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Indium-Mediated Blaise-Type Reaction of Bromomalonates with Nitriles and Isocyanates

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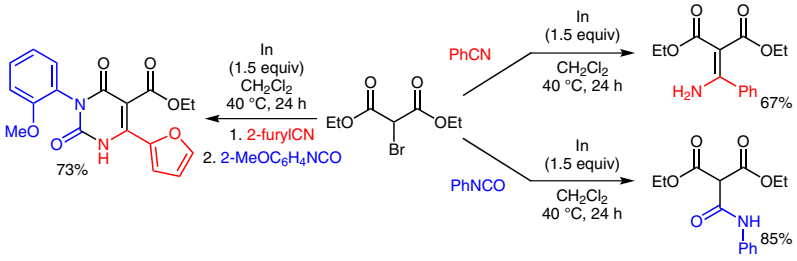

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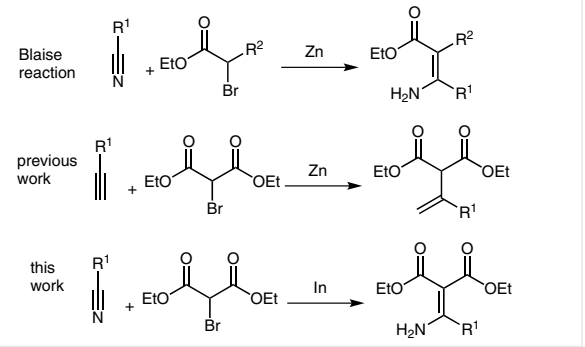
Abstract The indium-mediated Blaise-type reaction of bromomalonates with nitriles and isocyanates is described. The choice of the solvent is crucial for the successful reaction; the dependency on dichloromethane proved to be nonplussed. The reaction with nitriles led to the corresponding β-enamino diesters in moderate to good yields. The conversion with isocyanates generated carbamoyl malonates in good to excellent yields. Both reactions tolerated various functional groups regarding the electronic nature. Also, steric hindrance in the starting materials, as caused by mesityl isocyanate or diisopropyphenyl isocyanate, was well tolerated. In addition, a sequential three-component one-pot reaction sequence is described for the formation of 2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylates enabling future investigations in this field.

Key words Blaise reaction, bromomalonates, indium, isocyanates, nitriles, pyrimidines

The Blaise reaction[1] is originally a reaction of a bromoacetate with a nitrile for the synthesis of β-ketoesters. Nevertheless, under careful hydrolysis, β-enamino esters can be obtained as well (Scheme 1). The enamino esters are important intermediates for a number of very promising follow-up reactions to access a number of interesting functional-group assemblies. However, a major drawback of the Blaise reaction are the rather low yields[2] whereas the reaction rates can be improved by ultrasonic irradiation.[3] Also, the scope of the Blaise reaction remained rather narrow over the last centuries and is restricted towards bromoacetates as starting materials. In recent years, significant improvements were reported for the application of the Blaise reaction in tandem transformations to access more complex products.[4]

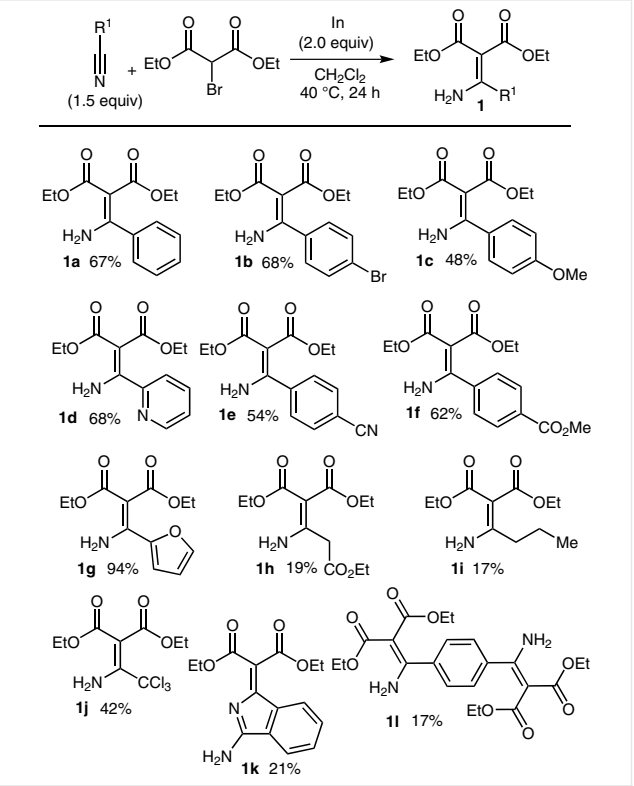


Scheme 1

To the best of our knowledge, zinc-mediated reactions of bromomalonates with nitriles are unknown. Therefore, we intended to expand our interest towards nitriles as unsaturated starting materials in metal-mediated reactions with bromo-functionalized starting materials.

In a previous investigation, we realized the zinc-mediated carbon–carbon bond formation of a bromomalonate with alkynes (Scheme 1)[5] and follow-up reactions of the in situ generated organo-zinc species.[6] One key observation for this reaction was the solvent dependency. The reaction failed in THF as solvent, whereas dichloromethane proved to be the optimal solvent for this transformation. As mentioned above, the Blaise reaction of bromomalonates has not been described, and we propose that the in situ generated zinc-ester enolate species are not nucleophilic enough to undergo a reaction with moderately active electrophiles. This result could successfully be reproduced in our laboratory in THF as well as CH_2Cl_2 as solvent, and no product formation from bromomalonates was observed.

In our ongoing investigation, we substituted zinc with metallic indium.[7] While the reaction in THF failed again, the transformation in CH_2Cl_2 as solvent at 40 °C in a sealed tube under inert atmosphere gave the desired product **1a** in moderate yields (Scheme 2).[8]

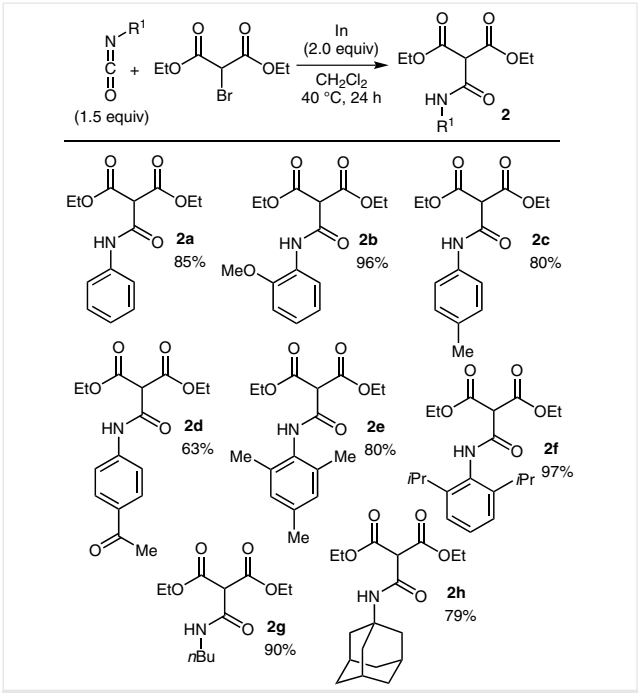


Scheme 2

To achieve complete conversion, a slight excess of metallic indium as well as a slight excess of the nitrile were used and after 24 hours reaction time the reaction mixture was quenched by addition of water to yield the adducts of type **1** after workup.

The reaction could be expanded to a number of aromatic nitriles. Electron-withdrawing functional groups (**1a**,**b**) as well as an electron-donating functional group were applicable (**1c**). The best result was obtained for the 2-furancarbonitrile, where the desired product **1g** could be isolated in an excellent yield of 94%. Aliphatic nitriles were much more problematic, resulting in low yields for butyronitrile (**1i**) and ethyl cyanoacetate (**1h**). However, the application of trichloroacetonitrile as nitrile component led to an acceptable yield of 42% of product **1j**. Noteworthy, additional bromo substituents (**1b**) were well accepted under the reaction conditions and no proto-debromination was observed. We then applied dinitriles as substrates in the indium-mediated Blaise-type reaction. As mentioned above, good results were obtained when the nitrile was used in excess, however, for this transformation two equivalents of the in situ generated indium reagent from bromomalonate had to react with the dinitrile starting material for the formation of **1l**. Accordingly, we were not surprised to isolate only 17% of **1l** as a highly polar product from benzo-1,4-dinitrile. A similar 2:1 adduct was expected for the reaction with benzo-1,2-dinitrile, however, only the isoindole derivative **1k** could be obtained as product. Although **1k** was only isolated in 21% yield. The unusual structure of the product and the straightforward approach to access such a molecule is highly appealing for investigations in perspective.

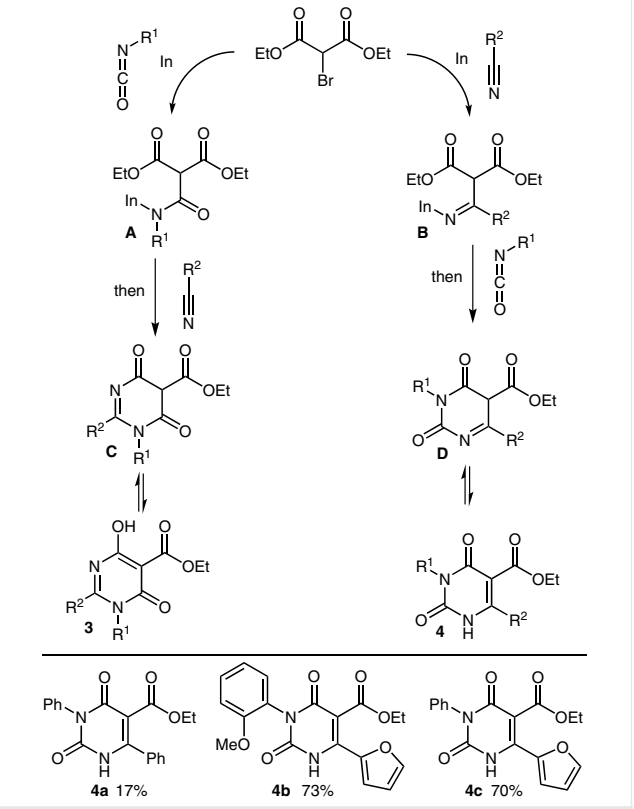
In a second set of experiments, we applied the indium-mediated Blaise-type reaction conditions to the addition to isocyanates (Scheme 3).[9] The results for these conversions are significantly better than for the nitrile substrates, which are presumably based on their higher electrophilicities. Accordingly, the products of electron-rich (**2b**,**c**), electron-deficient (**2d**),[10] simple aliphatic (**2g**), sterically more demanding aliphatic (**2h**), and congested aromatic isonitriles (**2e**,**f**) could be isolated in good to excellent yields.



Scheme 3

These two sets of reactions intrigued us to investigate the possibility for a sequential three-component reaction. Two scenarios were envisaged (Scheme 4): first reaction of the indium reagent with a more reactive isocyanate towards **A** and quenching of the secondary indium intermediate **C** with a less reactive nitrile for the formation of the heterocycle **3**. The second scenario is the reverse process, where first the reaction with a nitrile is conducted towards intermediate **B** and then conversion with the more reactive

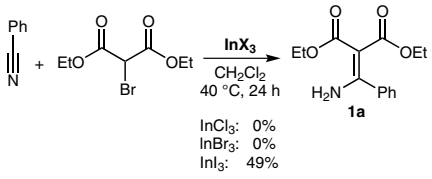
isocyanate to generate **D** which will undergo a 1,3-H-shift towards the heterocycle of type **4**. It has to be mentioned that the products of type **4** were reported by Lee and coworkers[9] who reacted bromoacetate with zinc and nitriles in a traditional Blaise reaction and reacted the corresponding zinc intermediate of type **B** first with isocyanates and then with triphosgene to obtain the products of type **4** (**4a** was synthesized in up to 73% yield).



Scheme 4

The conversion of the in situ generated organoindium species with nitriles and the subsequent quenching with isocyanates (pathway **A** → **C** → **3**) did not lead to the desired products of type **3** as expected. Thus, the organoindium species **A** is not nucleophilic enough to react with the nitrile to heterocycles of type **3**. However, when the alternative reaction sequence for the synthesis of 2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylates was investigated, the desired product **4b**[11] and **4c** derived from 2-cyanofurane could be isolated in good yields. Unfortunately, when the less reactive benzonitrile was applied, the corresponding pyrimidine derivative **4a** could only be isolated in 17% yield. This considerable drop in efficiency will be investigated in the future to overcome this bottleneck in the straightforward three-component synthesis of interesting heterocyclic compounds.

Finally, we were interested to disclose the role of indium-based Lewis acids as possible catalysts in the indium-mediated Blaise-type reaction. Therefore, the readily available indium halides were applied, and under otherwise identical reaction conditions, no conversion was observed with indium trichloride and indium tribromide (Scheme 5). On the other hand, when indium triiodide was applied, 49% of product **1a** was isolated after 24 hours reaction time.[12]



Scheme 5

Interestingly, the reaction led to a significant formation of iodine, indicated by a deep purple color of the reaction mixture. Under all reaction conditions described above, no significant colored solution was observed. Accordingly, the proposal emerged that indium triiodide was not stable under the reaction conditions and led to the decomposition of indium triiodide to metallic indium and iodine. When InI_3 was heated to reflux in CH_2Cl_2, no iodine formation was observed. Also, the addition of the benzonitrile or the product (**1a**, Scheme 5) to this mixture did not result in a color change. However, when bromomalonate was added, the immediate formation of iodine was observed. After 24 hours reaction time in the absence of benzonitrile, the formation of iodomalonate (>95%) was detected (GC–MS analysis). On a 1.00 mmol scale besides iodomalonate also the formation of 0.83 mmol iodine was determined by titration of the iodine.[13] Accordingly, the InI_3 decomposed to iodine and metallic indium.

In summary, we showed that the indium-mediated Blaise-type reaction of bromomalonate could be realized and the corresponding β-enamino esters were obtained. The reaction with isocyanates gave the desired carbamoyl malonates in good to excellent yields, and a sequential three-component reaction was established to obtain two 2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylates in good yields. Finally, a Lewis acid mediated reaction mechanism could be excluded and hints to a purely metal-induced reaction could be reported.

Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0035-1561973.

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(8) **Synthesis of Diethyl 2-[Amino(furan-2-yl)methylene]malonate (1g)**
The reactions were carried out in sealed tubes under argon atmosphere. Metallic indium pellets (2.00 mmol, 2.00 equiv) were sliced to smaller pieces and evacuated in a sealed tube for 15 min, then suspended with dry CH_2Cl_2 (1.0 mL). To the suspension was added diethyl bromomalonate (263 mg, 1.00 mmol, 1.00 equiv; 92% purity) and 2-furonitrile (140 mg, 1.50 mmol). The clear reaction mixture was heated to 40 °C for 24 h. The reddish-brown suspension was cooled to room temperature, poured into water (30 mL), and extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layers were dried over Mg_2SO_4 and filtered off. The solvent was removed under reduced pressure, and the crude product was purified by flash chromatography on silica gel (eluent: pentane–EtOAc = 5:1 → 3:1) to afford the enamino diester **1g** (239 mg, 0.94 mmol, 94%); yellowish solid, mp 33–34 °C; R_f = 0.32 (pentane–EtOAc = 3:1).
IR (neat): 3414, 3301, 3134, 2981, 2904, 1697, 1663, 1604, 1580, 1516, 1474 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$-d_1): δ = 7.40 (dd, *J* =1.7, 0.5 Hz, 1 H), 9.04–5.40 (m, 2 H), 6.69 (dd, *J* =3.6, 0.5 Hz, 1 H), 6.37 (dd, *J* =3.6, 1.8 Hz, 1 H), 4.09 (q, ^3J =7.1 Hz, 4 H), 1.17 (t, ^3J =7.4 Hz, 3 H), 1.12 (t, ^3J =7.4 Hz, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$-d_1): δ = 168.2, 167.8, 149.3, 147.3, 144.1, 112.9, 111.9, 92.3, 60.9, 59.8, 14.2, 13.8. HRMS (APCI$^+$–TOF): *m/z* [M + H]$^+$ calcd for $C_{12}H_{16}NO_5$: 254.1023; found: 254.1022.
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(10) **Synthesis of Diethyl 2-[(4-Acetylphenyl)carbamoyl]malonate (2d)**
The reactions were carried out in sealed tubes under argon atmosphere. Metallic indium pellets (2.00 mmol, 2.00 equiv) were sliced to smaller pieces and evacuated in a sealed tube for 15 min, then suspended with dry CH_2Cl_2 (1.0 mL). To the suspension was added diethyl bromomalonate (263 mg, 1.00 mmol, 1.00 equiv; 92% purity,) and 4-acetylphenyl isocyanate (242 mg, 1.50 mmol). The clear reaction mixture was heated to 40 °C for 24 h. The reddish-brown suspension was cooled to room temperature, poured into water (30 mL) and extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layers were dried over Mg_2SO_4 and filtered off. The solvent was removed under reduced pressure, and the crude product was purified by flash chromatography on silica gel (eluent: pentane–EtOAc = 5:1 → 3:1) to afford the malonyl amide **2d** (203 mg, 0.63 mmol; 63%); yellow solid, mp 85–86 °C; R_f = 0.13 (pentane–EtOAc = 3:1).
IR (neat): 3306, 3195, 3117, 2990, 2942, 2907, 1740, 1670, 1596, 1525 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$-d_1): δ = 9.56 (s, 1 H), 7.84 (d, ^3J =8.8 Hz, 2 H), 7.59 (d, ^3J =8.8 Hz, 2 H), 4.44 (s, 1 H), 4.20 (q, ^3J =7.1 Hz, 4 H), 2.48 (s, 3 H), 1.21 (t, ^3J =7.1 Hz, 6 H). ^{13}C NMR (75 MHz, $CDCl_3$-d_1): δ = 197.0, 165.4, 160.6, 141.6, 133.3, 129.6, 119.4, 62.9, 59.7, 26.3, 13.8. HRMS (APCI$^+$–TOF): *m/z* [M + H]$^+$ calcd for $C_{16}H_{20}NO_6$: 322.1285; found: 322.1286.
(11) **Synthesis of Ethyl 6-(Furan-2-yl)-3-(2-methoxyphenyl)-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4b)**
The reactions were carried out in sealed tubes under argon atmosphere. Metallic indium pellets (2.00 mmol, 2.00 equiv) were sliced to smaller pieces and evacuated in a sealed tube for 15 min, then suspended with dry CH_2Cl_2 (1 mL). To the suspension was added diethyl bromomalonate (263 mg, 1.00 mmol, 1.00 equiv; 92% purity) and 2-furonitrile (140 mg, 1.50 mmol, 1.50 equiv). The clear reaction mixture was heated to 40 °C for 24 h. To the reddish-brown suspension was added 4-acetylphenyl isocyanate (350 mg, 3.00 mmol, 3.00 equiv) and heated to 40 °C for 24 h. The reddish suspension was cooled to room temperature, diluted with EtOAc, poured into water (30 mL), and extracted with EtOAc (3 × 15 mL). The combined organic layers were dried over Mg_2SO_4 and filtered off. The solvent was removed under reduced pressure, and the crude product was purified by flash chromatography on silica gel (eluent: pentane–EtOAc = 1:1 → 0:1) and recrystallized (pentane–EtOAc = 5:1) to afford the pyrimidinone **4b** (259 mg, 0.73 mmol; 73%); yellowish solid, mp 215–216 °C; R_f = 0.29 (pentane–EtOAc = 1:1).
IR (neat): 3127, 2957, 2838, 1738, 1697, 1650, 1602, 1550, 1499, 1459, 1434 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$-d_1): δ = 10.01 (s, 1 H), 7.44 (d, *J* =1.6 Hz, 1 H), 7.40–7.30 (m, 1 H), 7.23–7.10 (m, 1 H), 7.01 (m, 1 H), 7.05–6.90 (m, 2 H), 6.39 (dd, *J* =3.7, 1.8 Hz, 1 H), 4.31 (q, ^3J =7.1 Hz, 2 H), 3.70 (s, 3 H), 1.27 (t, ^3J =7.1 Hz, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$-d_1): δ = 164.4, 160.6, 155.1, 151.2, 146.2, 143.1, 137.7, 130.7, 129.9, 122.7, 121.0, 116.2, 113.1, 112.0, 104.6, 62.3, 55.9, 14.2. HRMS data could not be obtained. The identity of the product was confirmed by X-ray analysis; see Supporting Information.
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