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A convenient synthesis of 3-aryl-δ-lactones

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Abstract—Various (±)-3-aryl-δ-lactones have been prepared from the corresponding arylacetic acids. The lithium dianion of the acid is alkylated with 1-bromo-3-chloropropane and the unpurified product is cyclized with DBU in typically ca. 80% yield over both steps. We have shown that lactones of this type can be converted to their corresponding 5,6-dihydropyan-2-ones and pyran-2-ones, which potentially provide useful sites for further functionalization of the lactone ring. © 2002 Published by Elsevier Science Ltd.

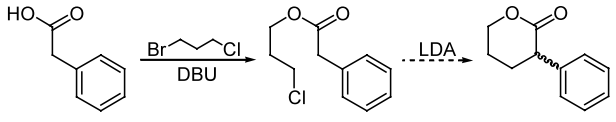
We were presented with the need to access δ-lactones with an aryl substituent in the 3-position. While there is precedent for the alkylation of δ-valerolactone by the reaction of its enolate with alkyl halides,[1] as well as its use as a Michael donor,[2] installation of an aryl group is not feasible by this method. A general synthesis for 3-aryl-γ-lactones is known,[3] as well as a high yielding reaction to prepare 5-aryl-δ-lactones.[4] In addition, Buchwald has recently reported a method for α-arylations of esters, including γ-lactones,[5,6] however general routes to 3-aryl-δ-lactones are not reported in the literature. One synthesis of **3a** was reported,[7] however, due to the use of oxetane as well as a very low overall yield, this method was undesirable for our purposes.

Considering the wide variety of commercially available arylacetic acids, as well as their generally low cost, we envisioned a synthesis in which these compounds could be utilized. Once a suitably activated 1,3-disubstituted propane was selected, it seemed reasonable that an arylacetic acid could be *O*- and *C*-alkylated to yield the desired lactone.

Initial attempts at assembling these lactones focused on *O*-alkylation of the acid followed by intramolecular ring-closure via the ester enolate (Scheme 1). Chloride **2** was prepared by the reaction of phenylacetic acid with 1-bromo-3-chloropropane. The enolate was generated with LDA, but upon warming to effect the chloride displacement the starting material decomposed without affording sufficient lactone **3a**.[8]

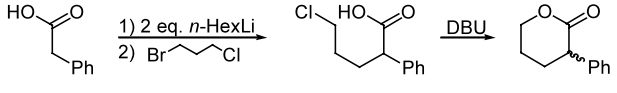
Noting the instability of the ester enolate, we decided to shift focus. It is known that the dianions of arylacetic acids can be generated by simple procedures, and are reactive toward *C*-alkylations.[9] Confident that we could prepare compounds such as **4** with little difficulty, all that remained would be the demonstration of a mild intramolecular *O*-alkylation to yield the desired 3-aryl-δ-lactones.

The dianion of phenylacetic acid was generated in THF using *n*-butyllithium and adding DMPU as a polar aprotic co-solvent. Upon quenching with 1-bromo-3-chloropropane, desired acid **4a** was cleanly formed (Scheme 2). It was initially hoped that, considering this intermediate existed in situ as the lithium carboxylate, simply heating the reaction after electrophile addition would induce cyclization. Unfortunately, no lactone was observed after 3 days at reflux, though **4a** proved to be surprisingly stable.



1a **2** **3a**

Scheme 1.



1 **4a** **3a**

Scheme 2.

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After work-up, **4a** was treated with NaH in THF, hoping that the sodium carboxylate would be more reactive towards an S_N2 displacement of the chloride. Again, no cyclization was observed after prolonged reflux. Repeating the reaction in DMF led to the first success, cleanly providing **3a** in under 2 h. However, the lactone was more labile than originally anticipated; upon aqueous work-up, extensive hydrolysis was observed. Nonetheless, the proof of concept was demonstrated, with merely some optimization remaining en route to a satisfactory procedure.

Desiring to replace the NaH/DMF cyclization reaction with milder conditions we noted precedent for DBU having the ability to enhance the nucleophilicity of carboxylates.[10] Indeed, when a THF solution of **4a** was treated with DBU and heated to reflux, DBU·HCl began to precipitate and **3a** was cleanly formed. The formation of this salt allowed us to use a filtration to eliminate an aqueous work-up, circumventing the hydrolytic instability of the product. Fortunately, 2D TLC showed no stability issues on silica gel, making flash chromatography of the final lactone a convenient method of purification.

During the course of process development, butyllithium was replaced with *n*-hexyllithium due to the fact that the latter is nonpyrophoric at higher concentrations.[11] In addition, evolution of butane is eliminated after deprotonation. Upon repeating the dianion alkylation with this base, a side product formed that had previously never been detected. This was identified as the hexyl adduct **5** (Fig. 1), presumably formed via a metal halogen exchange between excess *n*-hexyllithium and bromo chloropropane followed by alkylation of the resultant 1-bromohexane. Formation of **5** is avoided by ensuring no overcharge of base is made.

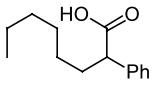
Envisioning the lactone synthesis as a through process, we removed DMPU from the first alkylation in order to simplify purification. There was no observed change in the reaction profile. Simple aqueous work-up afforded **4a** in nearly quantitative yield and of sufficient purity to carry forward directly.

With a process in hand, we explored the generality of the reaction sequence. A variety of arylacetic acids was carried through an identical procedure to determine what effect, if any, the nature of the aromatic group had on overall yield. For this purpose, electron-rich, electron-poor, sterically hindered and hetero aryl groups were examined (Table 1).

Surprisingly, with the exception of the entry 6, electronics and sterics seemed to play little role in the effectiveness of the two alkylations. Minor rate differences were observed in both reactions, but considering the products were stable under the reaction conditions, all examples were subjected to identical reaction times for the sake of consistency. However, it should be noted that physical characteristics of the lactone products did play a role in their stability. The entries (1, 3, 5) that existed as oils showed significant decomposition upon standing at room temperature after 1 week, while the crystalline solids (2, 4, 6) were stable for more than 1 month. This instability of δ-lactones has been reported in the literature.[12]

Looking to elaborate further on the core saturated lactone structure, we set out to add functionality to the 4-position by converting the tetrahydropyran-2-one to the corresponding 5,6-dihydropyran-2-one. It had been previously demonsrated that halogenation α to the lactone carbonyl followed by base-promoted elimination could be used to introduce unsaturation into the ring.[7]

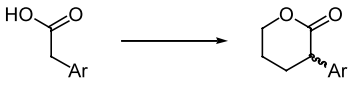
Indeed, when phenyl lactone **3a** was treated with NBS and catalytic AIBN, clean conversion to the 3-bromo-3-phenyl lactone **6** was observed (Scheme 3). Filtration of the succinimide byproduct followed by concentration afforded crystalline bromide of sufficient purity to carry forward directly. Elimination to 5,6-dihydropyran **7** was achieved with the use of *N*,*N*-diisopropylethylamine. After filtering off the amine·HBr, the product was purified by chromatography (1:1 EtOAc/hexanes)

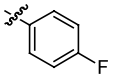
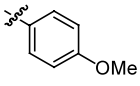
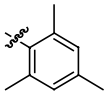
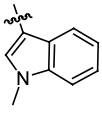


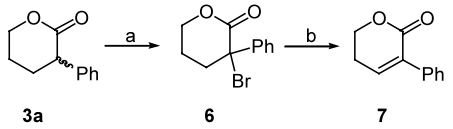
5

Figure 1.

Table 1. Isolated yields of 3-aryl-δ-lactones



entry	Ar	Product	Yield (%)
1		**3a**	84
2		**3b**	86
3		**3c**	81
4		**3d**	82
5		**3e**	79
6		**3f**	66



Scheme 3. *Reagents and conditions*: (a) NBS, AIBN, CCl_4, 80°C, 6, h; (b) Hünig's base, THF, 60°C, 24 h, 76% yield over both steps.

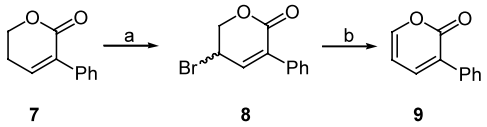
affording crystalline **7** in 76% yield (from saturated lactone).

Interestingly, when this reaction was performed without a radical initiator, complete bromination was observed (as expected) on very small scale, but the reaction would stall at various points on larger scale. Once the progress of the 3-bromination was halted, thermal elimination would occur (resulting in a visible release of HBr) and bromination at the newly formed allylic position was detected. Again, thermal elimination occurred leading to the formation of pyran-2-one **9**. Hence, without AIBN the bromination reaction led to a complex mixture of **6**–**9**.

This discovery led us to examine a controlled conversion of dihydropyran-2-one **7** to pyran-2-one **9**[13] (Scheme 4). The same conditions used in the initial bromination/elimination sequence were repeated, and except for minor rate differences the results were nearly identical. Hence, the potential for utilizing 3-aryl-δ-lactones as precursors to 3-aryl-5,6-dihydropyran-2-ones or 3-arylpyran-2-ones has been demonstrated.

In conclusion, we have successfully demonstrated a novel route for the synthesis of 3-aryl-δ-lactones. This chemistry utilizes inexpensive and readily available reagents, and has been shown to accommodate a wide variety of aryl substituents. In addition, the saturated lactones have the potential to serve as synthons for both 5,6-dihydropyran-2-ones and pyran-2-ones.

General procedure for the conversion of arylacetic acids to their corresponding 3-aryl-δ-lactones: A solution of arylacetic acid (25.0 mmol) in dry THF (100 mL) was cooled to −60°C while stirring under an inert atmosphere. To this solution was added *n*-hexyllithium (2.0 equiv., 20 mL of 2.5 M in hexane) dropwise such that the internal temperature was maintained below −40°C. Upon complete addition, the resultant slurry was slowly warmed to 0°C and stirred at that temperature for 2 h. 1-Bromo-3-chloropropane (2.70 mL, 27.3 mmol) was then added and the reaction allowed to warm to room temperature and stirred for 18 h.



Scheme 4. *Reagents and conditions*: (a) NBS, AIBN, CCl_4, 80°C, 4 h; (b) Hünig's base, THF, 60°C, 2 h, 68% yield over both steps.

The reaction was quenched with 1N NaOH (50 mL) and transferred to a separatory funnel. The aqueous layer was collected and the organic extracted again with 1N NaOH (50 mL). The combined aqueous cuts were re-acidified with 2N HCl (70 mL) and extracted with EtOAc (75 mL). The organic layer was washed with water (50 mL) and then concentrated in vacuo to an oil.

The oil was redissolved in THF (50 mL), treated with DBU (3.74 mL, 25.0 mmol) and heated to 60°C for 18 h. The resultant slurry was cooled to room temperature, diluted with EtOAc (50 mL) and filtered through a sintered glass funnel. The wet cake was rinsed with EtOAc (2×25 mL) and the combined filtrates concentrated in vacuo (at or below 25°C). The crude lactone was purified by flash chromatography (SiO_2, hexanes: EtOAc = 1:3).

5-Chloro-2-(4-fluorophenyl)pentanoic acid (4b): IR (neat): 1707 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 10.87 (br s, 1H), 7.32–7.27 (m, 2H), 7.07–7.01 (m, 2H), 3.58 (t, $J=7.6$ Hz, 1H), 3.53 (t, $J=6.4$ Hz, 2H), 2.21 (m, 1H), 1.96 (m, 1H), 1.84–1.65 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 179.7, 162.2 (d, $J=246.7$ Hz), 133.4 (d, $J=3.2$ Hz), 129.5 (d, $J=8.0$ Hz), 115.5 (d, $J=21.6$ Hz), 50.0, 44.2, 30.2, 30.1.

3-(4-Fluorophenyl)tetrahydropyran-2-one (3b): mp 62.3–62.5°C; IR (neat): 1733 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.24–7.19 (m, 2H), 7.07–7.01 (m, 2H), 4.51–4.41 (m, 2H), 3.76 (dd, $J=10.4$, 6.8 Hz, 1H), 2.29 (m, 1H), 2.10–1.97 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.3, 161.9 (d, $J=245.9$ Hz), 134.5 (d, $J=3.2$ Hz), 129.7 (d, $J=8.0$ Hz), 115.5 (d, $J=21.6$ Hz), 69.0, 46.2, 28.1, 21.9. Anal. calcd for $C_{11}H_{11}FO_2$: C, 68.03; H, 5.71; F, 9.78. Found: C, 67.99; H, 5.68; F, 9.80.

References

1. (a) Ibrahim-Ouali, M.; Parrain, J.; Santelli, M. *Org. Prep. Proced. Int.* **1999**, *31*, 467–505; (b) Bailey, W. F.; Khanolkar, A. D. *Tetrahedron Lett.* **1990**, *31*, 5993–5996; (c) Kowalczuk, M.; Kurcok, P.; Główkowski, W.; Jedlinski, Z. *J. Org. Chem.* **1992**, *57*, 389–391.
2. Shinohara, N.; Haga, J.; Yamazaki, T.; Kitazume, T.; Nakamura, S. *J. Org. Chem.* **1995**, *60*, 4363–4374.
3. Gu, J.-X.; Holland, H. L. *Synth. Commun.* **1998**, *28*, 3305–3315.
4. Ishii, Y.; Osakada, K.; Ikariya, T.; Saburi, M.; Yoshikawa, S. *J. Org. Chem.* **1986**, *51*, 2034–2039.
5. Spielvogel, D. J.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 3500–3501.
6. Lloyd-Jones, G. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 953–956.
7. Darko, L. L.; Cannon, J. G. *J. Org. Chem.* **1967**, *32*, 2352–2354.
8. Christoffers, J.; Oertling, H.; Fischer, P.; Frey, W. *Synlett* **2002**, *6*, 957–961.
9. (a) Petragnani, N.; Yonashiro, M. *Synthesis* **1982**, 521–578; (b) Ivanov, D.; Vassilev, G.; Panayotov, I. *Synthesis* **1975**, 83–98; (c) Brun, E. M.; Casades, I.; Gil, S.;

Mestres, R.; Parra, M. *Tetrahedron Lett*. **1998**, *39*, 5443–5446; (d) Kusumoto, T.; Ichikawa, S.; Asaka, K.; Sato, K.; Hiyama, T. *Tetrahedron Lett*. **1995**, *36*, 1071–1074; (e) Hauser, C. R.; Brasen, L.; Brasen, W. R. *J. Am. Chem. Soc*. **1958**, *80*, 4345–4348.

10. Ono, N.; Yamada, T.; Saito, T.; Tanaka, K.; Kaji, A. *Bull. Chem. Soc. Jpn*. **1978**, *51*, 2401–2404.
11. *Encyclopedia of Reagents for Organic Synthesis*; Paquette, L. A., Ed.; John Wiley & Sons: West Sussex, UK, 1995; Vol. 4, p. 2679.
12. Fazio, F.; Schneider, M. P. *Tetrahedron Lett*. **2002**, *43*, 811–814.
13. Posner, G. H.; Afarinkia, K.; Dai, H. *Org. Synth*. **1996**, *73*, 231–239.