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Case Study of a γ-Butyrolactone Alkylation with 1,3-Dimethyl-2-imidazolidinone as a Promoter

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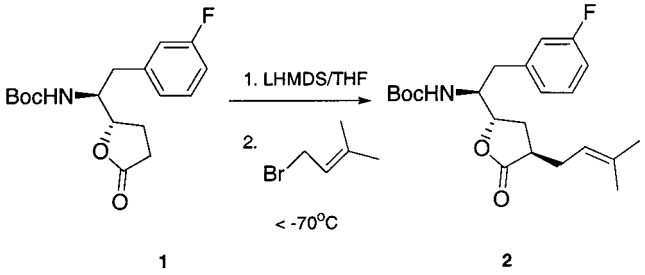
Abstract:

1,3-Dimethyl 2-imidazolidinone (DMI) is of lower toxicological risk than 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (DMPU), hexamethyl-phosphorus triamide (HMPT), and hexamethylphosphoramide (HMPA). Formation of dialkylation byproducts is a common problem in lactone alkylation. DMI, used in stoichiometric amount, increases the rate of alkylation of γ-butyrolactone 1 by >30-fold, therefore minimizing the dialkylation in multi-kilogram preparations. The isolated yield of the monoalkylated product 2 is >90%. The reaction protocol is also demonstrated to work on other lactone substrates and alkylating agents.

Functionalized lactone **2**, an intermediate of a drug candidate, is prepared from γ-butyrolactone **1**[1] (Scheme 1). α,α-Dialkylation was a major concern in this reaction. Initial attempts at the reaction without addition of additives, such as hexamethylphosphoramide (HMPA), led to either a substantial level of dialkylation or significant amount of starting material **1**.[2]

The formation of dialkylated product and the presence of unreacted lactone were most likely due to proton exchange between the monoalkylated product **4** and enolate **3** (Figure 1). There are two competing pathways for enolate **3**: reaction with the bromide to give the desired product **2** (k_1) via the formation of **4** or proton exchange with **4** to give the lactone **1** (k_2) and enolate **6**, which in turn reacts with the bromide to give rise to the dialkylation product **7**. In our initial experiments, to keep the reaction temperature below −70 °C, the alkyl bromide was added slowly to the enolate. The addition took several hours on ∼1 mol scale, as the reaction was extremely exothermic. Factors including the long reaction time[3] and localized exotherm during dimethylallyl bromide addition helped increase levels of **5** and **6** and hence the higher levels of **1** and **7,** respectively. It was evident that a more reactive enolate species and a higher concentration of the bromide would increase the reaction rate $\mathbf{r_1}$ and hence the ratio of $\mathbf{r_1/r_2}$. (Figure 1). Temperature, another important reaction variable, had to be kept below −70 °C, as elevated reaction temperature was found to compromise the diastereoselectivity.

Scheme 1



1 **2**

Use of HMPA[4] or hexamethylphosphorus triamide (HMPT) as a cosolvent in lactone alkylations is very common in both academic and industrial laboratories.[5] Both HMPA[6] and HMPT[7] are known to be potentially carcinogenic. 1,3-Dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (DMPU), another widely used HMPA substitute, is a possible chemical mutagen.[8] These reagents are typically used in large excess as a cosolvent in the reactions. 1,3-Dimethyl 2-imidazolidinone (DMI) has been used as a substitute for HMPT in dehydration and dehalogenation reactions,[9] and it has been used as solvent or cosolvent in acetylene alkylations,[10] Ullmann ether synthesis,[11] silane substitution,[12] and lactone alkylation.[13] More recently, it was shown to exert regiocontrol on a diene−diolate alkylation[14] and acylations.[15] It is

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(1) Kath, J. C.; Brown, M. F.; Poss, C. S.. PCT Int. Apl. WO 9940061, 1999; *Chem. Abstr*. **1999**, *131*, 157767.

(2) Use of 2.00−2.05 equiv of base gave 10−15% of dialkylation product, whereas 1.85 equiv of base gave ∼10% of starting material **1** and 3−5% dialkylation product.

(3) Goto, M.; Akimoto, K.-I.; Aoki, K.; Shindo, M.; Koga, K. *Tetrahedron Lett*. **1999**, *40*, 8129 wherein it was reported that the ratio of the monoalkylated product to the dialkylated product increased in a shorter reaction time.

(4) Herrmann, J. L.; Schlessinger, R. H. *J. Chem. Soc., Chem. Commun*. **1973**, 711.

(5) (a) Molander, G. A.; Harris, C. R. *J. Am. Chem. Soc*. **1996**, *118*, 4059. (b) Pellissier, H.; Michellys, P.-Y.; Santelli, M. *J. Org. Chem*. **1997**, *62*, 5588. (c) Takacs, J. M.; Weidner, J. J.; Newsome, P. W.; Takacs, B. E.; Chidambaram, R.; Shoemaker, R. *J. Org. Chem*. **1995**, *60*, 3473. (d) Kigoshi, H.; Ojika, M.; Ishigaki, T.; Suenaga, K.; Mutou, T.; Sakakura, A.; Ogawa, T.; Yamada, K. *J. Am. Chem. Soc*. **1994**, *116*, 7443. (e) Tanaka, Y.; Grapsas, I.; Dakoji, S.; Cho, Y. J.; Mobashery, S. *J. Am. Chem. Soc*. **1994**, *116*, 7475.

(6) Sarrif, A. M.; Krahn, D. F.; Donovan, S. M.; O'Neil, R. M. *Mutat. Res*. **1997**, *380*, 167

(7) Ashby, J.; Styles, J. A.; Paton, D. *Br. J. Cancer* **1978**, *38*, 418.

(8) Zijlstra, J. A.; Vogel, E. W. *Mutat. Res*. **1988**, *201*, 27.

(9) Spangler, C. W.; Kjell, D. P.; Wellander, L. L.; Kinesella, M. A. *J. Chem. Soc., Perkin. Trans. 1* **1981**, 2287.

(10) Shimizu, N.; Mori, N.; Kuwahara, Y.; Tsuji, T. *Biosci. Biotechnol. Biochem*. **1999**, *63*, 1478.

(11) Oi, R.; Shimakawa, C.; Takenaka, S. *Chem. Lett.* **1988**, *5*, 899.

(12) Ito, H.; Ishizuka, T.; Okumura, T.; Yamanaka, H.; Tateiwa, J.-I.; Sonoda, M.; Hosomi, A. *J. Organomet. Chem*. **1999**, *574*, 102.

(13) Preparation of 2-benzyl-3-hydroxy-γ-butyrolactone on millimole scale was reported using DMI as a cosolvent. In this reaction, benzyl bromide (1.0 equiv) was used as limiting reagent (DMI, 14 equiv, and the γ-butyrolactone, 5.2 equiv): Higamie, K.; Furukawa, Y.; Katsumura, S.; Takehira, Y. Jpn. Kokai Tokkyo Koho, JP 11189589, 1999.

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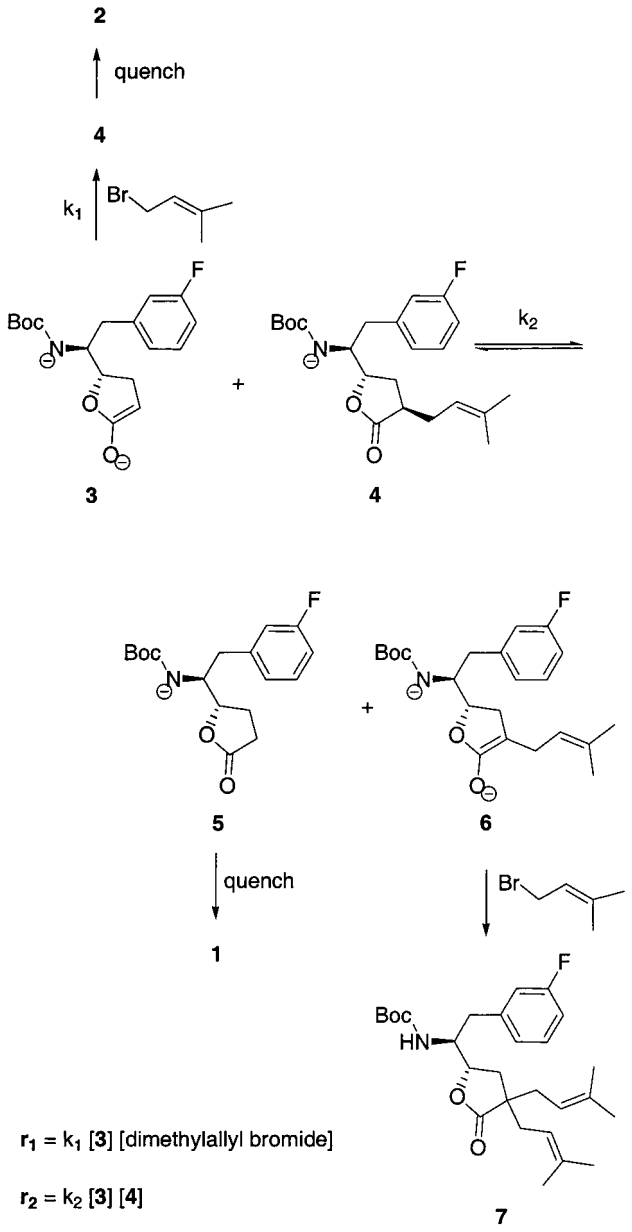
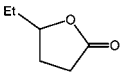
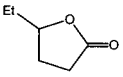
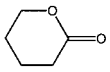


Figure 1.

structurally analogous to DMPU, but more water soluble and hence readily removed by aqueous wash in the extractive workup. More importantly, DMI appears to be of lower toxicological risk than HMPA, HMPT, and DMPU,[16] which makes it more attractive in the production environment.

We found the rate of the alkylation reaction was increased by >30-fold[17] in the presence of DMI (1.2 equiv). To increase the bromide concentration and lower the potential localized temperature spike, precooling of the bromide was needed so that fast transfer of the bromide (highly exothermic!) could be achieved while maintaining the reaction temperature at <−70 °C. In a 9.3 mol (3 kg of **1**) scale

Table 1. **Reactions of lactone enolates with alkyl halides[20]**

Entry	Substrate	Alkyl halide	Reaction Temperature	Yields
1		MeI	−70°C	93% (*trans*/*cis*: 72/28)
			−30°C	94% yield (*trans*/*cis*: 61/39)
2		$PhCH_2Br$	−70°C	90% (*trans*/*cis*: 91/9)
			−30°C	88% (*trans*/*cis*: 86/14)
3		Allylbromide	−70°C	95%
			−30°C	93%
4		Allylbromide	-30°C	85%

reaction, the addition of dimethylallyl bromide solution in THF (precooled to −78 °C) to the enolate solution at −85 °C (cooling to this temperature was needed to pre-empt the huge exotherm during the bromide addition) was completed within 2 min while maintaining the reaction temperature below −72 °C. Immediately after the electrophile addition, the reaction was determined to be completed by HPLC analysis of a reaction aliquot. Typically, the desired product **2** was formed in 90−92% yield with ∼1% of diastereomer, ∼2% of dialkylated product, and ∼4% of the unreacted lactone also present.[18,19] The S_N2' product was not detected in the reaction. The presence of DMI did not seem to have any impact on the diastereoselectivity which is probably controlled by the bulky group at the γ-position of the lactone. Reverse quench of the reaction by addition of the enolate

(14) Brun, E. M.; Gil, S.; Parra, M. *Syn. Lett.* **2001**, *1*, 156; *Tetrahedron Asymmetry*, **2001**, *12*, 915.
(15) Kondo, J.; Inoue, A.; Shinokubo, H.; Oshima, K. *Angew. Chem., Int. Ed.* **2001**, *40*, 2085.
(16) Lo, C. C.; Chao, P. M. *J. Chem. Ecol.* **1990**, *16*, 3245.
(17) In the presence of DMI, the reaction time needed was less than 2 min, 2 h or longer was needed in the absence of DMI.
(18) By HPLC area, monitored at 210 nm wavelength.
(19) In a typical experiment: Under nitrogen atmosphere, 1.0 M LHMDS solution in THF (6.49 L, 2.10 equiv) was charged to a three-neck flask, and cooled to −78 °C. Lactone **1** (1000 g, 3.09 mol) in 5.0 L of anhydrous THF was pre-cooled to −25 °C and then added to the LHMDS solution slowly while keeping the reaction temperature below −65 °C. After the addition, the reaction was stirred for 30 min at −65 to −78 °C. Dimethyl imidazolidinone (423 g, 3.71 mol, 1.2 equiv) was then added neat, and reaction mixture was then cooled to −85 °C. Dimethyl allyl bromide (497.8 g, 3.34 mol, 1.1 equiv) in 5.0 L of anhydrous THF was pre-cooled to −78 °C and added quickly (in 2 min) to the enolate solution while maintaining the reaction temperature below −72 °C. After the addition, the reaction was stirred for 10 min. The reaction was quenched with acetic acid (743 mL, 4.2 equiv)/THF (5.0 L), and ethyl acetate (20 L) is then added. After water wash (3 × 10 L), the ethyl acetate solution was dried over Na_2SO_4 and concentrated to an oil (1.14 kg, 94.3% yield). The crude product was sufficiently pure to be used in the downstream steps. An analytically pure sample can be obtained by silica gel chromatography: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.34 (s, 9H), 1.56 (s, 3H), 1.64 (s, 3H), 1.87−1.94 (m, 1H), 2.20−2.26 (m, 1H), 2.36−2.42 (m, 1H), 2.63−2.71 (m, 1H), 2.82−2.88 (m, 2H), 3.96 (dt, 2H, J = 8.4, 8.4 Hz), 4.41 (t, 1H, J = 6.4 Hz), 4.72 (d, 1H, J = 9.6 Hz), 4.99−5.00 (m, 1H), 6.87−7.00 (m, 3H), 7.20−7.26 (m, 1H); ^{13}C NMR ($CDCl_3$, 400 MHz) δ 17.78, 25.68, 28.08, 29.27, 29.33, 38.73, 38.92, 54.32, 78.41, 79.91, 113.43, 113.64, 115.98, 116.18, 119.42, 124.86, 124.88, 129.92, 130.00, 135.21, 139.70, 139.78, 155.79, 161.53, 163.98, 179.38.
(20) Enolates were generated at −78 °C with 1.0 M LHMDS (1.05 equiv) solution in THF as base. DMI (1.2 equiv) was added prior to the addition of the alkyl halide (1.10 equiv). The reaction temperature shown was maintained during the alkyl halide addition. Yields and diastereomer ratios were based on HPLC analysis at 210 nm.

solution to the dimethylallyl bromide solution in THF was also investigated. At temperatures below −70 °C, the reaction gave results comparable to that of the normal quench. N-alkylation on the Boc-NH group was observed at <1% under the reaction conditions on a 30 mmol scale, while in the normal quench, N-alkylation was not detected. Nonetheless, the reverse quench would require two large cryogenic reaction vessels, and the resource constraint makes it less practical oftentimes in production settings, whereas the normal quench only needed one cryogenic reaction tank and a flask to hold the bromide solution that was cooled in a dry ice−acetone bath (on a 10 mol scale, a 22 L flask would suffice).

The approach was found to be general in reactions of other lactone substrates and alkylating agents (Table 1). The diastereoselectivity appeared to be dependent on reaction temperature and the size of the alkylating group (entries 1 and 2). Comparable results were obtained for γ-butyrolactone alkylation with allylbromide at elevated reaction temperature (entry 3), and the reaction also worked well for δ-valerolactone (entry 4).

In summary, we have shown that DMI, an ecologically friendly reagent that is yet to gain popularity among the community of synthetic chemists, effectively promotes the rate of reaction in γ-butyrolactone alkylation when used in stoichiometric amount. The protocol described has been successfully used in multikilogram preparation of **2**.

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