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Ethyl lithiodiazoacetate: Extremely unstable intermediate handled efficiently in flow

Simon T. R. Müller[a], Tobias Hokamp[a], Svenja Ehrmann[a], Paul Hellier[b] and Thomas Wirth*[a]

Abstract: Ethyl diazoacetate (EDA) is one of the most prominent diazo reagents. It is frequently used in metal carbene type reactions. However, EDA can also be used as a nucleophile under base catalysis. Whilst the addition of EDA to aldehydes can be performed using organic bases, the addition of EDA to other carbonyl electrophiles requires the use of organometallics such as LDA. The generated ethyl lithiodiazoacetate is highly reactive and decomposes rapidly even at low temperatures. Herein, we report a continuous flow protocol that overcomes the problems associated with the instantaneous decomposition of ethyl lithiodiazoacetate. The addition of ethyl lithiodiazoacetate to ketones provides direct access to tertiary diazoalcohols in good yields.

Diazo compounds are among the most versatile classes of reagents in synthetic chemistry.[1] One of the most prominent members of this group of reagents is ethyl diazoacetate (EDA) **1**.[2] Ethyl diazoacetate is easily obtained by the reaction of glycine ethyl ester hydrochloride with sodium nitrite and sulfuric acid. The disadvantage of diazo compounds in general and ethyl diazoacetate in particular is their thermal profile.[3] Diazo compounds are energetic compounds which can react highly exothermally. This prevents their large-scale use under standard batch reaction conditions. Similar to other hazardous reagents, continuous flow technology can provide a solution to this problem.[4] The small quantities of dangerous compounds generated within the flow reactors combined with the high surface-to-volume ratio of these devices make flow chemistry a great enabling tool for the use of diazo compounds.[5] Consequently, some excellent protocols for the use of diazo compounds in flow synthesis have been reported in recent years.[6] Among those protocols are several methods for the continuous flow preparation and use of EDA.[7] We[8] and Kim *et al*.[9] independently developed multi-step continuous flow protocols for the generation of EDA and the subsequent nucleophilic addition to aldehydes using DBU as base. Although many different aldehydes were used as electrophiles successfully, the reactions are limited to aldehydes as carbonyl electrophiles. To expand the use of EDA as nucleophile to reactions with ketones or lactones in flow, the use of organometallics was necessary. We herein describe the first combination of a diazo compound with organometallics in continuous flow chemistry.

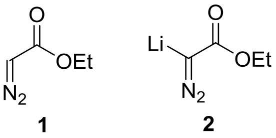

Figure 1. Ethyl diazoacetate **1** and ethyl lithiodiazoacetate **2**.

The reaction of EDA **1** with LDA generates highly reactive ethyl lithiodiazoacetate **2**. Ethyl lithiodiazoacetate **2** is very unstable, and decomposes at temperature above −50 °C instantaneously[10] into a brown gel insoluble in most organic solvents. The generation of ethyl lithiodiazoacetate[11] at very low temperatures and its addition to ketones has been known in synthetic chemistry for some time.[12] Also additions to lactones and thiolactones[13] or chromanones[14] have been investigated previously.

Batch experiments using **2** proved very unreliable, giving low yields and being difficult to repeat. The unstable nature of **2** also proved a major challenge in developing an efficient continuous flow protocol for the use of **2**. A very careful temperature control over the entire continuous flow set-up was absolutely mandatory to circumvent clogging of the microreactor. If any of the reactor tubes were placed outside the cooling bath, the system clogged immediately. Even the collection vial had to be dispersed in the dry ice/acetone cooling bath to ensure that no blockages occurred (Scheme 1). The efficient exclusion of air and water was achieved by drying the system according to a protocol of Ley *et al*. and keeping it under an argon atmosphere.[15] In this set-up, LDA was generated in a first reactor (R1) at room temperature within one minute and then cooled to −78 °C (C1). A stream of ethyl diazoacetate **1** in dry THF was cooled down in coil C2 and combined with the cooled LDA solution. The lithiation occurred at –78 ºC within 0.2 min in reactor R2, the ethyl lithiodiazoacetate **2** was then immediately trapped by a precooled (in coil C3) solution of the electrophile in the reactor R3. The formation of ethyl lithiodiazoacetate **2** within 0.2 min was confirmed by subsequent trapping with benzaldehyde as very reactive electrophile at –78 ºC. A reaction time of 1.2 min led to 79% conversion. Also a colour change to dark orange indicated a successful generation of **2**. Due to its instability no kinetic or calorimetric data could be obtained. Next studies were performed using acetophenone **3** which reacts also efficiently with the *in situ* generated ethyl lithiodiazoacetate **2** (Table 1). Due to the instability of **2**, all optimisations had to be performed by establishing the conversion and yield of product **4** by varying the equivalents of EDA **1** and LDA (Table 1, entries 1-4). An

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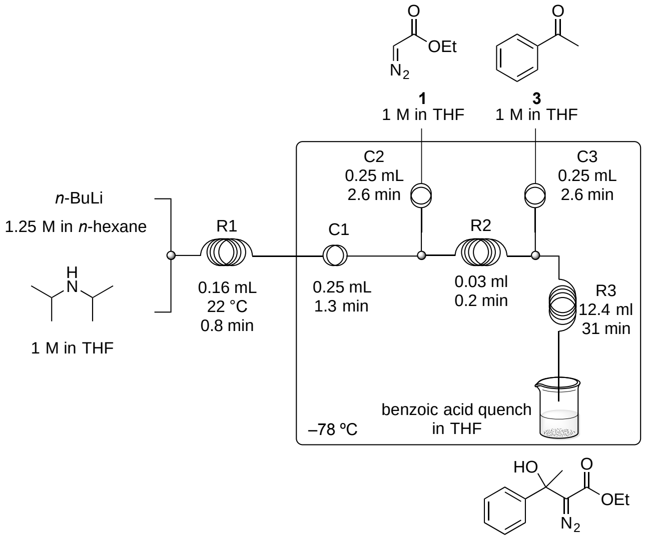
attempt to increase the temperature slightly to −72 °C did not improve the yield of the reaction product **4** any further (Table 1, entry 5). The yield of **4** obtained in the optimized flow process (62%) is higher than in the batch protocol reported previously (50%).[16]



Scheme 1. Continuous flow lithiation of ethyl diazoacetate **1**.

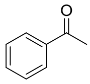
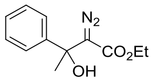
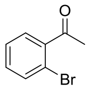
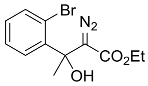
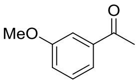
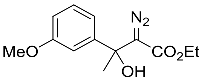
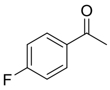
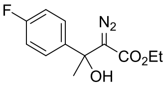
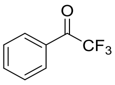
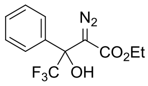
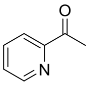
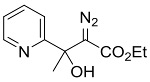
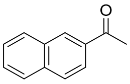
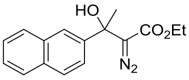
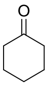
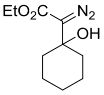
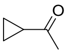
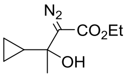
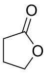
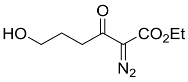
Table 1. Optimisation of the formation and use of ethyl lithiodiazoacetate **2** in reaction with acetophenone **3**

Entry	EDA **1** [equiv.]	LDA [equiv.]	T [°C]	Conversion **4** [%][a] (Yield **4** [%])
1	0.9	1	−78	46 (28)
2	1.3	1	−78	71 (58)
3	1.3	1.25	−78	80 (62)
4	1.3	1.5	−78	84 (62)
5	1.3	1.5	−72	79

[a] Conversion determined by ^{1}H NMR.

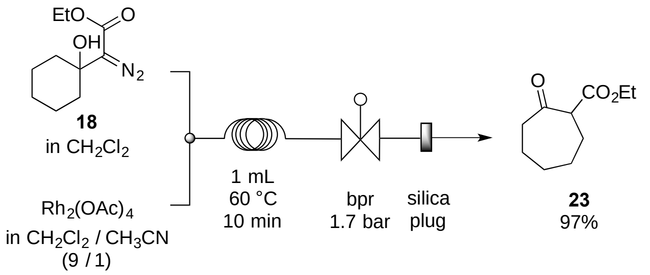
With the optimised reaction conditions in hand (Table 1, entry 4), the scope of ketones for the addition of ethyl lithiodiazoacetate **2** was investigated. Substitution on the aromatic moiety of the acetophenone is well tolerated and the reaction products (Table 2, entries 2-4) are obtained in good yields. However, pyridine as aromatic substituent gave the product **6b** in slightly reduced yield (53%, Table 2, entry 6) while the highest yield (71%) was obtained with 2,2,2-trifluoroacetophenone (Table 2, entry 5). Aliphatic ketones also produced the diazoalcohols **18** and **20** under the same reaction conditions (Table 2, entries 8-9). Unfortunately, the optimized reaction conditions were still not capable in furnishing substantial amounts of diazoester **22** when γ-butyrolactone **21** is used as electrophile (Table 2, entry 10) due to a mixture of side-products that were formed aside of **22**.

Table 2. Substrate scope of ethyl lithiodiazoacetate addition to carbonyl compounds

Entry	Electrophile	Product	Yield [%]
1	 **3**	 **4**	62
2	 **5**	 **6**	70
3	 **7**	 **8**	66
4	 **9**	 **10**	60
5	 **11**	 **12**	71
6	 **13**	 **14**	53
7	 **15**	 **16**	40
8	 **17**	 **18**	65
9	 **19**	 **20**	48
10	 **21**	 **22**	12

After screening various substrates as shown in Table 2, the ring expansion of compound **18** using rhodium catalysis in flow was investigated. Such ring-homologation reactions using diazo alcohols have already been investigated in batch and similar catalysts are being applied to the flow reaction.[16, 17] Diazo alcohol **18** can be rapidly decomposed to give the seven-membered ring system of product **23** in excellent yields in a short reaction time using rhodium acetate as catalyst (Scheme

2). The silica plug is used for an efficient removal of the rhodium catalyst.



Scheme 2. Continuous flow ring expansion reaction.

In conclusion, we report a new, highly efficient protocol using continuous flow technology for the *in situ* formation and the direct use of ethyl lithiodiazoacetate from EDA. Difficulties with the decomposition of ethyl lithiodiazoacetate were solved through careful temperature control of the entire continuous flow system. The system operated at low temperature (−78 °C) under exclusion of air and water in an argon atmosphere. The method gave excess to diversely substituted tertiary diazo alcohols derived from ketones in moderate to good yields. A symmetrical diazo alcohol was subsequently decomposed efficiently in continuous flow conditions to give the seven-membered ketone **23** in excellent yield.

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Keywords: diazo compounds • flow chemistry • hazardous intermediates • lithiation

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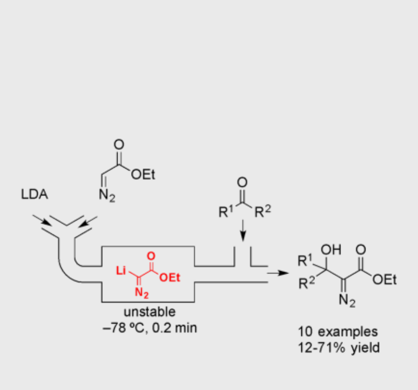
Entry for the Table of Contents

COMMUNICATION

Only flow synthesis allows the rapid generation and safe handling of ethyl lithiodiazoacetate as an extremely unstable, but highly versatile building block for flexible synthesis.



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