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Synthesis of 4-allylquinazolines from *N*-(2-cyanoaryl)amides via the In-mediated allylation of nitrile and dehydrative cyclization cascade

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ABSTRACT

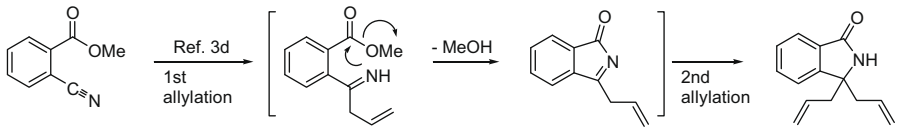
The reaction of allylindium reagents and *N*-(2-cyanoaryl)amides afforded 2-substituted-4-allylquinazolines in good yields via the indium-mediated Barbier-type allylation of nitrile and the following dehydrative cyclization cascade.

Allylindium reagents have been used extensively for the introduction of allyl group in a Barbier-type manner to various electrophiles.[1–3] Although many reactive electrophiles such as aldehydes and imines have been used in the indium-mediated allylations,[1] the reaction of less reactive nitrile has not been reported much except the first successful results of Yamamoto group[2a,b] and our recent Letters.[3]

Very recently, we reported a series of indium-mediated Barbier-type allylations of nitrile groups in γ-cyanoesters,[3a] γ-ketonitriles,[3b] δ-ketonitriles,[3c] and *ortho*-cyanobenzoates.[3d] The intrinsic reactivity of nitrile group toward allylindium reagents was found to be sufficient to form the corresponding imine or enamine intermediates, and the corresponding δ-valerolactams,[3a] pyrroles,[3b] isoquinolines,[3c] and isoindolones[3d] were obtained in good to moderate yields. Based on the results, we were convinced that a nitrile group can be attacked readily by allylindium reagents when the molecule has a suitable electrophilic quencher, whereas isolated nitrile did not react with allylindium reagents. As an electrophilic quencher, ester[3a,d] and sterically hindered ketone group[3b,c] have been successfully used. The synthesis of isoindolones from *ortho*-cyanobenzoates[3d] is a typical example, as shown in Scheme 1.

Quinazoline derivatives are important constituents in many biologically active substances and provide a scaffold for designing drugs and many functional organic materials.[4] Numerous synthetic methodologies of quinazolines are available; however, they suffer from many drawbacks such as harsh reaction conditions and multistep synthesis.[5] Thus a new protocol for the synthesis of quinazolines is highly required.

Based on our results,[3d] we presumed that a quinazoline skeleton could be constructed when we use *N*-(2-cyanoaryl)amide derivative, **1a** as an example, as a starting material, if the amide



Scheme 1.

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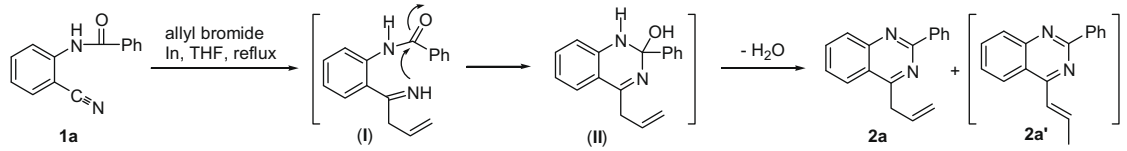


Scheme 2.

group could be used as an electrophilic quencher for the imine intermediate (**I**) generated via the indium-mediated Barbier-type allylation of nitrile, as shown in Scheme 2.

The starting material **1a** was prepared from 2-aminobenzonitrile (anthranilonitrile) and benzoic anhydride in 84%.[6] The reaction of **1a**, allyl bromide (2.0 equiv), and indium powder (1.0 equiv) in refluxing THF for 60 min afforded 4-allyl-2-phenylquinazoline (**2a**) in 71% yield.[7] Compound **2a** was contaminated by a trace amount of 1-propenyl derivative **2a**′ (<5%) in the ^{1}H NMR of **2a** (vide infra). The reaction mechanism could be suggested as an indium-mediated Barbier-type allylation of nitrile to form the imine intermediate (**I**) and following dehydrative cyclization cascade. Encouraged by the successful results we prepared various amides **1b**–**g** and examined the reactions with allylindium reagents. The results are shown in Table 1.

The reactions with trimethylacetamide **1b** (entry 2) and trifluoroacetamide **1c** (entry 3) showed a similar reactivity, and quinazolines **2b** and **2c** were isolated in good yields. The reactions of chloro- and dimethoxy-derivatives, **1d**–**f**, also produced **2d**–**f** in good yields (71–75%) as shown in entries 4–6. Furo[2,3-*d*]pyrimidine derivative **2g** was obtained in 60% yield from furan derivative **1g** similarly (entry 7). The reaction of **1a** and methallyl bromide produced **2h** in good yield (entry 8). However, the reactions of **1a** and crotyl bromide or cinnamyl bromide showed sluggish reactivity as in our previous Letters.[3]

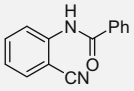
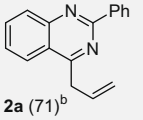
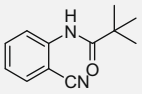
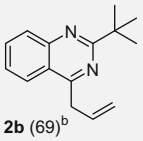
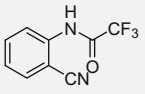
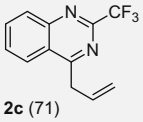
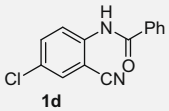
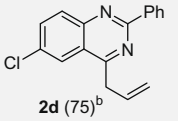
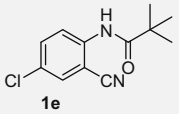
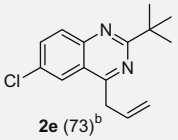
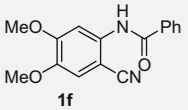
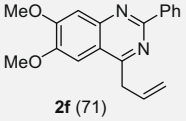
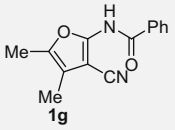
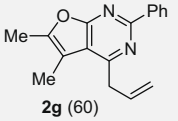
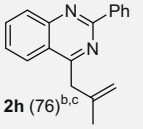
As mentioned above, the desired compounds were contaminated by a trace amount of 1-propenyl derivatives in some cases due to double bond isomerization. Allyl quinazoline **2a**, as an example, was converted into 1-propenyl derivative **2a**′ in 68% (*trans/cis* = 95:5) under the influence of DBU (0.3 equiv) in toluene at refluxing temperature for 15 h (Scheme 3).[7] The isomerization of double bond was slow and incomplete without DBU.

The intrinsically low reactivity of nitrile to allylindium reagents was observed in some substrates, as shown in Figure 1. The reaction of *ortho*-methyl derivatives **1h** and **1i** did not afford the corresponding quinazolines under the same reaction conditions. Only a trace amount of product was isolated in the reaction with **1h** (9%, as a 1:2 mixture of allyl and 1-propenyl isomers). Whereas the reaction of furan derivative **1g** produced quinazoline **2g** in a reasonable yield (60%), as shown in entry 7 in Table 1 (vide supra). Less steric hindrance around the nitrile of **1g** as compared to that of **1h** could be one of the reasons for the difference of reactivity between **1g** and **1h**. In addition, formamide and acetamide derivatives, **1j** and **1k**, did not produce the corresponding quinazolines, unexpectedly, although the reason is unclear at this stage.

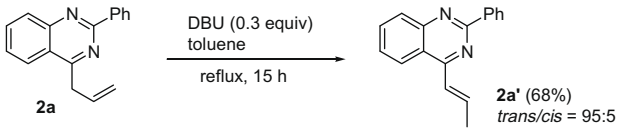
As the last entry, we prepared carbamate derivative **3** by the reaction of 2-aminobenzonitrile and ethyl chloroformate,[6] and examined the reaction with allylindium reagents (Scheme 4). As expected, the reaction of **3** produced quinazolone derivative **4** in good yield (88%) via the Barbier type double allylation.[3a,d] 2-Ethoxy-4-allylquinazoline was not formed at all.

In summary, a facile indium-mediated synthesis of allyl-substituted quinazolines has been disclosed starting from *N*-(2-cyanoaryl)amides. Further studies on the scope and limitations of the In-mediated allylation of nitrile are underway.

Table 1
Synthesis of quinazoline derivatives[a]

Entry	Nitrile	Product (%)
1	 **1a**	 **2a** (71)[b]
2	 **1b**	 **2b** (69)[b]
3	 **1c**	 **2c** (71)
4	 **1d**	 **2d** (75)[b]
5	 **1e**	 **2e** (73)[b]
6	 **1f**	 **2f** (71)
7	 **1g**	 **2g** (60)
8	**1a**	 **2h** (76)[b,c]

[a] Conditions: nitrile (0.5 mmol), allyl bromide (2.0 equiv), In (1.0 equiv), THF, reflux, 60 min.
[b] Contaminated by a trace amount of 1-propenyl derivative.
[c] Methallyl bromide (2.0 equiv) was used.



Scheme 3.

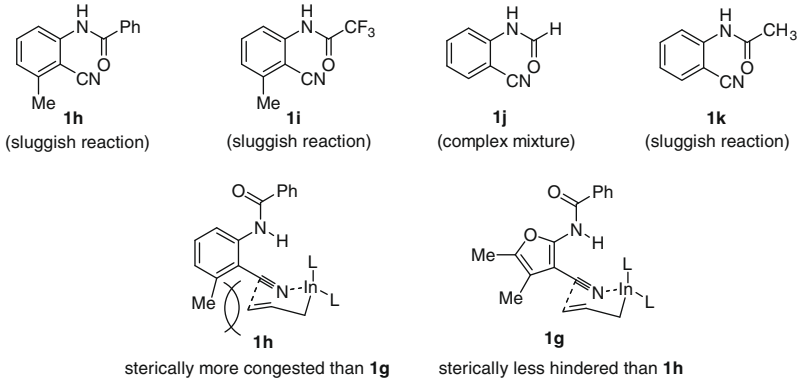
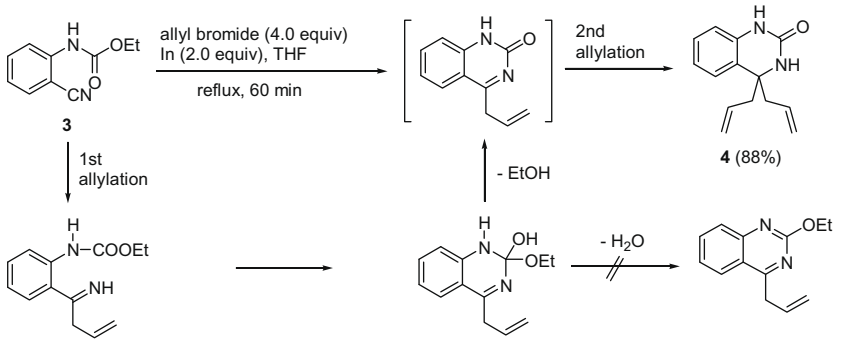


Figure 1.



Scheme 4.

Acknowledgments

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6. The starting materials **1a**–**i** and **1k** were prepared from the corresponding 2-aminoarylcarbonitriles and benzoic anhydride, pivalic anhydride, trifluoroacetic anhydride, or acetic anhydride. Compound **1j** was prepared with formic acid. Compound **3** was prepared from 2-aminobenzonitrile and ethyl chloroformate.
7. *Typical procedure for the synthesis of* **2a**: A stirred mixture of **1a** (111 mg, 0.5 mmol), allyl bromide (121 mg, 1.0 mmol), and indium (57 mg, 0.5 mmol) in THF (1.0 mL) was heated to reflux for 60 min. After the usual aqueous workup and column chromatographic purification process (hexanes/CH_2Cl_2/EtOAc, 15:1:1), we obtained compound **2a** (88 mg, 71%) as colorless oil. Other compounds were synthesized similarly, and the selected spectroscopic data of **2a–c**, **2g**, **2a′**, and **4** are as follows.
Compound **2a**: 71%; colorless oil; IR (film) 1568, 1548, 1491, 1344 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 4.09 (dt, J = 6.6 and 1.5 Hz, 2H), 5.18–5.28 (m, 2H), 6.22–6.35 (m, 1H), 7.47–7.55 (m, 4H), 7.81 (ddd, J = 8.4, 6.9 and 1.5 Hz, 1H), 8.04–8.08 (m, 2H), 8.63–8.66 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 39.51, 117.50, 122.36, 124.69, 126.82, 128.47, 128.56, 129.34, 130.38, 133.39, 134.16, 138.23, 150.81, 160.16, 168.89; ESIMS m/z 247 (M^++1). Anal. Calcd for $C_{17}H_{14}N_2$: C, 82.90; H, 5.73; N, 11.37. Found: C, 82.65; H, 5.94; N, 11.18.
Compound **2b**: 69%; colorless oil; IR (film) 2957, 1574, 1559, 1494, 1390 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.50 (s, 9H), 4.02 (dt, J = 6.6 and 1.5 Hz, 2H), 5.13–5.23 (m, 2H), 6.17–6.30 (m, 1H), 7.50 (ddd, J = 8.4, 6.9 and 1.2 Hz, 1H), 7.78 (ddd, J = 8.4, 6.9 and 1.5 Hz, 1H), 7.98 (dq, J = 8.4 and 0.6 Hz, 1H), 8.04 (dq, J = 8.4 and 0.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 29.57, 39.33, 39.47, 117.01, 121.59, 124.40, 126.27, 129.09, 132.76, 134.54, 150.23, 167.96, 172.78; ESIMS m/z 227

(M^++1). Anal. Calcd for $C_{15}H_{18}N_2$: C, 79.61; H, 8.02; N, 12.38. Found: C, 79.96; H, 8.37; N, 12.03.

Compound **2c**: 71%; white solid, mp 60–61 °C; IR (KBr) 1572, 1498, 1398 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 4.14 (dt, J = 6.6 and 1.5 Hz, 2H), 5.20–5.28 (m, 2H), 6.12–6.26 (m, 1H), 7.78 (ddd, J = 8.4, 6.9 and 1.2 Hz, 1H), 8.00 (ddd, J = 8.4, 7.2 and 1.5 Hz, 1H), 8.18 (d, J = 8.4 Hz, 1H), 8.23 (dt, J = 8.4 and 0.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 39.41, 118.34, 119.97 (q, J_{C-F} = 273.8 Hz), 123.95 (q, J_{C-F} = 0.75 Hz), 124.99, 129.56, 129.73 133.10, 134.73, 149.49 (q, J_{C-F} = 0.75 Hz), 152.13 (q, J_{C-F} = 35.8 Hz), 171.30; ESIMS m/z 239 (M^++1).

Compound **2g**: 60%; white solid, mp 120–121 °C; IR (KBr) 1597, 1560, 1416, 1405, 1381 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.27 (s, 3H), 2.40 (s, 3H), 3.86 (dt, J = 6.0 and 1.5 Hz, 2H), 5.08–5.19 (m, 2H), 6.13–6.27 (m, 1H), 7.42–7.50 (m, 3H), 8.50–8.54 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 9.99, 11.62, 39.53, 108.49, 116.51, 116.86, 128.08, 128.36, 129.97, 134.87, 137.84, 150.59, 158.80, 160.74, 166.74; ESIMS m/z 265 (M^++1). Anal. Calcd for $C_{17}H_{16}N_2O$: C, 77.25; H, 6.10; N, 10.60. Found: C, 77.44; H, 6.39; N, 10.33.

Compound **2a′**: 68%; pale yellow solid, mp 78–80 °C; IR (KBr) 1650, 1564, 1537, 1491, 1347 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.08 (dd, J = 6.9 and 1.8 Hz, 3H), 7.24 (dq, J = 15.0 and 1.5 Hz, 1H), 7.45–7.63 (m, 5H), 7.77 (ddd, J = 8.4, 6.9 and 1.5 Hz, 1H), 8.00–8.03 (m, 1H), 8.08–8.11 (m, 1H), 8.65–8.68 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 18.94, 120.97, 123.96, 124.73, 126.54, 128.39, 128.46, 129.05, 130.23, 133.21, 138.50, 138.91, 151.74, 159.93, 162.10.

Compound **4**: 88%; white solid, mp 137–138 °C; IR (KBr) 3230, 3214, 1688, 1666, 1606, 1456 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.47–2.65 (m, 4H), 5.05–5.10 (m, 4H), 5.64–5.78 (m, 2H), 6.06 (d, J = 1.5 Hz, 1H), 6.78–6.81 (m, 1H), 6.90–6.95 (m, 1H), 7.04–7.10 (m, 2H), 9.54 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 46.68, 59.95, 114.65, 119.60, 121.85, 122.46, 124.84, 128.04, 132.22, 136.55, 155.42; ESIMS m/z 229 (M^++1). Anal. Calcd for $C_{14}H_{16}N_2O$: C, 73.66; H, 7.06; N, 12.27. Found: C, 73.79; H, 7.34; N, 11.96.