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LOSSEN-TYPE REARRANGEMENT PRODUCTS IN THE REACTION OF *N*-(PHTHALIMIDOYLOXY)-3-PHENYLPROPIONATE AND – TOSYLATE WITH BENZYL ALCOHOL

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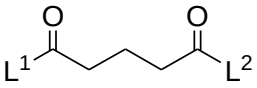
Abstract – This paper reports the reaction of *N*-(phthalimidoyloxy)-3-phenylpropionate (**2a**) and -tosylate (**6**) with benzyl alcohol as a nucleophile to afford the products via Lossen-type rearrangement. To study the scope of this reaction mechanism, we also studied the reaction of several *N*-sulfonyloxyimide derivatives with benzyl alcohol under similar conditions and found that the same types of products were obtained in high yields.

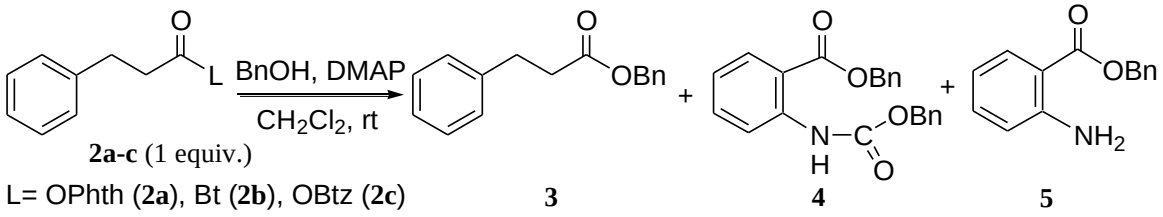
In the field of the conjugation chemistry, hetero-functional bi-dentate cross-linking reagents, such as MBS (*m*-Maleimidobenzoyl-*N*-hydroxysuccinimide ester) and related modified linkers, are widely used.[1-2] However, the limitation of MBS is that the maleimidoyl group is only useful fundamentally for the Michael addition of SH group, which is sometimes hard or laborious to introduce into the target molecule. Non-symmetrical bi-dentate cross-linking reagents bearing two different reactive groups towards nucleophiles (Figure 1) are apparently considered to be very useful for modification of organic compounds even biological compounds, but, their developments have been left unexplored. When these kinds of non-symmetrical bi-functional cross-linking reagents are newly developed, the chemical modification toward proteins (antigens formation) will become quite easy by almost one-pot procedure.
Recently, we succeeded in synthesizing several examples (**1a**: L^1 = OPhth, L^2 = OBtz; **1b**: L^1 = OPhth, L^2 = Bt; **1c**: L^1 = OPhth, L^2 = Cl) and demonstrated their usefulness for preparation of pre-antigen.[3] In the course of these syntheses, we need to determine the combination of the leaving groups and hence, to estimate the reactivity difference among these "active ester" and other leaving groups, i.e., phthalimidoyloxy, benzotriazolyloxy, benzothiazolyloxy, and benzotriazolyl groups.



L^1, L^2 = -OPhth (phthalimidoyloxy), -OBtz (benzothiazolyloxy),
-OBt (benzotriazolyloxy), -Bt (benzotriazolyl), -Cl, etc.

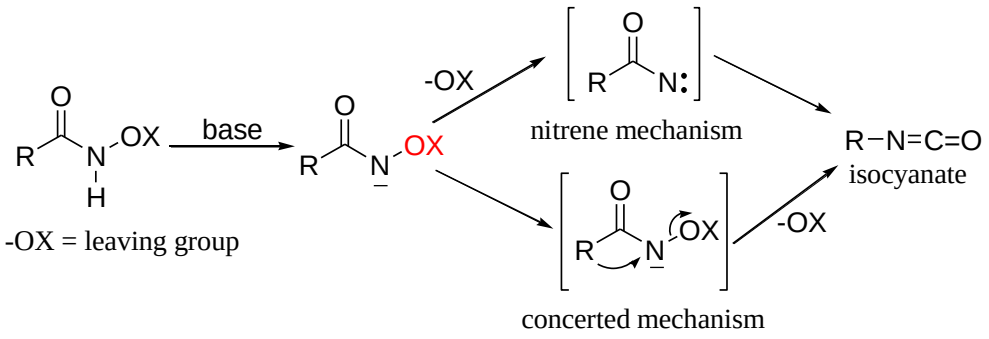
Figure 1. Examples of the non-symmetrical bi-dentate cross-linking reagents (**1a**-**1c**)

Therefore, we prepared the model compounds, ie., *N*-(phthalimidoyloxy)-3-phenylpropionate (**2a**), *N*-(3-phenylpropionyloxy)benzotriazole (**2b**), and 3-phenylpropionyloxybenzothiazole (**2c**), and their reactivities towards several nucleophiles were studied.[3-5] In the reaction of **2b** or **2c** with benzyl alcohol, benzyl 3-phenylpropionate (**3**) was obtained as a sole product. However, in the reaction of **2a** with benzyl alcohol in the presence of 4-dimethylaminopyridine (4-DMAP) for 24 h, we found unexpectedly the formation of 2-benzyloxycarbonyl 1-[*N*-(benzyloxycarbonyl)]aniline (**4**)[6] in very low yields (5% as shown in entry 1 in Table 1), besides the desired normal product **3** as shown in Scheme 1.



Scheme 1. Reaction of **2** with benzyl alcohol in the presence of base

We presumed that the reaction proceeded via Lossen-type rearrangement[7-17] as shown in Scheme 2.



Scheme 2. Mechanism of Lossen rearrangement

In order to obtain further clue, we examined the reaction of **2a** (1.0 equiv.) with benzyl alcohol (2.0-3.0 equiv.) in the presence of 1,8-diazabicyclo[5,4,0]-undec-7-ene (DBU) as a stronger base (2.0 equiv.) in CH_2Cl_2 changing the reaction time (12-24 h), and further, the reaction of the corresponding tosyl ester **6**

having a better leaving group than **2a** was also carried out under similar conditions. The results were summarized in Table 1.

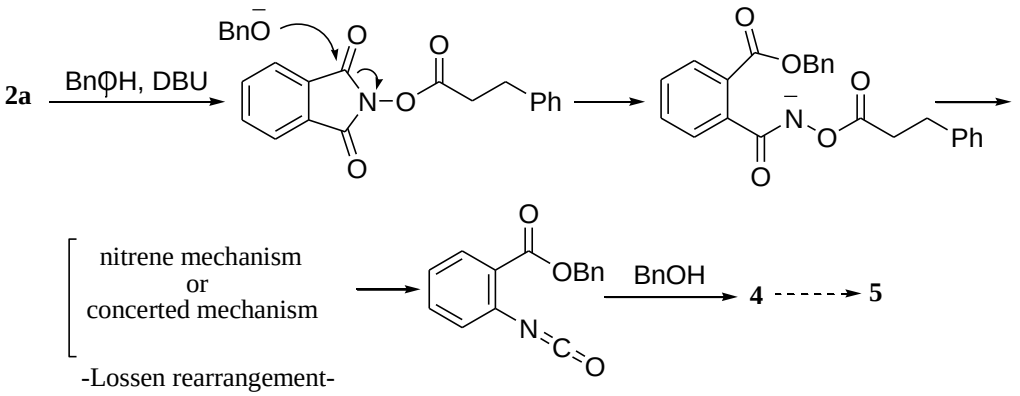
Table 1. Reaction of **2a** or **6** with benzyl alcohol in the presence of base

R = -CO(CH$_2$)$_2$Ph(**2a**), -Ts(**6**)

Entry	Compounds	Equiv.(BnOH)	Base	Time (h)	Product (% yield)*		
					3	**4**	**5**
1	**2a**	2.0	4-DMAP	24	82	5	0
2	**2a**	2.0	DBU	12	62	21	9
3	**2a**	3.0	DBU	24	48	24	20
4	**6**	2.0	DBU	0.5	0	91	trace
5	**6**	2.0	DBU	24	0	93	trace

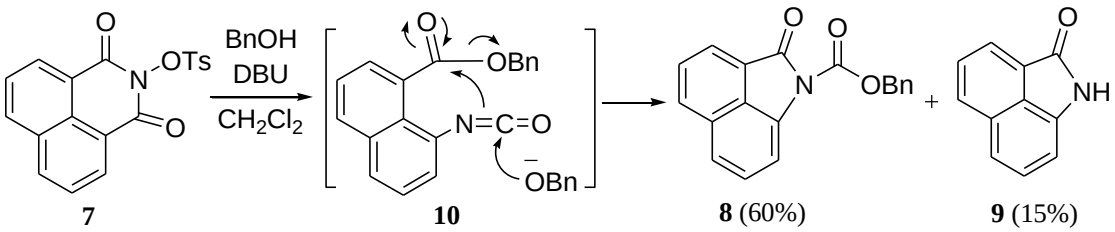
*: yields were not optimized

The yield of the rearranged product, i.e., **4** was greatly increased to 21% (12 h; entry 2) and 24% (24 h; entry 3), and in addition, the product 2-aminobenzoic acid benzyl ester (**5**) was also increased to 20% from 9%. The probable mechanism for the formation of **4** will be depicted as shown in Scheme 3. However, the mechanism for the formation of **5** was unclear yet. Furthermore, as seen in entry 4 and 5, the reaction of **6** revealed to afford the product **4** in excellent yield. The results clearly indicate that in the cases of the stronger base and better leaving group the Lossen-type rearrangement product **4** is favored and increased.



Scheme 3. Probable mechanism for the formation of **4**

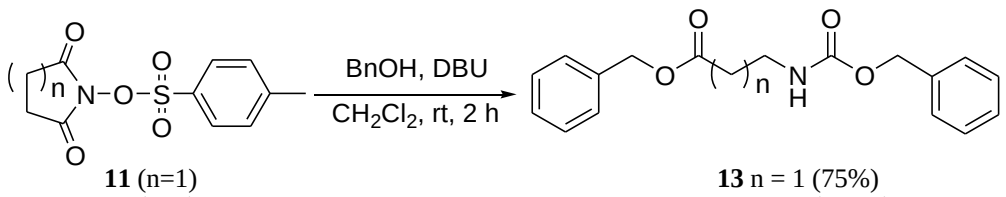
Next, we prepared 1,8-naphthalimidoyloxy tosylate (**7**) by the reaction of *N*-hydroxy-1,8-naphthalimide with tosyl chloride, and examined the reaction with benzyl alcohol (2.1 equiv.) in the presence of DBU (2.1 equiv.). In this case, the product 1-(benzyloxycarbonyl)benzo[*c,d*]indol-2-one (**8**)[18] was obtained in 60% yield after 2 h reaction together with benzo[*c,d*]indol-2-one (**9**) in 15% yield, probably via isocyanate **10** as shown in Scheme 4.



7 **10** **8** (60%) **9** (15%)

Scheme 4. Reaction of **7** with benzyl alcohol in the presence of DBU

It is interesting to apply in the reaction of the aliphatic dicarboxylic acid imide derivatives. Therefore, we prepared *N*-succinimidoyloxy tosylate (**11**) and *N*-glutalimidoyloxy tosylate (**12**), and examined their reaction with benzyl alcohol under similar conditions. The results are summarized in Scheme 5. Expectedly, the corresponding ω-amino acid derivatives, 3-benzyloxycarbonylaminopropionic acid benzyl ester (**13**)[19] and 3-benzyloxycarbonylaminobutinic acid benzyl ester (**14**)[20] were obtained in moderate to high yields 75% and 100% respectively.



11 (n=1)
12 (n=2)

13 n = 1 (75%)
14 n = 2 (100%)

Sheme 5. Reaction of aliphatic dicarboxylic acid imide derivatives with benzyl alcohol

In summary, we have examined the reaction of **2a** and **6** with benzyl alcohol in the presence of DBU under several conditions, and made clear that the product **4** and **5** is formed via the Lossen-type rearrangement. In order to obtain in additional examples, we prepared 1,8-naphthlene derivatives **7** and aliphatic dicarboxylic acide derivatives **11** and **12**, and examined their reactions with benzyl alcohols under the similar conditions, resulted in the formation of the Lossen-type rearrangement products **8** (+**9**) and **13** and **14** in moderate to high yields, respectively. These finding will provide the utilization in the new synthetic application of amino acid derivatives, which are usually hard to prepare, starting from less

expensive dicarboxylic acid derivatives. We are now undergoing to make clear the scope and limitations of the reactions using various nucleophiles.

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6. 2-Benzyloxycarbonyl-1-[*N*-(benzyloxycarbonyl)]aniline (**4**). Typical procedure: A solution of DBU (76.3 μL, 0.51 mmol) was added to a stirred solution of **2a** (50.0 mg, 0.17 mmol) and benzyl alcohol (52.8 μL, 0.51 mmol) in CH_2Cl_2 (2 mL) at rt under N_2 and stirred for 24 h. Then, the reaction mixture was neutralized by dil. AcOH and extracted with CH_2Cl_2. The organic layer was separated, successively washed with water and brine, and dried over anhydrous $MgSO_4$. Removal of solvent in vacuum gave a colorless oil crude product, which was purified by preparative TLC (3:1 CH_2Cl_2/hexane) to give **4** (15.2 mg, 24%) as a colorless solid. Mp 74.0-74.5 °C (from CH_2Cl_2/hexane); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.21 (s, 2H), 5.33 (s, 2H), 6.98-7.02 (m, 1H), 7.29-7.43 (m, 10H), 7.49-7.54 (m, 1H), 8.04 (dd, J = 2.0, 1.6 Hz, 1H), 8.46 (d, J = 8.4 Hz, 1H), 10.57 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 66.9, 66.9, 114.5, 118.8, 121.6, 128.2, 128.2, 128.2, 128.4, 128.5, 128.6, 130.9, 134.7, 135.4, 136.1, 141.8, 153.4, 167.7; IR (KBr) 1738, 1685 cm^{-1}. Anal. Calcd for $C_{22}H_{19}NO_4$: C, 73.12; H, 5.30; N, 3.88. Found: C, 73.37; H, 5.30; N, 3.97.
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18. Analytical data for **8**: Colorless solid. Mp 120-121 °C (from CH_2Cl_2-hexane); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.49 (s, 2H), 7.33-7.43 (m, 3H), 7.50-7.57 (m, 3H), 7.66 (d, *J* = 8.8 Hz, 1H), 7.71-7.75 (m, 2H), 7.80 (d, *J* = 7.6 Hz, 1H), 8.10 (t, *J* = 7.6 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 68.4, 112.4, 122.1, 124.5, 124.9, 126.1, 128.1, 128.5, 128.6, 128.7, 128.9, 129.3, 132.0, 135.1, 151.2, 165.0; IR (KBr) 1761, 1733 cm^{-1}. HRMS (EI) m/z calcd for $C_{19}H_{13}NO_3$: 303.0895. Found 303.0897.
19. Analytical data for **13**: Colorless liquid; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.58 (t, *J* = 4.0 Hz, 2H), 3.47 (q, *J* = 4.0 Hz, 2H), 5.08 (s, 2H), 5.11 (s, 2H), 7.24-7.34 (m, 10H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 34.4, 36.5, 66.4, 66.6, 128.0, 128.0, 128.1, 128.3, 128.4, 128.5, 135.5, 136.4, 156.2, 172.1. IR (KBr) 1728, 1719 cm^{-1}. HRMS (EI) calcd for (M^+) 313.1314, found 313.1311.
20. Analytical data for **14**: Colorless liquid; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.81-1.88 (m, 2H), 2.40 (t, *J* = 7.2 Hz, 2H), 3.20-3.25 (q, *J* = 6.4 Hz, 2H), 4.92 (s, 1H), 5.08 (s, 1H), 5.08 (s, 2H), 5.10 (s, 2H), 7.24-7.38 (m, 10H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 25.1, 31.4, 40.3, 66.3, 66.6, 128.1, 128.2, 128.2, 128.5, 135.8, 136.5, 156.4, 172.9; IR (KBr) 1730, 1706 cm^{-1}. HRMS (EI) calcd for (M^+) 327.1471, found 327.1452.