 150.1, 133.3, 130.7, 129.9, 129.0, 122.6, 55.2, 53.6, 49.2, 37.0; ESI-MS: 316 [(M-Cl) $^+$ , 100%], 318 [(M+2-Cl) $^+$ , 67%].

#### Preparation of hydrochloride (15b)

Procedure similar to that of (**15a**).  $^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  8.25 (s, 1H), 7.28-7.34 (m, 4H), 4.46 (s, 2H), 3.95 (s, 3H), 3.90 (s, 4H), 3.46 (s, 4H), 2.40 (s, 3H);  $^{13}\text{C NMR}$  (500 MHz,  $\text{CDCl}_3$ ): 167.1, 150.4, 141.5, 130.6, 130.2, 129.5, 129.4, 55.3, 53.5, 49.5, 37.1, 21.7; ESI-MS: 330 [(M-Cl) $^+$ , 100%], 332 [(M+2-Cl) $^+$ , 67%].

#### Preparation of hydrochloride (15d)

Procedure similar to that of (**15a**).  $^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  8.11 (s, 1H), 7.79 (m, 2H), 7.67 (m, 2H), 4.15 (br s, 2H), 3.96 (s, 3H), 3.80 (m, 4H), 3.32 (m, 4H);  $^{13}\text{C NMR}$  (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  167.1, 145.4, 138.2, 133.2, 130.4, 118.3, 113.8, 55.7, 53.5, 50.3, 38.8; ESI-MS: 341 [(M-Cl) $^+$ , 100%], 343 [(M+2-Cl) $^+$ , 67%].

#### Preparation of hydrochloride (15f)

Procedure similar to that of (**15a**).  $^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  8.28 (b, 1H), 7.43-7.57 (m, 5H), 4.47 (s, 2H), 4.36 (t,  $J = 7.5$  Hz, 2H), 3.83-3.92 (m, 4H), 3.48-3.52 (m, 4H), 1.76-1.84 (m, 2H), 1.24-1.42 (m, 26H), 0.90 (t,  $J = 7.0$  Hz, 3H);  $^{13}\text{C NMR}$  (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  166.9, 150.2, 133.0, 130.8, 129.9, 129.3, 121.9, 67.1, 66.1, 55.4, 49.5, 37.1, 32.1, 29.93, 29.92, 29.89, 29.84, 29.76, 29.6, 29.5, 28.8, 26.2, 22.9, 15.5, 14.4.

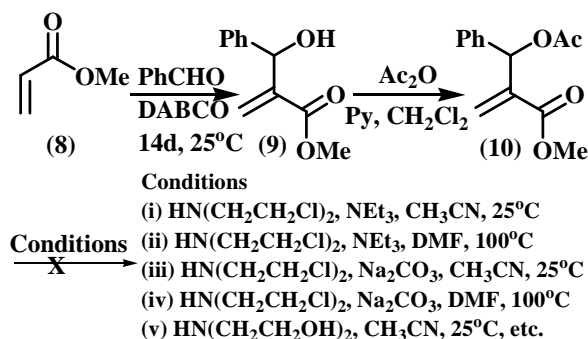
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## RESULTS AND DISCUSSION

Baylis-Hillman reaction is an important C-C bond forming reaction and it offers densely functionalized alcohols and amines in one step<sup>[3]</sup>. The reaction is highly atom efficient, compatible with wide variety of functional groups and the reaction does not require any organic solvents, thus making it environmentally benign. The product allylic alcohols undergo facile isomerization with a variety of nucleophiles in  $SN_2$  fashion to afford valuable synthetic intermediates.

We envisaged that  $SN_2$  type isomerization of Baylis-Hillman acetates or  $SN_2$  substitution of Baylis-Hillman bromides with diethanolamine followed by chlorination of the resulting diols would provide an easy access to functionalized bis(chloroethyl)amines (nitrogen mustards) with high tunability for further structural modifications.

We initiated the synthesis via the Baylis Hillman reaction of benzaldehyde with methyl acrylate in the presence of DABCO to obtain the allylic alcohol (**9**) that upon acetylation afforded the acetate (**10**). Initial efforts towards the nucleophilic substitution of acetate with bis(2-chloroethyl)amine failed under a variety of conditions. Changing the base, temperature, and solvents also did not effect the formation of the product



SCHEME 1: Attempted  $SN_2$  substitution of baylis-hillman acetates

cleanly. Substitution of the acetate with diethanolamine also proved futile and no product formation was observed (SCHEME 1).

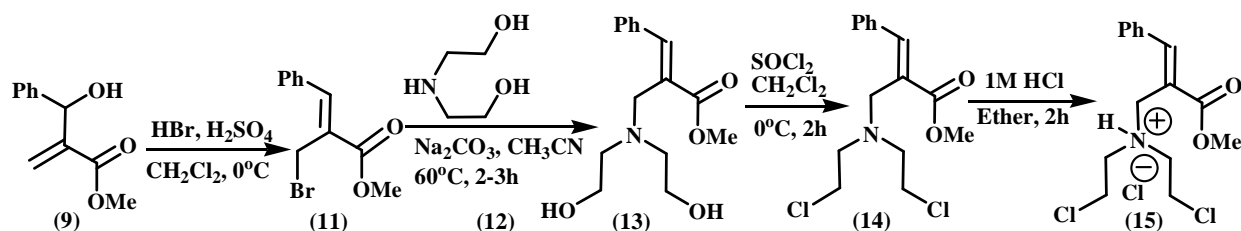
We then attempted the substitution of the allylic bromide (**11**) obtained by the reaction of alcohol (**9**) with  $HBr$  and  $H_2SO_4$ <sup>[4]</sup>. The direct reaction of bis(chloroethyl)amine with bromide (**11**) also did not provide the product. Finally, the substitution was realized by the reaction of diethanolamine (**12**) with (**11**) in the presence of  $Na_2CO_3$ . The reaction at ambient temperature was observed to be relatively slow and lower yields of the corresponding diol (**13**) were obtained. Heating the reaction at  $60^\circ C$  in  $CH_3CN$  accelerated the product formation and the reaction was complete within 2 hours. Reaction of the diol with excess thionyl chloride<sup>[5]</sup> resulted in the clean formation of bis(chloroethyl)amine (**14**). To increase the hydrophilicity of (**14**), the corresponding hydrochloride salt (**15**) was prepared by treatment with hydrogen chloride solution in anhydrous ether (SCHEME 2).

To demonstrate the applicability of the protocol,

TABLE 1: Synthesis of functionalized bis(chloroethyl) amines

Sr. no.	R <sub>1</sub>	R <sub>2</sub>	Diol <sup>a</sup>		Dichloride		Hydrochloride	
			Compd.	Yld (%)	Compd.	Yld (%)	Compd.	Yld (%)
1	Ph	Me	<b>13a</b>	72	<b>14a</b>	75	<b>15a</b>	90
2	4-MePh	Me	<b>13b</b>	73	<b>14b</b>	73	<b>15b</b>	92
4	4-ClPh	Me	<b>13c</b>	69	<b>14c</b>	76	<b>15c</b>	89
5	4-CNPh	Me	<b>13d</b>	74	<b>14d</b>	75	<b>15d</b>	94
6	H	Me	<b>13e</b>	75	<b>14e</b>	70	<b>15e</b>	88
7	Ph	$C_{16}H_{33}$	<b>13f</b>	71	<b>14f</b>	76	<b>15f</b>	90

<sup>a</sup>5-10% of  $SN_2$  substitution product was also observed



SCHEME 2: Synthesis of functionalized bis(chloroethyl) amines

various functionalized nitrogen mustards (**14a-g**) and their hydrochloride salts (**15a-g**) were prepared via  $SN_2$ -substitution-halogenation procedure. The requisite allylic bromides (**11a-g**) were prepared by the reaction of corresponding aldehydes with methyl acrylate followed by treatment with HBr. The reaction of diethanolamine with the bromides (**11a-g**) yielded the diols (**13a-g**) in 69-76% yields. Thionyl chloride treatment yielded the dichlorides (**14a-g**) which were further converted to the hydrochlorides (**15a-g**) in good yields (TABLE 1). Studies are underway to determine the efficacy of these molecules as anti-cancer agents.

### CONCLUSIONS

In conclusion, we have synthesized several functionalized bis(chloroethyl)amine (nitrogen mustard) small molecules as potential anticancer agents. The Baylis-Hillman template provides various possibilities for structural modifications as well as opportunities for linking with biologically relevant carrier molecules for targeted delivery. Owing to the significance of Baylis-Hillman reaction, ease of functionalization, high flexibility, and the importance of nitrogen mustards as cancer chemotherapeutics, the present study could be applied to obtain novel DNA alkylating agents for cancer treatment.

### ACKNOWLEDGMENT

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