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Reactions of organolithiums with dialkyl oxalates. A flow microreactor approach to synthesis of functionalized α-keto esters†

Cite this: *Chem. Commun.*, 2013, **49**, 3242

Received 17th January 2013,
Accepted 28th February 2013

DOI: 10.1039/c3cc40392k

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Reactions of functionalized aryllithiums with dialkyl oxalates were achieved using a flow microreactor to obtain α-keto esters with high selectivity by virtue of fast 1 : 1 micromixing.

α-Keto carboxylic acids and esters play an important role in organic synthesis as useful building blocks for synthesizing a variety of complex molecules such as biologically active natural products.[1,2] Various methods for synthesizing α-keto carboxylic acids and esters have been reported so far,[3] and the most commonly used method is the reaction of organometallics with dialkyl oxalates or oxalyl chloride. However, the method often suffers from low yields of the desired products because the initial products react with another molecule of organometallics to produce byproducts such as alcohols and diketones even if one equivalent of the organometallics is used (the problem of competitive consecutive reactions).[4] Therefore, alkyl oxalyl chloride, alkyl cyanoformate, and alkyl α-oxo-1*H*-imidazole-1-acetate are often used to suppress such side reactions.[5] However, these reagents are more expensive and, therefore, are not suitable for large-scale synthesis. These methods using organometallics suffer from another problem, *i.e.* functional group compatibility in preparation and reactions of organometallics.[6] Therefore, it is highly desired to develop a method for synthesizing α-keto esters bearing functional groups on a large scale. However, to the best of our knowledge, no study to solve these problems has yet been reported in the literature. We envisaged that the use of a flow microreactor system[7,8] would be effective in solving these problems.

We have already reported that the problem of disguised chemical selectivity[9] in competitive consecutive reactions is solved by extremely fast 1 : 1 micromixing based on short diffusion paths and that product selectivity close to the kinetically based one is obtained.[10] We have also reported that highly reactive and unstable reactive intermediates could be generated and used before they decompose by virtue of short residence times in flow microreactors[11] (flash chemistry[12]). For example, aryllithiums bearing electrophilic functional groups such as cyano, nitro, alkoxycarbonyl and ketone carbonyl groups were successfully generated and used for reactions with electrophiles using flow microreactor systems.[13]

With such information in hand, we set out to investigate reactions of functionalized organometallics with dialkyl oxalates using flow microreactor systems and found that selective formation of α-keto esters was achieved.

Before studying flow microreactor reactions, we examined the reaction in a flask (a 50 mL round bottom glass flask with a magnetic stirrer). Thus, phenyllithium, which was generated by the halogen–lithium exchange reaction of bromobenzene with *n*-BuLi, was allowed to react with one equivalent of diethyl oxalate (Fig. 1). The yields of ethyl 2-oxo-2-phenylacetate (**2**, mono-addition product), 1,2-diphenylethane-1,2-dione (**3**, di-addition product), ethyl 2-hydroxy-2,2-diphenylacetate (**4**, di-addition product), and 2-hydroxy-1,2,2-triphenylethanone (**5**, tri-addition product) were determined by GC. The addition of diethyl oxalate to a stirred solution of phenyllithium at −78 °C gave **2** and **3** in low yields (Table 1). In contrast, the simultaneous addition and the reverse addition gave better results, but the yield of **2** and selectivity were not enough. The selectivity and yield decreased with an increase in the temperature, and a significant amount of **3**, and **5** was produced. It is interesting to note that di-addition product **4** was not obtained at all indicating that the ester carbonyl group of **2** is more reactive than the ketone carbonyl group presumably because of the steric effect. In addition, it should be kept in mind that the batch method cannot be applied to functionalized organolithium species because they decompose very quickly.

In the next step, we examined the reaction using a flow microreactor system composed of two T-shaped micromixers (**M1** and **M2**) and two microtube reactors (**R1** and **R2**) as shown in Fig. 2.

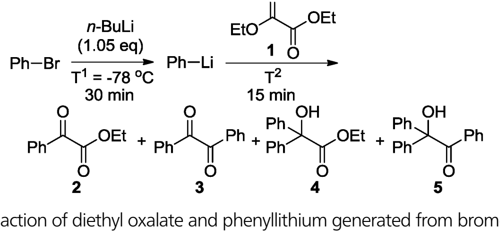

Fig. 1 Reaction of diethyl oxalate and phenyllithium generated from bromobenzene.

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† Electronic supplementary information (ESI) available: Experimental section. See DOI: 10.1039/c3cc40392k

Table 1 Reaction of diethyl oxalate and phenyllithium using a conventional macro-batch system

T^2 (°C)	Method of addition	Conversion of **1** (%)	Yield (%) 2	3	4	5
−78	Addition of **1** to PhLi	59	25	21	0	1
−78	Simultaneous addition of **1** and PhLi	66	56	17	0	6
−78	Addition of PhLi to **1**	70	63	9	0	7
−60	Addition of PhLi to **1**	71	66	13	0	3
−40	Addition of PhLi to **1**	81	62	15	0	5
−20	Addition of PhLi to **1**	83	55	18	0	9
0	Addition of PhLi to **1**	82	53	15	0	7
20	Addition of PhLi to **1**	72	43	18	0	10

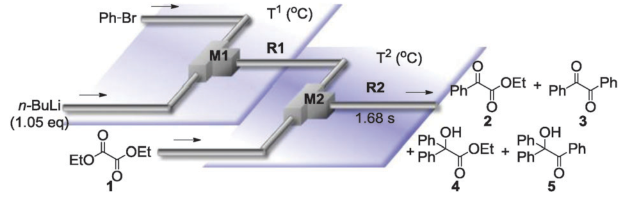


Fig. 2 A flow microreactor system for reaction of diethyl oxalate and phenyllithium generated from bromobenzene.

Table 3 Reaction of diethyl oxalate and phenyllithium generated from bromobenzene using a flow microreactor system. The effect of mixing

Inner diameter of **M2** (µm)	Total flow rate at **M2** (mL $\min^{-1}$)	Conversion of **1** (%)	Yield (%) 2	3	4	5
250	17.5	98	95	5	0	0
250	14.0	98	93	5	0	0
250	10.5	96	90	5	0	0
250	7.0	92	80	8	0	2
250	3.5	60	29	10	0	5
500	14.0	88	77	17	0	2
800	14.0	72	47	22	0	8

The results were obtained by varying the temperature ($T^1 = T^2 = -78$–20 °C), the inner diameter of **M2**, and the flow rate. The effect of the temperature is interesting. As shown in Table 2, the yield of **2** and selectivity were much higher than those for flask reactions, and the highest yield and selectivity were obtained at −60 °C. The yield and selectivity gradually decrease with an increase in *T*. It is noteworthy that satisfactory yield and selectivity were obtained at −20 °C and thereafter we carried out the reactions at this temperature from a practical point of view because it was difficult to achieve lower temperatures using brine, which is a common coolant in industry.

To examine the effect of mixing, we carried out the reactions by varying the total flow rate at **M2** because it is well known that mixing efficiency of micromixers strongly depends on the flow rate.[14] As shown in Table 3, the yield of **2** and the selectivity decreased with a decrease in the flow rate, indicating the importance of mixing efficiency. The fact that the yield of **2** and selectivity decreased with an increase in the diameter of micromixer **M2** also indicates the importance of mixing. Therefore, it is reasonable to conclude that extremely fast 1 : 1 mixing is responsible for selective formation of α-ketoester **2**.

With the optimized conditions for selective synthesis of α-ketoester **2** ($T^1 = T^2 = -20$ °C, inner diameter of **M2** = 250 µm, total flow rate at **M2** = 14.0 mL $\min^{-1}$) in hand, we next examined reactions of various aryllithiums generated from functionalized halobenzenes. In the case of bromobenzenes *n*-BuLi was used as a lithiating agent. In the case of iodobenzenes PhLi was used as a lithiating agent. The halogen–lithium exchange was conducted with the residence times (t^{R1}) optimized for each halobenzenes.[13] As shown in Table 4, dimethyl oxalate and di-*tert*-butyl oxalate in addition to diethyl oxalate could be used and the corresponding α-keto esters were obtained in good yields and selectivity. Notably, various aryllithiums bearing electrophilic functional groups such as cyano, nitro, and alkoxycarbonyl groups at *ortho*-, *meta*- and *para*-positions reacted with diethyl oxalate to give the corresponding α-ketoesters in high yields and selectivity. In the case of aryllithiums bearing an alkoxycarbonyl group, the reactions with diethyl oxalate were carried out at $T^1 = T^2 = -60$ °C in order to avoid their decomposition. Such transformations are very difficult or impossible

Table 2 Reaction of diethyl oxalate with phenyllithium generated from bromobenzene using a flow microreactor system. The effect of the temperature

T^1, T^2 (°C)	t^{R1} (s)	Conversion of **1** (%)	Yield (%) 2	3	4	5
−78	9.42	96	87	3	0	0
−60	9.42	100	96	1	0	0
−40	2.35	100	96	2	0	0
−20	2.35	98	93	5	0	0
0	2.35	95	88	7	0	0
20	2.35	93	82	9	0	1

The reactions were carried out under the following conditions: the flow rates: PhBr solution 8 mL $\min^{-1}$, BuLi solution 2 mL $\min^{-1}$, diethyl oxalate solution 4 mL $\min^{-1}$; the inner diameter of **M2** 250 mm.

Table 4 Selective reaction of dialkyl oxalate with organometallics using flow microreactors

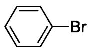
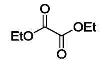
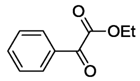
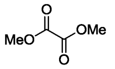
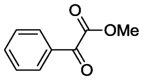
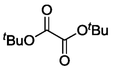
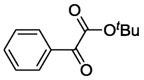
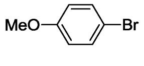
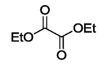
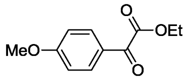
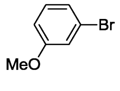
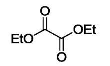
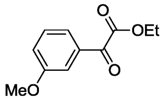
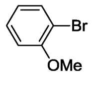
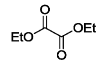
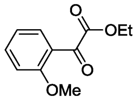
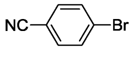
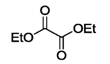
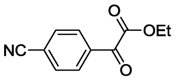
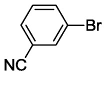
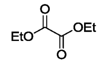
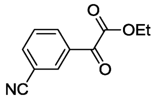
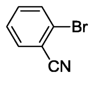
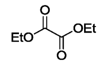
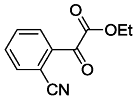
Halobenzene	T^1, T^2 (°C)	t^{R1} (s)	Dialkyl oxalate	Product	Yield (%)
	−20	4.71			93
	−20	4.71			90
	−20	4.71			75
	−20	2.35			91
	−20	2.35			95
	−20	2.35			94
	−20	0.28			75
	−20	0.28			87
	−20	0.28			63

Table 4 (*continued*)

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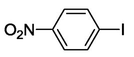
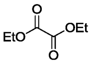
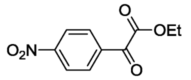
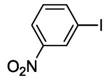
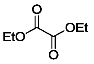
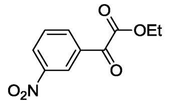
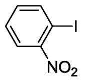
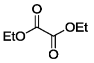
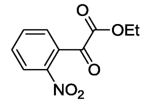
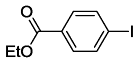
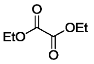
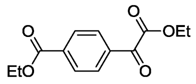
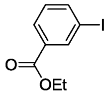
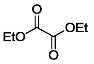
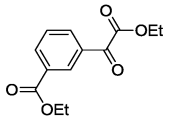
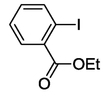
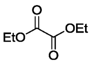
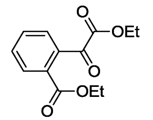
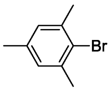
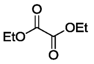
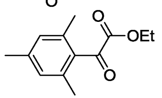
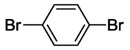
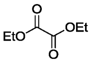
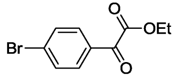
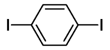
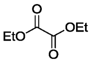
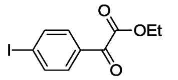
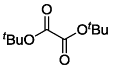
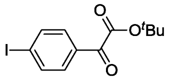
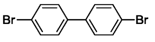
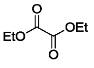
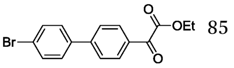
	−20	0.041			89
	−20	0.041			92
	−20	0.041			90
	−60	0.041			88
	−60	0.041			83
	−60	0.041			89
	−20	4.71			73
	−20	2.35			91
	−20	0.28			93
	−40	0.28			75
	−20	2.35			85

to achieve using conventional batch reactors. Moreover, the monoselective Br–Li exchange reaction of *p*-dibromobenzene followed by the reaction with diethyl oxalate gave the corresponding bromo-substituted α-keto esters in a good yield. Highly sterically hindered mesityllithium could also be used for the present transformation.

In conclusion, we have developed an efficient method for introduction of α-ketoester groups into the aromatic ring based on the generation and reaction of organometallics such as aryllithiums at temperatures that are easily accessible in industry by virtue of fast mixing in flow microreactor systems. The generation of various highly unstable functionalized aryllithiums followed by the selective formation of α-ketoesters can be achieved by using integrated flow microreactor systems. The method adds a new dimension in the selective synthesis of complex molecules having α-ketoester groups.

Notes and references

1 (*a*) E. J. Corey, D. H. Hua, B. C. Pan and S. P. Seitz, *J. Am. Chem. Soc.*, 1982, **104**, 6818; (*b*) T. Takahashi, T. Okano, T. Harada, K. Imamura and H. Yamada, *Synlett*, 1994, 121.

2 (*a*) M. R. Angelastro, S. Mehdi, J. P. Burkhart, N. P. Peet and P. Bey, *J. Med. Chem.*, 1990, **33**, 11; (*b*) V. G. Oleksandr, V. K. Pavel, V. S. Oleg, K. M. Pavel, A. Z. Olga and A. Andrey, *Synthesis*, 2011, 1633.

3 (*a*) E. J. Corey and B. W. Erickson, *J. Org. Chem.*, 1971, **36**, 3553; (*b*) K. Yamada, M. Kato, M. Iyoda and Y. Hirata, *J. Chem. Soc., Chem. Commun.*, 1973, 499; (*c*) J. M. Photis, *Tetrahedron Lett.*, 1980, **21**, 3539; (*d*) A. J. L. Cooper, J. Z. Ginos and A. Meister, *Chem. Rev.*, 1983, **83**, 321; (*e*) J. P. Burkhart, N. P. Peet and P. Bey, *Tetrahedron Lett.*, 1988, **29**, 3433; (*f*) H. H. Wasserman and W. B. Ho, *J. Org. Chem.*, 1994, **59**, 4364; (*g*) L. S. Li and Y. L. Wu, *Tetrahedron Lett.*, 2002, **43**, 2427; (*h*) M. Ma, C. Li, L. Peng, F. Xie, X. Zhang and J. Wang, *Tetrahedron Lett.*, 2005, **46**, 3927; (*i*) J. Zhuang, C. Wang, F. Xie and W. Zhang, *Tetrahedron*, 2009, **65**, 9797; (*j*) A. Raghunadh, S. B. Meruva, N. A. Kumar, G. S. Kumar, L. V. Rao and U. K. S. Kumar, *Synthesis*, 2012, 283.

4 F. Hollwedel and G. Koßmehl, *Synthesis*, 1998, 1241.

5 (*a*) J. S. Nimitz and H. S. Mosher, *J. Org. Chem.*, 1981, **46**, 211; (*b*) F. Babudri, V. Fiandanese, G. Marchese and A. Punzi, *Tetrahedron*, 1996, **52**, 13513 and references cited therein; (*c*) G. Guercio, S. Bacchi, A. Perboni, C. Leroi, F. Tinazzi, I. Bientinesi, M. Hourdin, M. Goodyear, S. Curti, S. Provera and Z. Cimarosti, *Org. Process Res. Dev.*, 2009, **13**, 1100.

6 P. Knochel, *Handbook of Functionalized Organometallics*, Wiley-VCH, Weinheim, 2005.

7 Microreactor: (*a*) P. Watts and S. J. Haswell, *Chem. Soc. Rev.*, 2005, **34**, 235; (*b*) K. Geyer, J. D. C. Codee and P. H. Seeberger, *Chem.–Eur. J.*, 2006, **12**, 8434; (*c*) G. Whitesides, *Nature*, 2006, **442**, 368; (*d*) A. J. deMello, *Nature*, 2006, **442**, 394; (*e*) J. Kobayashi, Y. Mori and S. Kobayashi, *Chem.–Asian J.*, 2006, **1**, 22; (*f*) M. Brivio, W. Verboom and D. N. Reinhoudt, *Lab Chip*, 2006, **6**, 329; (*g*) B. P. Mason, K. E. Price, J. L. Steinbacher, A. R. Bogdan and D. T. McQuade, *Chem. Rev.*, 2007, **107**, 2300; (*h*) B. Ahmed-Omer, J. C. Brandtand and T. Wirth, *Org. Biomol. Chem.*, 2007, **5**, 733; (*i*) P. Watts and C. Wiles, *Chem. Commun.*, 2007, 443; (*j*) T. Fukuyama, M. T. Rahman, M. Sato and I. Ryu, *Synlett*, 2008, 151; (*k*) W. Lin, Y. Wang, S. Wang and H. Tseng, *Nano Today*, 2009, **4**, 470; (*l*) K. Geyer, T. Gustafsson and P. H. Seeberger, *Synlett*, 2009, 2382; (*m*) S. Marrea and K. F. Jensen, *Chem. Soc. Rev.*, 2010, **39**, 1183; (*n*) D. Webb and T. F. Jamison, *Chem. Sci.*, 2010, **1**, 675; (*o*) J. Yoshida, H. Kim and A. Nagaki, *ChemSusChem*, 2011, **4**, 331.

8 Recent examples: (*a*) A. Nagaki, K. Kawamura, S. Suga, T. Ando, M. Sawamoto and J. Yoshida, *J. Am. Chem. Soc.*, 2004, **126**, 14702; (*b*) L. Ducry and D. M. Roberge, *Angew. Chem., Int. Ed.*, 2005, **44**, 7972; (*c*) P. He, P. Watts, F. Marken and S. J. Haswell, *Angew. Chem., Int. Ed.*, 2006, **45**, 4146; (*d*) K. Tanaka, S. Motomatsu, K. Koyama, S. Tanaka and K. Fukase, *Org. Lett.*, 2007, **9**, 299; (*e*) H. R. Sahoo, J. G. Kralj and K. F. Jensen, *Angew. Chem., Int. Ed.*, 2007, **46**, 5704; (*f*) C. H. Hornung, M. R. Mackley, I. R. Baxendale and S. V. Ley, *Org. Process Res. Dev.*, 2007, **11**, 399; (*g*) T. Fukuyama, M. Kobayashi, M. T. Rahman, N. Kamata and I. Ryu, *Org. Lett.*, 2008, **10**, 533; (*h*) D. L. Browne, M. Baumann, B. H. Harji, I. R. Baxendale and S. V. Ley, *Org. Lett.*, 2011, **13**, 3312; (*i*) C. F. Carter, H. Lange, D. Sakai, I. R. Baxendale and S. V. Ley, *Chem.–Eur. J.*, 2011, **17**, 3398; (*j*) N. Zaborenko, M. W. Bedore, T. F. Jamison and K. F. Jensen, *Org. Process Res. Dev.*, 2011, **15**, 131; (*k*) Y. Tomida, A. Nagaki and J. Yoshida, *J. Am. Chem. Soc.*, 2011, **133**, 3744; (*l*) A. C. Gutierrez and T. F. Jamison, *Org. Lett.*, 2011, **13**, 6414.

9 Recent examples: P. Rys, *Acc. Chem. Res.*, 1976, **9**, 345.

10 (*a*) A. Nagaki, M. Togai, S. Suga, N. Aoki, K. Mae and J. Yoshida, *J. Am. Chem. Soc.*, 2005, **127**, 11666; (*b*) S. Suga, A. Nagaki and J. Yoshida, *Chem. Commun.*, 2003, 354; (*c*) A. Nagaki, N. Takabayashi, Y. Tomida and J. Yoshida, *Org. Lett.*, 2008, **10**, 3937; (*d*) A. Nagaki, Y. Tomida and J. Yoshida, *Macromolecules*, 2008, **41**, 6322; (*e*) J. Yoshida, A. Nagaki, T. Iwasaki and S. Suga, *Chem. Eng. Technol.*, 2005, **3**, 259.

11 (*a*) H. Usutani, Y. Tomida, A. Nagaki, H. Okamoto, T. Nokami and J. Yoshida, *J. Am. Chem. Soc.*, 2007, **129**, 3047; (*b*) A. Nagaki, E. Takizawa and J. Yoshida, *J. Am. Chem. Soc.*, 2009, **131**, 1654; (*c*) A. Nagaki, A. Kenmoku, Y. Moriwaki, A. Hayashi and J. Yoshida, *Angew. Chem., Int. Ed.*, 2010, **49**, 7543; (*d*) Y. Tomida, A. Nagaki and J. Yoshida, *J. Am. Chem. Soc.*, 2011, **133**, 3744; (*e*) A. Nagaki, C. Matsuo, S. Kim, K. Saito, A. Miyazaki and J. Yoshida, *Angew. Chem., Int. Ed.*, 2012, **51**, 3245.

12 (*a*) J. Yoshida, *Flash Chemistry. Fast Organic Synthesis in Microsystems*, Wiley-Blackwell, 2008; (*b*) J. Yoshida, A. Nagaki and T. Yamada, *Chem.–Eur. J.*, 2008, **14**, 7450; (*c*) J. Yoshida, *Chem. Rec.*, 2010, **10**, 332.

13 (*a*) A. Nagaki, H. Kim and J. Yoshida, *Angew. Chem., Int. Ed.*, 2008, **47**, 7833; (*b*) A. Nagaki, H. Kim and J. Yoshida, *Angew. Chem., Int. Ed.*, 2009, **48**, 8063; (*c*) A. Nagaki, H. Kim, Y. Moriwaki, C. Matsuo and J. Yoshida, *Chem.–Eur. J.*, 2010, **16**, 11167; (*d*) A. Nagaki, H. Kim, C. Matsuo, H. Usutani and J. Yoshida, *Org. Biomol. Chem.*, 2010, **8**, 1212; (*e*) H. Kim, A. Nagaki and J. Yoshida, *Nat. Commun.*, 2011, **2**, 264.

14 W. Ehrfeld, K. Golbig, V. Hessel, H. Lowe and T. Richter, *Ind. Eng. Chem. Res.*, 1999, **38**, 1075.