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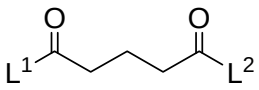
Abstract – This paper reports the reaction of *N*-(phthalimidoyloxy)-3-phenylpropionate (**2a**) and -tosylate (**6**) with benzyl alcohol as a nucleophile to afford the pr oducts via Lossen-type rearrangem ent. To study the scope of this reaction mechanism, we also studied the reaction of several *N*-sulfonyloxyimide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

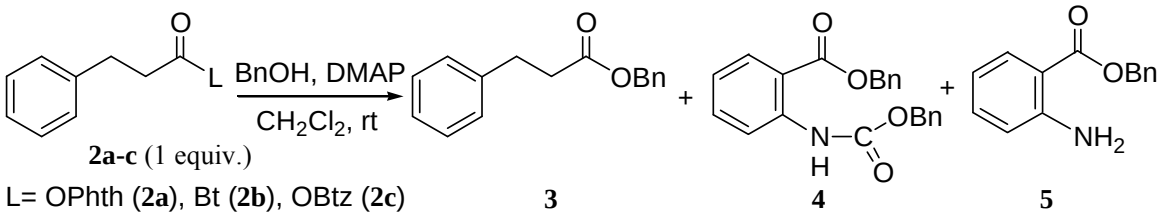
In the field of the conj ugation chem istry, hetero-func tional bi-den tate cross-linking reagents, such as MBS (*m*-Maleimidobenzoyl-*N*-hydroxysuccinimide ester) and relate d m odified linke rs, are widely used.[1-2] However, the lim itation of MBS is that the m aleimidoyl group is only useful funda mentally for the Michael addition of SH group, which is som etimes hard or laborious to in troduce into the target molecule. Non-symme trical bi-denta te cross-linking reagents beari ng two different reactive groups towards nucleophiles (Figure 1) are apparently considered to be very useful fo r modification of organic compounds even biological com pounds, but, their devel opments have been left unexplored. W hen these kinds of non-symm etrical bi-func tional cross-linking reagents are newly developed, the chem ical 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 dem onstrated their usef ulness for p reparation of pre-antigen.[3] In the course of these syntheses, we ne ed to determ ine the com bination of the leaving groups and hence, to estimate th e reactivity difference a mong these "active ester" an d other leaving grou ps, i.e., phthalimidoyloxy, benzotriazolyloxy, benzothiazolyloxy, and benzotriazolyl groups.



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

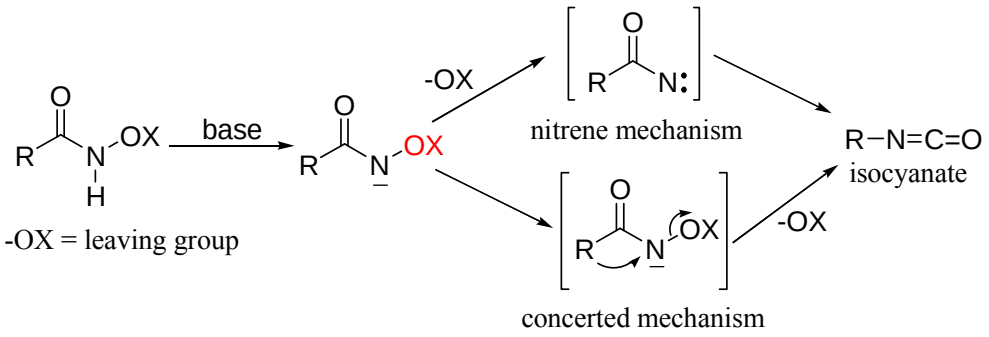
Figure 1. Examples of the non-symmetrical bi-dentate cross-linking reagents (**1a-1c**)

Therefore, we prepared the m odel com pounds, ie., *N*-(phthalimidoyloxy)-3-phenylpropionate (**2a**), *N*-(3-phenylpropionyloxy)benzotriazole (**2b**), and 3-phenylpropi onyloxybenzothiazole (**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-di methylaminopyridine (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.

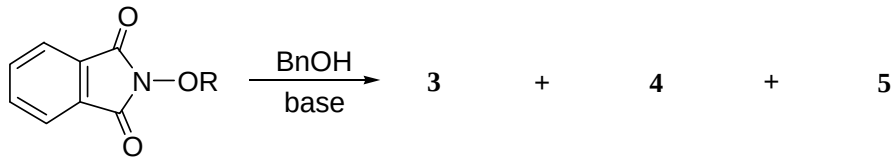


Scheme 2. Mechanism of Lossen rearrangement

In order to obtain furth er clue, we exam ined 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 stronge r base (2.0 equiv.) in CH_2Cl_2 changing the reaction tim e (12-24 h), and furthe r, 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

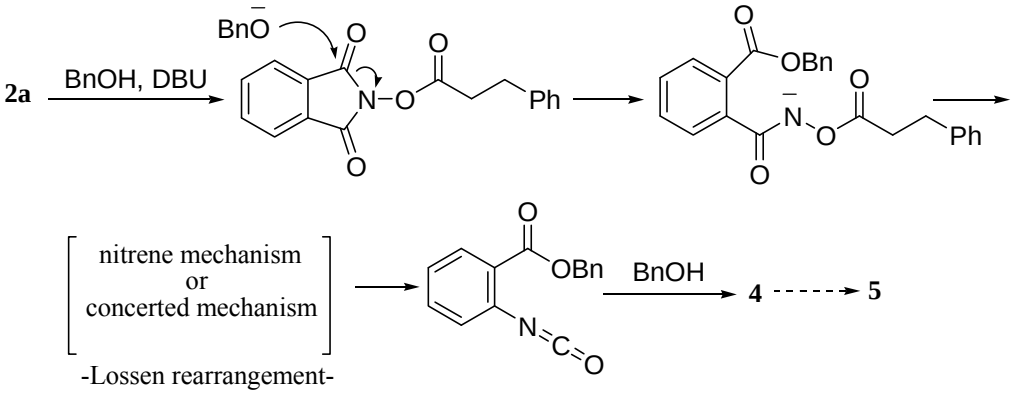


R = -CO(CH$_2$)$_2$Ph(**2a**), -Ts(**6**)

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

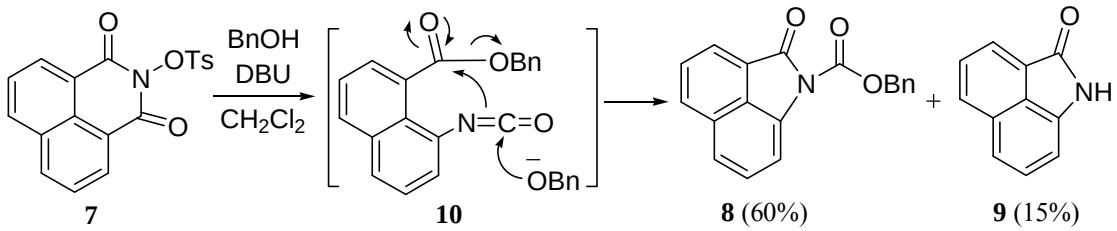
*: yields were not optimized

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.



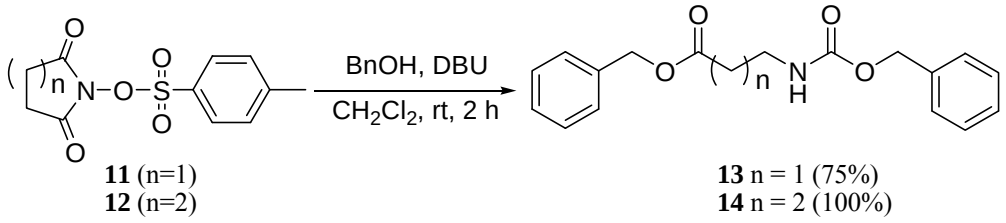
Scheme 3. Probable mechanism for the formation of **4**

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



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

It is interesting to apply in the reaction of the aliphatic di carboxylic acid imide derivatives. Therefore, we prepared *N*-succinimidoyloxy tosylate (**11**) an d *N*-glutalimidoyloxy tosylate (**12**), and exam ined thei r reaction with benzyl alcohol under sim ilar co nditions. The resu lts are summ arized in Sch eme 5. Expectedly, the corresponding ω-amino acid derivatives, 3-benz yloxycarbonylaminopropionic acid benzyl ester (**13**)[19] and 3-benzyloxycarbonylam inobutinic acid benzyl ester (**14**)[20] were obtained in moderate to high yields 75% and 100% respectively.



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

In summ ary, we have exam ined the reaction of **2a** and **6** with benzyl alcohol in the presence of DBU under several conditions, and m ade clear that the product **4** and **5** is for med via the Lossen-type rearrangement. In order to obtain in additional exam ples, we prep ared 1,8-naphthlene derivatives **7** and aliphatic dicarboxylic acide derivatives **11** and **12**, and exam ined their reacti ons with benzyl alcohols under the sim ilar conditions, resulted in the form ation of the Lossen-type rearrangement products **8** (+**9**) and **13** and **14** in m oderate to h igh yields, respe ctively. Th ese finding will p rovide the utiliza tion in the new synthetic application of a mino acid derivatives, which are usually ha rd 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, 12 8.3, 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 c m^{-1}. HRMS (EI) calcd for (M^+) 327.1471, found 327.1452.