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Syntheses and Bioactivities of Novel Carbamates Combining Platelet Activating Factor (PAF) Receptor Antagonist with Thromboxane Synthase Inhibitor (TxSI)

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Abstract—Synthesis of carbamates **3b** which possess dual-acting PAF antagonist/TxSI using unstable esters **1**, diazepines **2**, K_2CO_3 and 18-crown-6 is described. © 2002 Published by Elsevier Science Ltd.

Many alkanoic acid derivatives, such as compounds **1**, have been developed as Thromboxane A_2 (TxA_2) synthase inhibitors or TxA_2 receptor antagonists.[1,2] We have also generated a series of compounds represented by **3**,[3] which possess dual-acting Platelet activating factor (PAF)[4] antagonist and TxA_2[5] synthase inhibitor.

In the course of our works,[2,3] we have found that the characteristic features of compounds **1** having a mesylate group were unstable, and that, interestingly, the mesylate group can be readily converted to chlorine atom by treatment with brine. In this publication, we would like to report an efficient synthesis of carbamates **3b** by utilizing its character, K_2CO_3 and 18-crown-6, and their bioactivities.

In general, compound **3a** was obtained as shown in Scheme 1 by reaction of ethyl esters **1**[2] and diazepines **2**[6] in the presence of a base. Experiments were carried out to test the effect of reagents on the yield of compounds **3a** and **3b** (Table 1).

In an initial experiment, we attempted the reaction using only K_2CO_3. Reaction at 70 °C afforded only compound **3a** in 23% isolated yield. At more than 70 °C, these reactions gave lower yields of compound **3a** along with ready decomposition of compound **1a**. Therefore, we examined this reaction on addition of 18-crown-6. Namely, to a solution of esters **1** and diazepines **2** in DMF was added K_2CO_3 followed by 18-crown-6 at room temperature, and the mixture was stirred under the same condition. Addition of 0.6 equiv of 18-crown-6 improved the yield of compound **3a** (entry 1 vs 2). However, unexpectedly, it was found that compound **3b** was obtained in addition to the desired compound **3a** (entries 2–5). Further, in the case of addition of 1.0 equiv of 18-crown-6, it is noteworthy that compound **3b** was obtained as a major product (entry 6).

We considered that dialkyl carbonates should be formed due to 18-crown-6, and reacted with amines to give carbamates in the same way as generating trialkyl phosphates from tripotassium phosphate by Fukui's group (Scheme 2).[7] Therefore, it was expected that reaction with diazepines **2** after converting more than 2.0 equivalents of esters **1** into 1.0 equiv of dialkyl carbonates should, at least, preferentially lead to compound **3b**. According to the above consideration, the use of 2.4 equivalents of ester **1b** and 1.0 equivalent of 18-crown-6 afforded compound **3b** in 87% isolated yield (entry 7). Furthermore, although the dialkyl carbonates could not be identified, compound **3b** and the hydroxyl substituted ester was obtained in 92% and recovered in 81% isolated yield, respectively, when using 1.2 equiv of 18-crown-6 (entry 8).[8] From this result, we confirmed a equation shown in Scheme 2.

On the other hand, compound **3a** was obtained in 81–90% isolated yield by treatment with Et_3N in refluxing THF for 1 h, but in 38% isolated yield in refluxing $CHCl_3$ for 4 h (entries 9–11).

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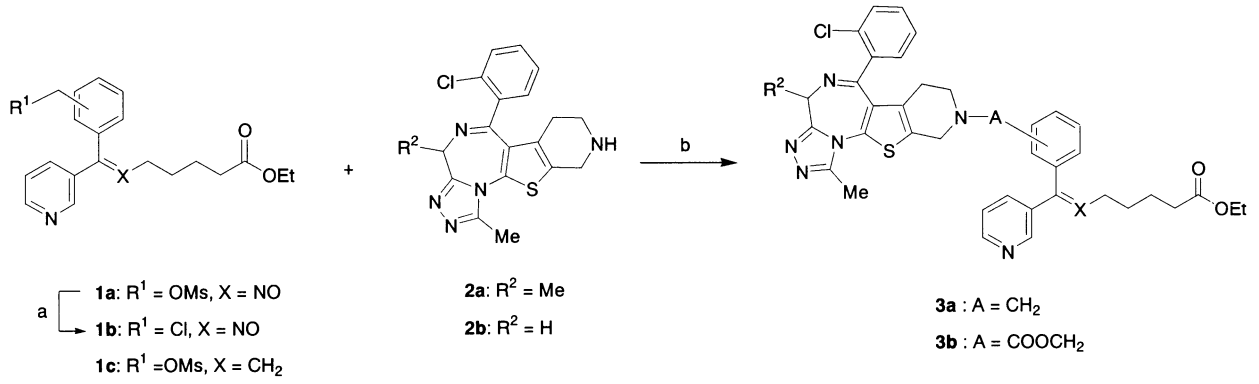
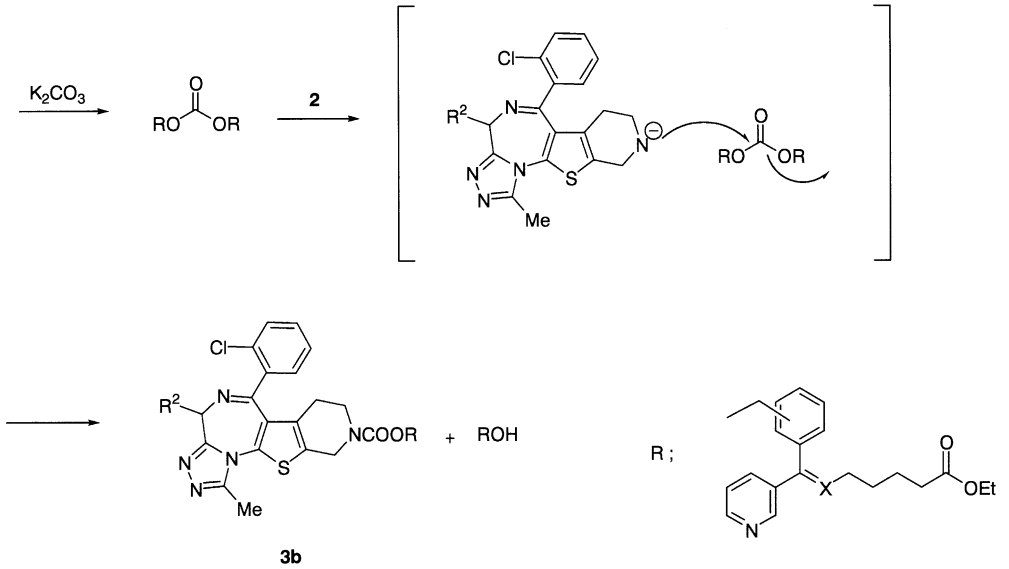


Scheme 1. Reagents and conditions: (a) Brine, $CHCl_3$, rt, 77% quant.; (b) see Table 1.

Table 1. Coupling of esters **1** with diazepines **2** to the target compounds **3**

				3a		3b	
Entry	Ester[a] + Diazepine	Reagents[b] and conditions	Position	Yield (%)[c]	E/Z[d]	Yield (%)[c]	E/Z[d]
1	**1a** (1.2 equiv) + **2a**	K_2CO_3, DMF, 70 °C, 2 h	3	(23)	2:3		
2	**1a** (1.2 equiv) + **2a**	K_2CO_3, $_{18}C_6$ (0.6 equiv), DMF, 70 °C, 2 h	3	43	1:2	16	1:3
3	**1a** (1.2 equiv) + **2a**	K_2CO_3, $_{18}C_6$ (0.6 equiv), DMF, 70 °C, 2 h	4	(43)	2:3	trace	nd[e]
4	**1c** (1.2 equiv) + **2a**	K_2CO_3, $_{18}C_6$ (0.6 equiv), DMF, 70 °C, 2 h	3	63	1:1[f]	28	
5	**1c** (1.2 equiv) + **2a**	K_2CO_3, $_{18}C_6$ (0.6 equiv), DMF, 70 °C, 2 h	4	52	2:3	21	1:3
6	**1a** (1.2 equiv) + **2a**	K_2CO_3, $_{18}C_6$ (1.0 equiv), DMF, 70 °C, 2 h	3	18	1:4[f]	26	
7	**1b** (2.4 equiv) + **2b**	K_2CO_3, $_{18}C_6$ (1.0 equiv), DMF, 70 °C, 1 h	3			(87)	1:6
8[g]	**1a** (2.4 equiv) + **2a**	K_2CO_3, $_{18}C_6$ (1.2 equiv), DMF, 70 °C, 2 h	3			(92)	1:9
9	**1a** (1.2 equiv) + **2a**	Et_3N, THF, reflux, 1 h	3	(81)	1:2		
10	**1a** (1.2 equiv) + **2a**	Et_3N, $CHCl_3$, reflux, 4 h	3	(38)	1:2		
11	**1a** (1.2 equiv) + **2b**	Et_3N, THF, reflux, 1 h	3	(90)	1:2		

[a]Equivalents based on diazepines **2**.
[b]Equivalents based on diazepines **2**. 2.4 equivalents of K_2CO_3 was used.
[c]Determined by ^{1}H NMR spectra and HPLC analysis; isolated yields are given in parentheses.
[d]Determined by ^{1}H NMR spectra and HPLC analysis.
[e]nd, not determined.
[f]Combined **3a** and **3b**.
[g](*E*/*Z*)-5-[[[3-(hydroxymethyl)phenyl-3-pyridyl]methylene]aminooxy]pentanoic acid ethyl ester was obtained in 81% isolated yield.



Scheme 2.

Table 2. PAF antagonist and TxA_2 synthase inhibitory activities of compounds **3a** and **3b**

Entry[a]	Product	R^2	X	IC_{50} (μM)		ED_{50} (mg/kg, iv)		ED_{50} (mg/kg, po)	
				PAF antagonist[b]	TxA_2 synthase[c]	PAF antagonist[d]	TxA_2 synthase[e]	PAF antagonist[d]	TxA_2 synthase[e]
7	**3b**	H	NO	0.139	0.062	0.7	0.1	>10.0	>10.0
8	**3b**	Me	NO	0.041	0.069	0.2	0.1	>10.0	>10.0
11	**3a**	H	NO	0.190	0.067	0.8	0.1	>10.0	>10.0
9	**3a**	Me	NO	0.047	0.060	0.2	0.1	>10.0	>10.0
	(±)-E6123[f]			0.036	>1.000	0.02	NT	0.025	NT
	UK74505[g]			0.029	NT	0.1	NT	1.55	NT
	Ozagrel			NT	0.024	NT	0.02	NT	0.1
	Isbogrel[h]			NT	0.0009	NT	0.01	NT	0.05

[a]Corresponded to entry in Table 1.
[b]Inhibition of the PAF-induced platelet aggregation in rabbit platelet rich plasma(PRP). This was performed according to the method of Terashita et al. with slight modification.[9]
[c]Inhibition of TxB_2 production by incubating prostaglandin H_2(PGH_2) with human platelet microsomes. This was performed according to the method of Terashita et al. with slight modification.[10]
[d]Activity in vivo was demonstrated by the ability to protect mice from the lethal effects of an injection of PAF. The ED_{50} values represent the dose reduced mortality by 50%. This was performed according to the method of Cooper et al. with slight modification.[11]
[e]Inhibition of serum TxB_2 production in the rats. This was performed according to the method of Terashita et al. with slight modification.[10]
[f]See ref 12.
[g]See ref 11.
[h]See ref 13.

Table 2 summarizes PAF antagonist and TxA_2 synthase inhibitory activities. Compounds **3a** and **3b** synthesized by entries **7**–**9** and **11** in Table 1 were tested in vitro and in/ex vivo. As the result, **3a** and **3b** showed little difference on activities. However, in a PAF-induced death assay after intravenous administration in mice, the action time of compounds **3b** were quarter of compounds **3a**, respectively (data not shown). From the result previously reported,[3] these compounds appeared to be not parted in the diazepine and the ester in vivo.

In conclusion, we have developed an efficient method for the synthesis of carbamates **3b** in good yield by utilizing esters **1**, 2.4 equiv of K_2CO_3 and 1.0 equiv of 18-crown-6. Moreover, the hydroxyl substituted ester was recovered in good yield, and could be recycled. Hence, this method would become one tool for bulk synthesis of the compound or carbamates. Extension of this methodology to other compounds is under investigation in order to define the scope of this synthesis of carbamates. On the other hand, carbamates **3b** indicated excellent dual activity by intravenous administration. Further synthetic studies and detailed biological investigations including the study of diastereoisomers are currently in progress and will be reported elsewhere.

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8. Typical procedure for the synthesis of carbamates;
To a solution of **1a** (543 mg, 1.25 mmol) in DMF (5 mL) was added K_2CO_3 (173 mg, 1.25 mmol) followed by 18-crown-6 (165 mg, 0.62 mmol) at room temperature. After stirring for 30 min at room temperature, **2a** (200 mg, 0.52 mol) was added and the mixture was stirred at 70 °C for 2 h. After cooling and conventional work-up, the mixture was subjected to chromatography to yield **3b** with R^2 = Me as an orange foam (367 mg, 92%). **3b**: ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 1.16 (3H, t, J = 7.2 Hz), 1.50–1.81 (5H, m), 1.90–2.15 (1H, m), 2.04 (3H, d, J = 6.9 Hz), 2.24 (2H, t, J = 6.9 Hz), 2.60 (3H, s), 3.14 (1H, brs), 3.55–4.00 (1H, m), 4.03 (2H, q, J = 7.2 Hz), 4.14 (2H, t, J = 6.0 Hz), 4.21 (1H, dd, J = 6.6, 13.5 Hz), 4.39 (1H, brd, J = 16.8 Hz), 4.78 (1H, brd, J = 16.8 Hz), 5.05 (2H, brs) 7.10–7.50 (9H, m), 7.64, 7.78 (total 1H, each d, J = 8.1 Hz), 8.51 (1H,

s), 8.56 (1H, d, $J = 4.8$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 11.9, 14.2, 17.6, 21.4, 28.4, 33.9, 42.8, 52.7, 60.2, 67.2, 74.4, 123.0, 127.2, 127.6, 128.7, 129.0, 129.3, 130.1, 131.1, 132.6, 134.3, 136.0, 136.5, 136.9, 137.2, 149.6, 149.7, 149.9, 153.1, 156.4, 173.3; IR (KBr) 3420, 2936, 1731, 1705, 1592, 1538, 1416, 1378, 1304, 1231, 1113, 1038, 985 cm^{-1}; HRMS (FAB^+) *m*/*z* exact mass calcd for $C_{40}H_{41}ClN_7O_5S$ 766.2578, found 766.2579.

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