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Blaise-Type Reaction

Expanding Blaise-Type Reactions towards Indium-Mediated Transformations of α-Bromo-β-keto Esters with Nitriles

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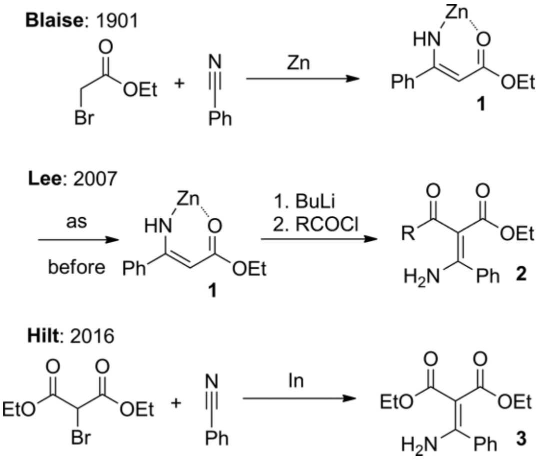
Abstract: The aim of this work is the identification of mild reaction conditions for the Blaise-type transformation of brominated β-keto esters with nitriles to generate enamino-substituted keto esters. The best results were obtained when a combination of indium metal (0.7 equiv.) with indium trichloride (1.6 equiv.) were applied at 60 °C for 20 to 72 hours, and these conditions could be applied to a broad range of nitriles and a significant number of different β-keto esters. The transformation of aliphatic nitriles proved to be difficult and gave only moderate yields. However, aromatic nitriles gave good yields in many cases. The applicability range of β-keto esters is acceptable while some electron-deficient aryl-substituents on the keto ester were challenging substrates. Nevertheless, we were able to expand the scope of the Blaise-type reaction towards brominated β-keto esters significantly.

Introduction

The zinc-mediated Blaise reaction has long been known.[1] Its limitation is mostly the application of bromo-substituted acetic esters, which can be reacted with nitriles to generate either aminoacrylates or β-keto esters depending on the work-up conditions applied to the zinc intermediate **1** (Scheme 1). Although established more than a century ago, recent advances in new conditions to overcome the limitations of the traditional Blaise reaction have to be mentioned. First of all, the Lee group reported the application of α-bromoacetates in combination with nitriles. In this case the primary intermediate **1** was deprotonated with a strong base (*n*BuLi) and quenching of the anion with an acyl chloride was reported to generate the formal product **2** of a Blaise reaction starting from an α-bromo-β-keto ester with a nitrile.[2] Shortly thereafter, the Lee group reported the reaction of aminoacrylates with hydrazine derivatives to generate pyrazoles,[3] whereas the Thomas group used the formylation of the aminoacrylates and subsequent cyclisation to generate interesting pyridine derivatives.[4] Additionally, the reaction of the aminoacrylates with alkynes was reported to generate polysubstituted 1-amino-substituted 1,3-dienes, which led to a number of promising follow-up reactions.[5] Depending on substituents and the reaction conditions, different types of products could be synthesised, including a palladium-catalysed carbonylative cyclisation sequence for the formation of isoindolines.[6] Recently, the Fan group reported the intramolecular version of a protocol in which an α-bromoester was treated with a 2-alkynyl benzonitrile derivative, and either 2-aminonaphthalenes or naphtho[2,3-*c*]furanes were obtained.[7]



Scheme 1. Blaise reaction and recent advances.

Some time ago, we were able to expand the scope of the Blaise-type transformation towards α-bromo-malonates and to realise carbon–carbon bond formations with nitriles to generate products of type **3** as well as isocyanates to form 2-carbamoyl malonates.[8] Although similar transformations of non-brominated starting materials with nitriles have been reported, we continued our efforts to find mild reaction conditions for the Blaise-type reactions with brominated β-keto esters instead of malonates to enlarge the scope even further. Thereby, we wanted to establish a versatile alternative to the Lewis acid induced transformation of non-brominated β-keto esters with nitriles, such as $TiCl_4$ or $SnCl_4$.[9]

Results and Discussion

In this report, we focus on the carbon–carbon bond formation of bromo-substituted β-keto esters with nitriles for the synthe-

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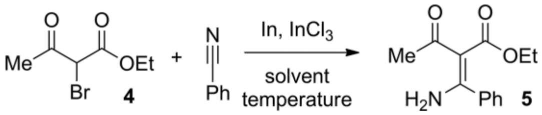
sis of enamino-substituted β-keto esters (**5**). As test system, we chose the ethyl 2-bromo-3-oxobutenoate (**4**, Scheme 2) and benzonitrile as suitable starting materials. Like the reaction with bromomalonate for the formation of **3**, the corresponding transformation towards **5** with zinc powder as activating agent failed.[8]



Scheme 2. Outline of the optimisation of the reaction conditions of **4** with benzonitrile.

Also, when indium trichloride[10] was used without a reducing metal, only traces of product were observed. However, when zinc powder was added as additive, 26 % yield of **5** could be achieved. When the zinc powder was substituted with indium metal, a significantly higher yield was obtained.[11] Accordingly, different reaction conditions were screened to achieve reasonable turnovers of **4**. The results of this series of experiments are summarised in Table 1.

Table 1. Optimisation studies on the indium/indium trihalide mediated Blaise-type reaction for the synthesis of **5**.[a,b]

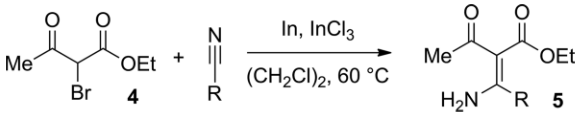
Entry	Solvent	InX$_3$	Indium[c]	*T* [°C]	Yield[a]
1	$(CH_2Cl)_2$	0.7 equiv. $InCl_3$	0.7 equiv.	60	58 %
2	$(CH_2Cl)_2$	1.0 equiv. $InCl_3$	0.7 equiv.	60	74 %
3	$(CH_2Cl)_2$	1.4 equiv. $InCl_3$	0.7 equiv.	60	76 %
4	***$(CH_2Cl)_2$***	***1.6 equiv. $InCl_3$***	***0.7 equiv.***	***60***	***83 %***[d]
5	$(CH_2Cl)_2$	1.6 equiv. $InBr_3$	0.7 equiv.	60	81 %
6	$(CH_2Cl)_2$	1.6 equiv. $InCl_3$	0.7 equiv.[e]	60	75 %
7	$(CH_2Cl)_2$	1.8 equiv. $InCl_3$	0.7 equiv.	60	73 %
8	$(CH_2Cl)_2$	1.6 equiv. $InCl_3$	0.5 equiv.	60	75 %
9	$(CH_2Cl)_2$	1.6 equiv. $InCl_3$	0.8 equiv.	60	75 %
10	$(CH_2Cl)_2$	1.6 equiv. $InCl_3$	0.9 equiv.	60	82 %
11	$(CH_2Cl)_2$	1.6 equiv. $InCl_3$	0.9 equiv.	60	78 %
12	$(CH_2Cl)_2$	1.6 equiv. $InCl_3$	0.7 equiv.	70	66 %
13	THF	1.6 equiv. $InCl_3$	0.7 equiv.	60	4 %
14	toluene	1.6 equiv. $InCl_3$	0.7 equiv.	60	66 %
15	CH_2Cl_2	1.6 equiv. $InCl_3$	0.7 equiv.	50	70 %

[a] Reaction conditions: ethyl 2-bromo-3-oxobutanoate (1.0 mmol), benzonitrile (2.0 mmol), solvent (1.0 mL), sealed tube. [b] The yields were determined by ^1H NMR with 1,3,5-trimethoxybenzene as internal standard. [c] Cut indium shots were used. [d] The product was isolated in 83 % yield.

The optimisation process of the indium-mediated Blaise-type reaction showed that indium alone led to a very low yield of the desired product **5**. Also, the application of indium trichloride in the absence of any metal gave only trace amounts of **5**. As mentioned before, the results for the application of zinc powder and indium trichloride furnished product **5** already in 26 % yield. The replacement of zinc towards indium metal gave satisfactory results when more than 0.5 equiv. of indium were used while with more than 0.7 equiv. of indium (entries 9–11) no further increase of the yield could be achieved. The optimum amount of indium trichloride was 1.6 equiv. Higher as well as lower amounts of $InCl_3$ were found to be not beneficial (entries 1–3 and 7), and the replacement of $InCl_3$ toward $InBr_3$ gave no significant change (entry 5). Also, the application of other solvents (entries 13–15) proved to be inferior to 1,2-dichloroethane, which is the solvent of choice. Concerning the reaction temperature, 60 °C was found to be the optimum temperature. Below 50 °C the reaction is very slow, and at higher temperatures (entry 12) side reactions were encountered.

The product (**5**) was isolated in up to 83 % yield when indium shots were applied whereas the yield dropped slightly to 75 % when indium powder was applied.

With the optimised conditions in hand, we then investigated the application of a number of nitriles in the indium metal/indium trichloride mediated Blaise-type reaction (Scheme 3). The results of this series of experiments are summarised in Table 2.



Scheme 3. Indium metal/indium trichloride-mediated transformation of α-bromo-β-keto ester **4** with different nitriles.

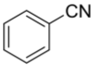
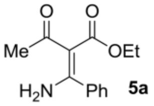
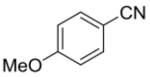
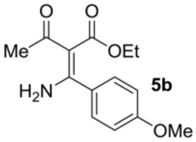
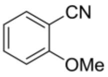
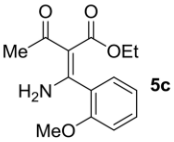
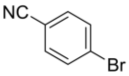
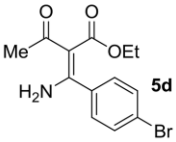
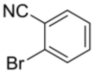
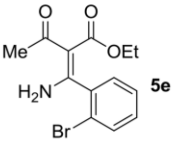
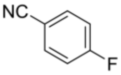
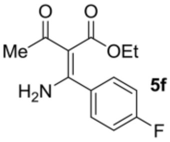
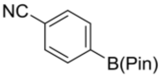
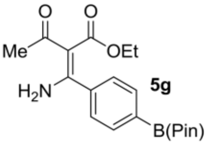
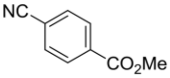
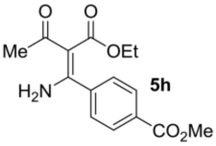
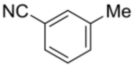
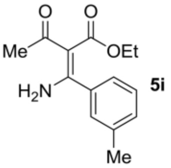
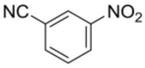
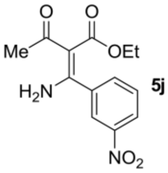
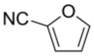
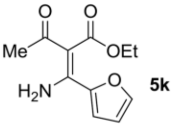
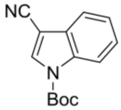
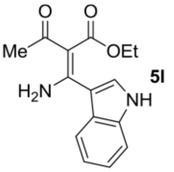
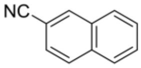
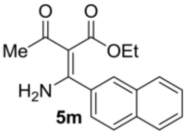
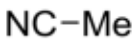
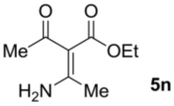
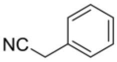
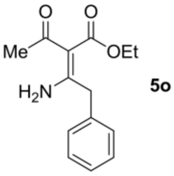
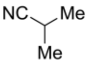
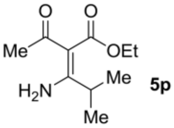
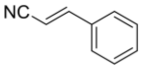
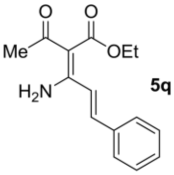
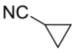
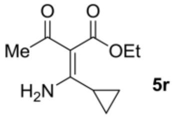
For this set of experiments, a number of aromatic nitriles, including electron-rich as well as electron-deficient aryl nitriles, were applied successfully. On the other hand, the application of aliphatic nitriles was more challenging and led to significantly lower yields. Nevertheless, we would like to highlight the finding that the application of cyclopropanecarbonitrile is of mechanistic interest (entry 19).[12] The reaction does not seem to proceed through a radical mechanism because ring-opened products could not be detected and only product **5r** was isolated in 53 % yield.

The functional-group tolerance of the transformation is quite acceptable; alkoxy groups, aryl halides, esters, aromatic nitro groups as well as heterocyclic substrates were applicable. Only in a few cases, functional groups seem to give lower yields, such as nitro groups (entry 10) or pinacolboronic ester groups (entry 7). Unfortunately, the application of the boronic ester gave only low yields, though this would be an interesting building block for further transformations. Sterically hindered nitriles, such as 2-methoxybenzonitrile, gave the desired product **5c** in only slightly diminished yield (entry 3). Also, 2- and 4-bromo- as well as 4-fluorobenzonitrile are well accepted as starting materials and no dehalogenation of the arene moiety was observed (entries 4–6). Moreover, heterocyclic nitriles were applicable (entries 11 and 12) and it is noteworthy that in case of product **5l** the Boc protecting group was removed under the reaction condition. On the other hand, the unprotected indole-3-carbonitrile did not undergo the desired reaction. Unfortunately, the application of aliphatic nitriles gave only diminished yields of up to 23 % yield (entries 14–16) with the exception of the cyclopropanecarbonitrile as already mentioned.

In the next set of experiments, we focused our attention on the application of different α-bromo-β-keto esters **6** (Scheme 4) in the reaction with benzonitrile to afford enamino-substituted keto esters **7**. The results of these experiments are summarised in Table 3.

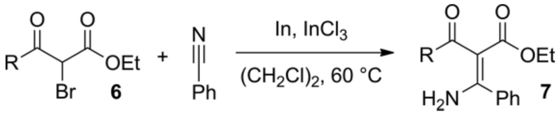
The scope of the β-keto esters was evaluated by applying electron-rich (4-methoxyphenyl-substituted), electron-neutral (phenyl) and electron-deficient (4-fluorophenyl-substituted) α-bromo-β-keto esters as starting materials (entries 1–5). These

Table 2. Results of the indium metal/indium trichloride mediated Blaise-type reaction of **4** with different nitriles.

Entry	Substrate	Product	Time	Yield[a]
1		 **5a**	20 h	83%
2		 **5b**	23 h	81%
3		 **5c**	24 h	66%
4		 **5d**	21 h	72%
5		 **5e**	26 h	53%
6		 **5f**	21 h	70%
7		 **5g**	24 h	34%
8		 **5h**	20 h	81%
9		 **5i**	36 h	33%
10		 **5j**	48 h	29%
11		 **5k**	24 h	51%
12		 **5l**	23 h	44%
13		 **5m**	48 h	59%
14		 **5n**	48 h	23%
15		 **5o**	48 h	23%
16		 **5p**	72 h	11%
17		 **5q**	26 h	51%
18		 **5r**	23 h	53%

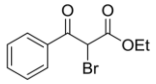
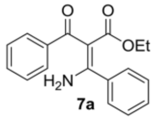
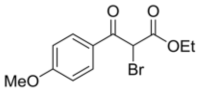
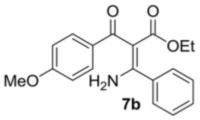
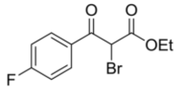
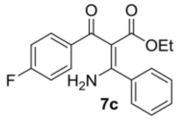
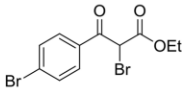
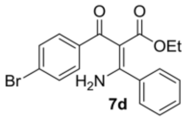
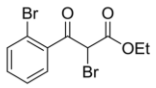
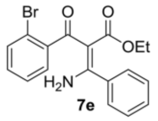
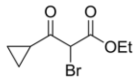
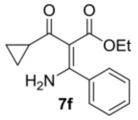
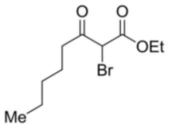
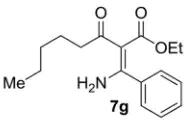
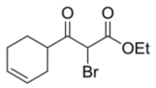
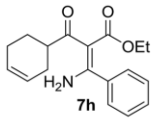
[a] Reaction conditions: α-bromo-β-keto ester **4** (1.0 mmol), nitrile (2.0 mmol), cut indium shots (0.7 mmol), indium trichloride (1.7 mmol), DCE (1.0 mL), 60 °C, sealed tube. [b] Crystallographic data for **5a**, see CCDC 1555178.

reactions revealed that electron-neutral as well as electron-rich starting materials are well accepted (59 % for **7a** and 54 % for **7b**), while electron-deficient starting materials gave only a very poor yield (**7c**: 14 %). The yields for the bromophenyl-substituted starting materials were not significantly higher, as **7d** and **7e** were isolated in 22 % and 21 %, respectively. Aliphatic β-keto esters gave moderate yields of around 40 % for **7g** and **7h**, while the cyclopropyl-substituted derivative **7f** could be obtained in a good yield of 70 %. As already observed for the transformation of cyclopropanecarbonitrile (Table 2, entry 18),



Scheme 4. Indium metal/indium trichloride mediated reaction applying different α-bromo-β-keto esters of type **6**.

Table 3. Results of the indium metal/indium trichloride mediated Blaise-type reaction of α-bromo-β-keto esters **6** with benzonitrile.

No	Substrate	Product	Time	Yield[a] (*E*:*Z*)
1		 **7a**	26 h	59% (1:1.7)
2		 **7b**	25 h	54% (1:3.5)
3		 **7c**	48 h	14% (1:2.4)
4		 **7d**	48 h	22% (1:2.0)
5		 **7e**	48 h	21% (6.0:1)
6		 **7f**	30 h	70% *E* only
7		 **7g**	48 h	38% *E* only
8		 **7h**	48 h	40% *E* only

[a] Reaction conditions: α-bromo-β-keto ester **6** (1.0 mmol), benzonitrile (2.0 mmol), cut indium shots (0.7 mmol), indium trichloride (1.7 mmol), DCE (1.0 mL), 60 °C, sealed tube.

no ring-opened side product could be detected in the case of the formation of **7f**.

In principle, the products of type **5** could be obtained as a mixture of *E* and *Z* isomers. However, the products of type **5** (Table 2) were isolated as *E* isomers only. In contrast, the application of aryl-substituted α-bromo-β-keto esters gave mixtures of *E*/*Z* isomers of products **7** (see Table 3). For the assignment of the *E* and *Z* isomer, the CH$_3$ group of the ethyl ester proved to be an excellent indicator. For the *Z* isomer ***Z*-7**, the CH$_3$ protons gave a signal ^{1}H NMR spectrum around δ = 1.0 ppm, whereas for the *E*-isomer ***E*-7**, a resonance was found around δ = 0.7 ppm. Thereby, an easy assignment of the two sets of signals could be made (Figure 1).

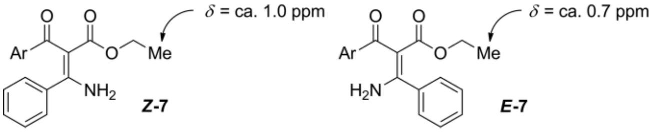
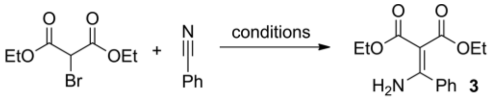


Figure 1. Assignment of the *E*/*Z* isomers of **7** based on ^{1}H NMR shifts.

When a single crystal, used for the X-ray analysis of ***Z*-7a** (CCDC 1555179), was dissolved in CDCl$_3$ and analysed by ^{1}H NMR, nearly the same ratio of *E*/*Z* isomers as in the original sample was obtained. Accordingly, we assume that the *E*/*Z* isomerisation takes place in situ and is not dependent on the reaction mechanism or any possible induction by either the indium metal or the indium Lewis acid applied.

Last but not least, we compared the reaction conditions optimised for the application of α-bromo-β-keto esters with those found previously for the reaction of diethyl α-bromo-malonate with benzonitrile (Scheme 5).[8]



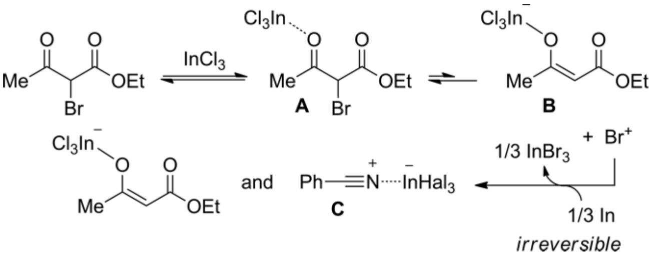
previous conditions: In (2.0 equiv.), CH$_2$Cl$_2$, 40 °C, 24 h – **67%**
new conditions: In (0.7 equiv.), InCl$_3$ (1.7 equiv.), (CH$_2$Cl)$_2$, 60 °C, 20 h – **95%**

Scheme 5. Comparison of the indium metal mediated with the indium metal/indium trichloride mediated synthesis of **3**.

The overall amounts of indium metal and indium salts applied in these reactions are similar and the reaction conditions concerning solvent, reaction temperature and reaction time are comparable. However, the desired product **3** could be isolated in nearly quantitative yield (95 %), representing a significant improvement compared to the earlier reported reaction conditions.

Finally, the question of the activation mode of the α-bromo-β-keto ester was investigated by ^{1}H NMR experiments. The interpretation of these spectra suggest that the Lewis acid coordinates to the α-bromo-β-keto ester (**A**) and leads to the release of a bromonium ion (Br$^+$) and the formation of an indium-enolate equivalent (**B**) (Scheme 6).

The equilibrium of this process is probably shifted irreversibly towards the indium enolate when the Br$^+$ ion is reduced by



Scheme 6. Comparison of the indium metal mediated with the indium metal/indium trichloride mediated synthesis of **3**.

the indium metal to generate $InBr_3$, and the Lewis acid further activates the nitrile (**C**) for the nucleophilic attack of the indium-enolate **B**, which leads to the formation of the products.

Conclusions

With the results presented herein, we have been able to identify mild reaction conditions for the successful application of α-bromo-β-keto esters in indium metal/indium trichloride mediated Blaise-type reactions with nitriles. A broad scope of the reaction concerning different nitriles and various α-bromo-β-keto esters could be demonstrated. A number of interesting products was obtained, which open the way to explore promising follow-up reactions. These results justify the extra step to generate the brominated keto ester compared to similar transformations with strong Lewis acids because not all functional groups will tolerate harsh reaction conditions.

Experimental Section

CCDC 1555178 (for **5a**), 1555179 (for **Z-7a**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

Supporting Information (see footnote on the first page of this article): Experimental procedures for the synthesis of starting materials, reaction protocols, analytical data and NMR spectra of previously unknown compounds.

Keywords: Blaise reaction · Synthetic methods · Enamines · Indium · Lewis acids

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