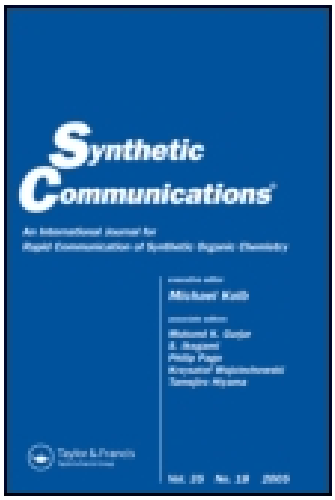

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PALLADIUM-CATALYSED CONVENIENT SYNTHESIS OF 3-METHYLENEISOINDOLIN-1-ONES

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PALLADIUM-CATALYSED CONVENIENT SYNTHESIS OF 3-METHYLENEISOINDOLIN-1-ONES

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ABSTRACT

2′-Bromoacetophenone reacts with an array of aliphatic primary amines under carbon monoxide pressure in the presence of a catalytic amount of a palladium catalyst to afford 3-methyleneisoindolin-1-ones in moderate yields.

Key Words: Carbon monoxide; Cyclisation; Isoindolinone; Palladium; Primary amine

Homogeneous palladium-catalysed cyclisation reaction has been used as convenient and efficient synthetic method for the construction of the structural core of many pharmacological and biological active compounds.[1–3] Thus, the formation of isoindolinones also has been attempted by the catalytic action of transition metals.[4] During the course of our continuing studies on homogeneous transition metal-catalysed

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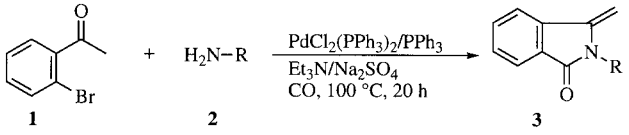
synthesis of *N*-heterocycles, we recently developed and reported a palladium-catalysed synthetic approach for the formation of a wide variety of isoindolinones.[5–12] It was suggested that all reactions proceed via intra- and intermolecular carbopalladative addition across carbon–nitrogen double bonds as an organometallic key step. Herein, we report another palladium-catalysed approach for the synthesis of isoindolinones from 2′-bromoacetophenone and an array of aliphatic primary amines via intramolecular carbopalladative addition across carbon–nitrogen double bond.

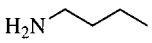
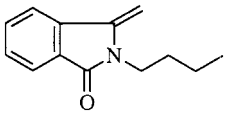
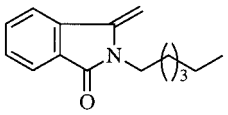
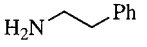
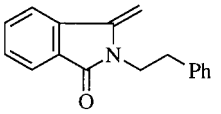
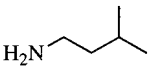
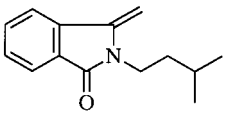
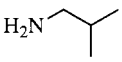
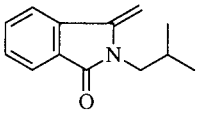
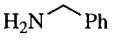
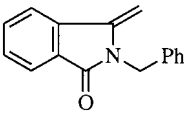
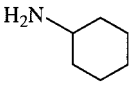
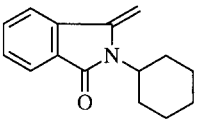
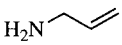
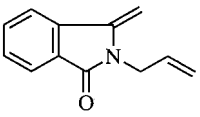
We accomplished the three components carbonylative cyclisation of 2′-bromoacetophenone (**1**) with an array of aliphatic primary amines (**2**) and carbon monoxide under a similar palladium catalyst system which we introduced for the synthesis of several isoindolinones (Eq. 1).[5–12] Treatment of **1** with two equivalents of **2** in anhydrous acetonitrile in the presence of *bis*(triphenylphosphine)palladium(II) chloride [$PdCl_2(PPh_3)_2$, 5 mol% based on **1**] and triphenylphosphine (10 mol% based on **1**) together with triethylamine and anhydrous sodium sulfate at 100°C for 20 h under carbon monoxide (20 atm) afforded 3-methyleneisoindolin-1-ones (**3**) in moderate yields. Buchwald et al reported that haloarenes are coupled with primary and secondary amines in the presence of a palladium catalyst to give aminoarenes.[13] However, no amination product was observed in the present reaction.



1 **2** **3** (1)

The present carbonylative cyclisation was applicable to various straight and branched aliphatic primary amines, and several representative results are summarised in Table 1. With aliphatic primary amines which has no substituent at α-position the reaction proceeded well toward **3** and the yield was not affected significantly by the structural nature of the amine chain (runs 1–6). In the reaction with cyclohexylamine, which bears α-substituent, the product yield was similar to that obtained with the amine described above (run 7). Even in the reaction with allylamine, which has olefinic site to be activated under Heck arylation conditions,[1–3] the corresponding carbonylative cyclised product **3** was also obtained in a similar yield (run 8). However, with aniline the reaction was not satisfactory under the employed reaction conditions.

Table 1. Palladium-Catalysed Synthesis of 3-Methyleneisoindolin-1-ones[a]

Run	Primary Amine **2**	Product **3**	Isolated Yield (%)
1			42
2			51
3			46
4			40
5			44
6			45
7			42
8			35

[a]Reaction conditions: **1** (1 mmol), **2** (2 mmol), $PdCl_2(PPh_3)_2$ (0.05 mmol), PPh_3 (0.1 mmol), Na_2SO_4 (10 mmol), Et_3N (5 mmol), acetonitrile (10 ml), 100°C, 20 h, under CO (20 atm).

In summary, we have demonstrated that 3-methyleneisoindolin-1-ones can be conveniently synthesized from 2′-bromoacetophenone and aliphatic primary amines in the presence of a palladium catalyst under carbon monoxide pressure via an intramolecular carbopalladation across carbon–nitrogen double bond.

EXPERIMENTAL

General procedure for palladium-catalysed synthesis of 3-methylene-isoindol-1-ones: 2′-bromoacetophenone (0.199 g, 1 mmol), primary amine (2 mmol), $PdCl_2(PPh_3)_2$ (0.035 g, 0.05 mmol), PPh_3 (0.026 g, 0.1 mmol), Et_3N (0.506 g, 5 mmol), anhydrous Na_2SO_4 (1.420 g, 10 mmol), and MeCN (10 ml) were placed in a 50 ml stainless autoclave and allowed to react under carbon monoxide (20 atm) at 100°C for 20 h. The reaction mixture was filtered through a short silica gel column (ethyl acetate), washed with brine and dried over Na_2SO_4. Removal of the solvent left on oil which was separated by column chromatography (ethyl acetate/hexane = 1/10) to give the corresponding product.

2-Butyl-3-methylene-2,3-dihydroisoindol-1-one: pale yellow oil; IR (neat) 1706 (C=O) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.96 (t, $J = 7.3$ Hz, 3H), 1.35–1.44 (m, 2H), 1.63–1.70 (m, 2H), 3.78 (t, $J = 7.3$ Hz, 2H), 4.86 (d, $J = 2.5$ Hz, 1H, C=CH_EH$_Z$), 5.19 (d, $J = 2.5$ Hz, 1H, C=CH$_E$$H_Z$), 7.48 (t, $J = 7.5$ Hz, 1H), 7.56 (dt, $J = 7.5$ and 1.0 Hz, 1H), 7.68 (d, $J = 7.5$ Hz, 1H), 7.82 (d, $J = 7.5$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.8, 20.2, 30.4, 39.2, 88.5, 119.8, 123.0, 129.4, 129.5, 131.7, 136.3, 141.9, 167.1 (C=O); M/S m/z (relative intensity) 201 (M^+, 39), 186 (20), 159 (100), 146 (31), 130 (40), 103 (37), 77 (33). Anal. calcd for $C_{13}H_{15}NO$: C, 77.58; H, 7.51; N, 6.96. Found: C, 77.29; H, 7.78; N, 7.06.

2-Hexyl-3-methylene-2,3-dihydroisoindol-1-one: pale yellow oil; IR (neat) 1710 (C=O) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.88 (t, $J = 7.0$ Hz, 3H), 1.24–1.39 (m, 6H), 1.63–1.73 (m, 2H), 3.77 (t, $J = 7.0$ Hz, 2H), 4.85 (d, $J = 2.0$ Hz, 1H, C=CH_EH$_Z$), 5.19 (d, $J = 2.0$ Hz, 1H, C=CH$_E$$H_Z$), 7.49 (dt, $J = 7.5$ and 1.0 Hz, 1H), 7.56 (dt, $J = 7.5$ and 1.0 Hz, 1H), 7.68 (d, $J = 7.5$ Hz, 1H), 7.82 (d, $J = 7.5$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0, 22.6, 26.7, 28.3, 31.5, 39.5, 88.5, 119.8, 123.0, 129.4, 129.5, 131.7, 136.3, 141.9, 167.1 (C=O); M/S m/z (relative intensity) 229 (M^+, 33), 172 (12), 159 (100), 146 (39), 130 (42), 103 (47), 77 (43). Anal. calcd for $C_{15}H_{19}NO$: C, 78.56; H, 8.35; N, 6.11. Found: C, 78.31; H, 8.49; N, 6.20.

3-Methylene-2-phenethyl-2,3-dihydroisoindol-1-one: pale yellow oil; IR (neat) 1708 (C=O) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.97 (t, $J = 7.5$ Hz,

2H), 3.99 (t, $J = 7.5$ Hz, 2H), 4.82 (d, $J = 2.0$ Hz, 1H, C=CH_EH$_Z$), 5.18 (d, $J = 2.0$ Hz, 1H, C=CH$_E$$H_Z$), 7.22–7.31 (m, 5H), 7.49 (dt, $J = 7.5$ and 1.0 Hz, 1H), 7.57 (dt, $J = 7.5$ and 1.0 Hz, 1H), 7.68 (d, $J = 7.5$ Hz, 1H), 7.82 (d, $J = 7.5$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 34.6, 41.0, 88.6, 119.8, 123.1, 126.6, 128.6, 128.8, 129.3, 129.5, 131.9, 136.3, 138.6, 141.7, 166.9. (C=O); M/S m/z (relative intensity) 249 (M^+, 51), 158 (100), 129 (14), 104 (36), 77 (30).

2-Isoamyl-3-methylene-2,3-dihydroisoindol-1-one: pale yellow oil; IR (neat) 1715 (C=O) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.98 (t, $J = 6.4$ Hz, 6H), 1.53–1.59 (m, 2H), 1.63–1.68 (m, 1H), 3.79 (t, $J = 7.6$ Hz, 2H), 4.85 (d, $J = 2.0$ Hz, 1H, C=CH_EH$_Z$), 5.19 (d, $J = 2.0$ Hz, 1H, C=CH$_E$$H_Z$), 7.48 (t, $J = 7.2$ Hz, 1H), 7.56 (dt, $J = 7.2$ and 0.8 Hz, 1H), 7.68 (d, $J = 7.6$ Hz, 1H), 7.81 (d, $J = 7.6$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.9, 26.5, 37.4, 38.2, 88.9, 120.1, 123.4, 129.8, 132.1, 134.2, 136.7, 142.2, 167.4 (C=O); M/S m/z (relative intensity) 215 (M^+, 17), 172 (8), 159 (100), 146 (24), 130 (32), 103 (28), 77 (26). Anal. calcd for $C_{14}H_{17}NO$: C, 78.10; H, 7.96; N, 6.51. Found: C, 77.86; H, 8.09; N, 6.60.

2-Isobutyl-3-methylene-2,3-dihydroisoindol-1-one: pale yellow oil; IR (neat) 1713 (C=O) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.96 (d, $J = 7.0$ Hz, 6H), 2.09–2.22 (m, 1H), 3.60 (d, $J = 7.5$ Hz, 2H), 4.85 (d, $J = 2.0$ Hz, 1H, C=CH_EH$_Z$), 5.20 (d, $J = 2.0$ Hz, 1H, C=CH$_E$$H_Z$), 7.49 (dt, $J = 7.5$ and 1.0 Hz, 1H), 7.57 (dt, $J = 7.5$ and 1.0 Hz, 1H), 7.68 (d, $J = 7.5$ Hz, 1H), 7.83 (d, $J = 7.5$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.3, 27.8, 46.9, 88.8, 119.7, 123.1, 129.3, 129.4, 131.8, 136.3, 142.4, 167.5 (C=O); M/S m/z (relative intensity) 201 (M^+, 53), 186 (8), 158 (100), 146 (62), 130 (21), 103 (44), 89 (14), 77 (35). Anal. calcd for $C_{13}H_{15}NO$: C, 77.58; H, 7.51; N, 6.96. Found: C, 77.20; H, 7.68; N, 7.01.

2-Benzyl-3-methylene-2,3-dihydroisoindol-1-one: pale yellow oil; IR (neat) 1706 (C=O) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.79 (d, $J = 2.0$ Hz, 1H, C=CH_EH$_Z$), 5.01 (s, 2H), 5.15 (d, $J = 2.0$ Hz, 1H, C=CH$_E$$H_Z$), 7.24–7.31 (m, 5H), 7.52 (dt, $J = 7.5$ and 1.0 Hz, 1H), 7.59 (dt, $J = 7.5$ and 1.0 Hz, 1H), 7.67 (d, $J = 7.5$ Hz, 1H), 7.89 (d, $J = 7.5$ Hz, 1H), ^{13}C NMR (100 MHz, $CDCl_3$) δ 43.2, 90.0, 119.9, 123.4, 127.1, 127.4, 128.7, 129.2, 129.5, 132.1, 136.4, 136.8, 141.6, 167.3 (C=O); M/S m/z (relative intensity) 235 (M^+, 46), 104 (29), 91 (100), 77 (29).

2-Cyclohexyl-3-methylene-2,3-dihydroisoindol-1-one: white solid; m.p. 118–120°C; IR (KBr) 1705 (C=O) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.21–1.46 (m, 4H), 1.71–1.92 (m, 4H), 2.17–2.30 (m, 2H), 4.09 (t, $J = 12.1$ Hz, 1H), 5.00 (d, $J = 2.0$ Hz, 1H, C=CH_EH$_Z$), 5.22 (d, $J = 2.0$ Hz, 1H, C=CH$_E$$H_Z$), 7.47 (dt, $J = 7.5$ and 1.0 Hz, 1H), 7.55 (dt, $J = 7.5$ and 1.0 Hz, 1H), 7.65 (d, $J = 7.5$ Hz, 1H), 7.79 (d, $J = 7.5$ Hz, 1H); ^{13}C NMR

(100 MHz, $CDCl_3$) δ 25.5, 26.3, 29.8, 52.4, 89.4, 119.5, 122.9, 129.3, 129.4, 131.6, 136.6, 141.4, 167.3 (C=O); M/S *m*/*z* (relative intensity) 227 (M^+, 4), 146 (17), 132 (100), 104 (13), 77 (17). Anal. calcd for $C_{15}H_{17}NO$: C, 79.26; H, 7.54; N, 6.16. Found: C, 78.95; H, 7.78; N, 6.30.

2-Allyl-3-methylene-2,3-dihydroisoindol-1-one: pale yellow oil; IR (neat) 1712 (C=O) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.42–4.44 (m, 2H), 4.86 (d, $J = 2.5$ Hz, 1H, $C{=}CH_EH_Z$), 5.15–5.20 (m, 2H), 5.19 (d, $J = 2.5$ Hz, 1H, $C{=}CH_EH_Z$), 5.81–5.91 (m, 1H), 7.50 (dt, $J = 7.5$ and 1.0 Hz, 1H), 7.58 (dt, $J = 7.5$ and 1.0 Hz, 1H), 7.69 (d, $J = 7.5$ Hz, 1H), 7.85 (d, $J = 7.5$ Hz, 1H), ^{13}C NMR (100 MHz, $CDCl_3$) δ 41.8, 89.5, 116.8, 119.8, 123.2, 129.3, 129.5, 132.0, 132.4, 136.4, 141.6, 166.8 (C=O); M/S *m*/*z* (relative intensity) 185 (M^+, 100), 156 (46), 129 (30), 115 (26), 102 (34), 77 (36). Anal. calcd for $C_{12}H_{11}NO$: C, 77.81; H, 5.99; N, 7.56. Found: C, 77.50; H, 6.11; N, 7.62.

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