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Practical and high stereoselective synthesis of 3-(arylmethylene)isoindolin-1-ones from 2-formylbenzoic acid

Miguel Angel Reyes-González, Angel Zamudio-Medina, Mario Ordóñez *

Centro de Investigaciones Químicas - Universidad Autónoma del Estado de Morelos Av. Universidad 1001, 62209 Cuernavaca, Morelos, Mexico

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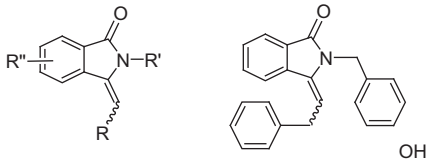
ABSTRACT

Practical and high stereoselective synthesis of 3-(arylmethylene)isoindolin-1-ones is reported. The synthetic method involves the preparation of dimethyl isoindolin-1-one-3-yl-phosphonates by a 'one-pot' three-component reaction of 2-formylbenzoic acid with 4-methoxybenzylamine or aminoacetaldehyde dimethyl acetal and dimethyl phosphite under solvent and catalyst free-conditions, followed by a Horner reaction with several aryl aldehydes.

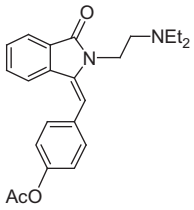
Introduction

Substituted 3-methyleneisoindolin-1-ones type **1** are present in a great variety of natural products and are also known to possess a broad range of biological activities. For example, AKS 186 was found to inhibit vasoconstriction induced by thromboxane A2 analog,[1] whereas the derivative **2** has been claimed to exhibit local anesthetic activity superior to that of procaine,[2] and the compound **3** that presented sedative activity.[3] Additionally, the 3-(arylmethylene)isoindolin-1-ones are useful intermediates in the synthesis of aristolactams,[4] lennoxamine,[5] narceine imide,[6] aristocularines,[7] fumaridine,[8] fumaramidine,[9] and in the synthesis of other heterocyclic compounds.[10]



1

AKS 186



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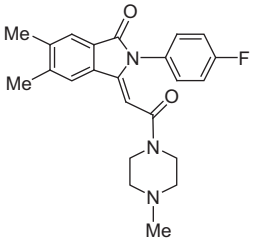

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Due to the utility of substituted 3-methyleneisoindolin-1-ones as key synthetic intermediates in conjunction with their biological activity, several synthetic protocols for their synthesis have been developed in the last years, including the heteroannulation of *o*-(1-alkynyl)benzamides induced by treatment with a base[11] or a palladium(II) catalyst, Pd-catalyzed heteroannulations involving 2-iodobenzamides and terminal alkynes,[12] palladium(0)-catalyzed three-component reaction of 2-bromoacetophenone and a variety of primary amines under carbon monoxide pressure or titanium-isocyanate complex and carbon monoxide,[13] palladium-catalyzed carbonylation-hydroamination reaction of 1-halo-2-alkynylbenzene with amines,[14] 'one-pot' regioselective elimination cyclization-Suzuki approach[15] or Sonogashira reaction of 2-(2,2-dihalovinyl)-benzamides,[16] reaction of phthalic anhydride with phenylacetic acid and sodium acetate and subsequent treatment with the appropriate amine,[17] CuI/L-proline catalyzed coupling of 2-bromobenzamides and terminal alkynes,[18] the Heck–Suzuki–Miyaura domino reactions involving ynamides,[19] iodocyclization of (*E*)-2-alk-1-enyl-*N*-benzylbenzamides,[20] reaction of isoindolin-1-ones with aldehydes,[21] photodecarboxylative benzylations of phthalimide,[22] and the Horner condensation of 3-(diphenyl-phosphinoyl)isoindolin-1-ones with aldehydes.[23] However, in spite of their potential utility, these procedures typically suffer from one or more disadvantages such as the use of expensive reagents or poor regioselectivity in the cases of unsymmetrical substrates, therefore is desirable to develop a more efficient, simple, and milder protocol.

During our program aimed at the convenient synthesis of cyclic α-aminophosphonates,[24] herein, we report a new synthetic strategy for the high stereoselective synthesis of 3-(arylmethylene)-isoindolin-1-ones *N*-substituted **7** and **8** by the Horner reaction of

* Corresponding author. Tel./fax: +52 777 329 7997
E-mail address: palacios@uaem.mx (M. Ordóñez).

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several aromatic aldehydes and dimethyl isoindolin-1-one-3-yl-phosphonates easily available from an 'one-pot' three-component reaction of 2-formylbenzoic acid with the appropriate amines and dimethyl.

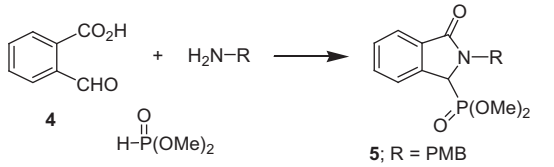
Results and discussion

For the synthesis of the target compounds **7** and **8** initially we decided to explore the use of 2-formylbenzoic acid **4** as starting material taking into account its recent application in the synthesis of *N*-substituted isoindolin-1-ones reported by us.[25,26] Thus, the 'one-pot' three-component reaction of 2-formylbenzoic acid **4** with 4-methoxybenzylamine and dimethyl phosphite under microwave irradiation (55 °C/180 W, 10 min.) and solvent free-conditions, afforded the corresponding dimethyl 2-(4-methoxybenzyl)isoindolin-1-one-3-yl-phosphonate **5** in 30% yield (Table 1, entry 1). In order to establish the optimal conditions, the reaction was carried out using methanol as solvent and reacted at different temperatures and times, found that 55 °C/180 W, 10 min. were the best conditions, obtaining phosphonate **5** in 71% yield (Table 1, entry 2).[27]

Although this synthetic procedure proved to be a suitable methodology to obtain the phosphonate **5**, the low yield prompted us to explore a new method for its preparation in a high yield manner. With this purpose in mind, and looking for alternative protocols under mild and environmentally friendly reaction conditions, we decided to explore the 'one-pot' three-component reaction of 2-formylbenzoic acid **4** with 4-methoxybenzylamine and dimethyl phosphite at 50 °C under solvent and catalyst free-conditions, obtaining the expected isoindolin-1-one-3-phosphonate **5** in 87% yield (Table 1, entry 3).[28] In a similar way, the 'one-pot' three-component reaction of 2-formylbenzoic acid **4** with aminoacetaldehyde dimethyl acetal and dimethyl phosphite under microwave irradiation gave the corresponding isoindolin-1-one-3-phosphonate **6** in 19 and 50% yield (Table 1, entries 4 and 5). Finally, the same reaction at 50 °C under solvent and catalyst free-conditions provided the isoindolin-1-one-3-phosphonate **6** in 91% yield (Table 1, entry 6).[29]

With the isoindolin-1-one-3-phosphonates **5** and **6** in hand, in the next step we turned our attention to the Horner reaction with several aromatic aldehydes to obtain the desired 3-(aryl-methylene)isoindolin-1-ones **7a–f** and **8a–d**. In this context, the treatment of the isoindolin-1-one-3-phosphonate **5** with *n*-BuLi in THF a −78 °C followed by the addition of benzaldehyde afforded the corresponding 3-(benzylidene)isoindolin-1-one **7a** in quantitative yield and with a selectivity *E*:*Z* of 90:10 (Table 2, entry 1).[30]

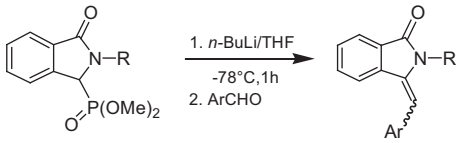
Table 1
Synthesis of isoindolin-1-one-3-phosphonates **5**, **6**



Entry	R	Conditions	Yield (%)
1	4-$MeOC_6H_4CH_2$	55 °C, 10 min.[a]	30
2	4-$MeOC_6H_4CH_2$	MeOH, 55 °C, 10 min.[a]	78
3	4-$MeOC_6H_4CH_2$	50 °C, 5 h.[b]	87
4	$(MeO)_2CHCH_2$	55 °C, 10 min.[a]	19
5	$(MeO)_2CHCH_2$	MeOH, 55 °C, 10 min.[a]	50
6	$(MeO)_2CHCH_2$	50 °C, 5 h.[b]	91

[a] The reaction was carried out at 180 watts.
[b] The reaction was carried under conventional heating.

Table 2
Synthesis of 3-arylmethyleneisoindolin-1-ones **7**, **8**



5; R = PMB
6; R = $CH_2CH(OMe)_2$

7a-f; R = PMB
8a-d; R = $CH_2CH(OMe)_2$

Entry	Ar	Yield (%)	*E*:*Z*
1	C_6H_5	98	90:10
2	4-ClC_6H_4	97	83:17
3	2-BrC_6H_4	91	75:25
4	4-$MeOC_6H_4$	85	91:09
5	2-Br,5-$MeOC_6H_3$	75	63:37
6	3,4-$(MeO)_2C_6H_3$	91	89:11
7	C_6H_5	95	85:15
8	4-ClC_6H_4	87	87:13
9	4-$MeOC_6H_4$	82	>98:02
10	3,4-$(MeO)_2C_6H_3$	86	92:08

The *E*-form predominantly was assigned from their ^{1}H NMR spectra with the help of NOE experiment and confirmed by analogy with the results reported in the literature.[11b,14]

After optimization of experimental conditions of the Horner reaction of isoindolin-1-one-3-phosphonate **5** with benzaldehyde, we extended this protocol with other aromatic aldehydes, obtaining the corresponding 3-(arylmethylene)isoindolin-1-ones **7b–f** in excellent yields and with a selectivity *E*:*Z* from 63:37 to 91:09 (Table 2, entries 2–6).

Identically, the Horner reaction of isoindolin-1-one-3-phosphonate **6** with several aromatic aldehydes using *n*-BuLi as base in THF a −78 °C gave the corresponding 3-(arylmethylene)-isoindolin-1-ones **8a–d** in 82–95% yield and with an excellent selectivity *E*:*Z* 85:15 to >98:02 (Table 2, entries 7–10).

In summary, we have reported an efficient and high stereoselective access to (*E*)-3-(arylmethylene)isoindolin-1-ones by using the Horner reaction of aromatic aldehydes and dimethyl isoindolin-1-one-3-yl-phosphonates easily available in large scale in only one step under solvent and catalyst free-conditions. This process, which further expands the synthetic utility of (*E*)-3-(arylmethylene)isoindolin-1-ones, will be applied to the preparation of natural and/or biologically active compounds.

Acknowledgments

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27. Synthesis of dimethyl 2-(4-methoxybenzyl)isoindolin-1-one-3-yl-phosphonate **5** under microwave irradiation: 4-Methoxybenzyl-amine (1.0 g, 7.3 mmol) was added to 2-formylbenzoic acid (1.0 g, 6.7 mmol) in methanol 10 mL, was irradiated under CEM microwave at 55 °C and 180 W for 5 min. After this time, dimethyl phosphite (879 mg, 8 mmol) was added and the reaction mixture was irradiated again at 55 °C, 180 W for 5 min. The crude product was purified by flash column chromatography (AcOEt/hexanes = 1:1), obtaining (1.9 g, 78%).
28. Dimethyl 2-(4-methoxybenzyl)isoindolin-1-one-3-yl-phosphonate **5**. 4-Methoxybenzylamine (910 mg, 6.6 mmol) was added to 2–formylbenzoic acid (1.0 g, 6.7 mmol) and the mixture was stirred at room temperature for 15 min prior to the addition of dimethyl phosphite (879 mg, 8 mmol). The reaction mixture was stirred at 50 °C for 5 h, and the crude product was purified by flash column chromatography (AcOEt/hexanes = 1:1), obtaining (2.1 g, 87%) as a white solid; mp 113–116 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.58 (d, J = 10.8 Hz, 3H, $(CH_3O)_2P$), 3.75 (d, J = 10.8 Hz, 3H, $(CH_3O)_2P$), 3.77 (s, 3H, CH_3O), 4.48 (system AB, J = 14.8 Hz, 1H, CH_2N), 4.68 (d, J = 13.6 Hz, 1H, $CHP(OCH_3)_2$), 5.51 (system AB, J = 14.8 Hz, 1H, CH_2N), 6.80–6.84 (m, 2H, H_{arom}), 7.23–7.26 (m, 2H, H_{arom}), 7.50–7.58 (m, 2H, H_{arom}), 7.67–7.69 (m, 1H, H_{arom}), 7.90–7.92 (m, 1H, H_{arom}). ^{13}C NMR (100 MHz, $CDCl_3$): δ 44.6, 53.8 (d, J = 7.6 Hz, $(CH_3O)_2P$), 55.1 (d, J = 7.6 Hz, $(CH_3O)_2P$), 55.2, 55.7 (d, J = 155.0 Hz, $CHP(OMe)_2$), 114.2, 124.2, 124.5, 129.1, 129.9, 130.5, 131.8, 132.1, 138.5, 159.3, 168. (C=O). ^{31}P NMR (81 MHz, $CDCl_3$): δ 21.45. HRMS [CI$^+$]: Anal. Calcd for $C_{18}H_{21}NO_5P$: 362.1079. Found: 362.1141.
29. Dimethyl 2-(2,2-dimethoxyethyl)isoindolin-1-one-3-ylphosphonate **6**. Aminoacetaldehyde dimethyl acetal (1.68 g, 16 mmol) was added to 2-formylbenzoic acid (2.0 g, 13.3 mmol) and the mixture was stirred at room temperature for 15 min prior to the addition of dimethyl phosphite (1.76 g, 16 mmol). The reaction mixture was stirred at 50 °C for 5 h, and the crude product was purified by flash column chromatography (AcOEt/hexanes = 3:1), obtaining (3.94 g, 91%) as a white solid; mp 63–65 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.37 (s, 3H, CH_3O), 3.42 (s, 3H, CH_3O), 3.52 (d, J = 11.2 Hz, 3H, $(CH_3O)_2P$), 3.68 (dd, J = 6.4, 6.8 Hz, 1H, CH_2N), 3.78 (d, J = 10.8 Hz, 3H, $(CH_3O)_2P$), 4.32 (dd, J = 3.6, 3.6 Hz, 1H, NCH_2), 4.55 (dd, J = 6.8, 3.6 Hz, 1H, $CH(OCH_3)_2$), 5.24 (d, J = 13.2 Hz, 1H, $CHP(OMe)_2$), 7.51–7.54 (m, 1H, H_{arom}), 7.58–7.62 (m, 1H, H_{arom}), 7.77–7.79 (m, 1H, H_{arom}), 7.88–7.90 (m, 1H, H_{arom}). ^{13}C NMR (100 MHz, $CDCl_3$): δ 42.8, 53.7 (d, J = 7.6 Hz, $(CH_3O)_2P$), 53.8 (d, J = 7.6 Hz, $(CH_3O)_2P$), 54.1, 54.9, 57.9 (d, J = 153.2 Hz, $CHP(OMe)_2$), 102.9, 124.0, 124.6, 128.8, 131.9, 139.0, 139.1, 169.1 (C=O). ^{31}P NMR (81 MHz, $CDCl_3$): δ 21.71. HRMS [CI$^+$]: Anal. Calcd for $C_{14}H_{21}NO_6P$: 330.1028. Found: 330.1123.
30. Typical procedure for the synthesis of 3-(arylmethylene)-isoindolin-1-ones **7a–f** and **8a–d**. A solution of *n*-BuLi (1.0 equiv) was added dropwise to a stirred solution of the isoindolin-1-one-3-yl-phosphonates **5** or **6** (1.0 equiv) in THF (15 mL) at −78 °C under nitrogen. The solution was stirred for 15 min at this temperature and after this time the corresponding aryl aldehyde (1.0 equiv) was added. The reaction mixture was stirred at −78 °C for 15 min and then warmed to room temperature over a period of 1 h. The reaction mixture was quenched by the addition of saturated solution of NH_4Cl and extracted with AcOEt (2 × 20 mL). The organic extracts were dried over Na_2SO_4, filtered and evaporated in vacuo. The crude product was analyzed by ^{1}H NMR and then purified by flash column chromatography (AcOEt/hexanes = 2:1), obtaining the corresponding 3-(arylmethylene)isoindolin-1-ones. Spectroscopic data for **7a**,[11b,14] **7c**,[11b] **7d**,[4b] and **8d**[5a] were identical with those reported in the literature. **7b**; Yield: 303 mg, 97% (*E*/*Z* isomers ratio 83:17) as a white solid; mp 123–126 °C. (*E*)-isomer; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.77 (s, 3H, CH_3O), 5.03 (s, 2H, CH_2N), 6.38 (s, 1H, CH), 6.84–6.87 (m, 2H, H_{arom}), 7.21–7.36 (m, 8H, H_{arom}), 7.42–7.46 (m, 1H, H_{arom}), 7.88–7.90 (m, 1H, H_{arom}). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 42.8, 55.4, 110.1, 114.3, 123.2, 123.6, 128.5, 128.9, 129.6 (2C), 130.3, 131.0, 131.9, 133.7, 133.8, 135.0, 136.6, 159.0, 167.0 (C=O). HRMS [CI$^+$]: Anal. Calcd for $C_{23}H_{19}NO_2Cl$: 376.1026. Found: 376.1119. **7e**; Yield: 180 mg, 75% (*E*/*Z* isomers ratio 63:37) as a yellow solid; mp 150–153 °C. (*E*)-isomer; ^{1}H NMR (400 MHz, $CDCl_3$ δ: 3.73 (s, 3H, CH_3O), 3.76 (s, 3H, CH_3O), 5.06 (s, 2H, CH_2N), 6.33 (s, 1H, CH), 6.49–6.52 (m, 1H, H_{arom}), 6.61–6.63 (m, 1H, H_{arom}), 6.84–6.86 (m, 2H, H_{arom}), 6.99–7.0 (m, 1H, H_{arom}), 7.20–7.31 (m, 4H, H_{arom}), 7.49–7.52 (m, 1H, H_{arom}), 7.88–7.92 (m, 1H, H_{arom}). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 42.9, 55.4, 55.7, 110.8, 113.8, 114.3, 115.8, 119.8, 123.3, 123.6, 127.6, 128.7, 129.6, 130.5, 131.9, 133.6, 135.0, 136.4, 136.7, 158.8, 159.1, 166.8. HRMS [CI$^+$]: Anal. Calcd for $C_{24}H_{21}NO_3Br$: 450.0627. Found: 450.0719. **7f**. Yield: 300 mg, 91% (*E*/*Z* isomers ratio 89:11) as a white solid; mp 181–185 °C. (*E*)-isomer; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.77 (s, 3H, CH_3O), 3.83 (s, 3H, CH_3O), 3.92 (s, 3H, CH_3O), 5.04 (s, 2H, CH_2N), 6.46 (s, 1H, CH), 6.84–6.92 (m, 5H, H_{arom}), 7.23–7.45 (m, 5H, H_{arom}), 7.88–7.90 (m, 1H, H_{arom}). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 42.8, 55.4, 56.1 (2C), 111.3, 111.6, 112.7, 114.2, 122.3, 123.4, 123.5, 127.7, 128.5, 129.2, 129.3, 130.3, 131.6, 135.3, 135.8, 148.9, 149.0, 159.0, 166.8 (C=O). HRMS [CI$^+$]: Anal. Calcd for $C_{25}H_{24}NO_4$: 402.1627. Found: 402.1706. **8a**; Yield: 267 mg, 95% (*E*/*Z* isomers ratio 85:15) as a green oil. (*E*)-isomer; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.45 (s, 6H, CH_3O), 4.03 (d, J = 5.2 Hz, 1H, CH_2N), 4.72 (t, J = 5.2 Hz, 1H, $CH(OCH_3)_2$), 6.74 (s, 1H, CH), 7.28–7.45 (m, 8H, H_{arom}), 7.83–7.87 (m, 1H, H_{arom}). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 42.3, 54.7, 102.6, 111.4, 123.4, 127.8, 127.9, 128.9 (2C), 129.3, 129.8, 131.7, 134.1, 135.5, 136.8, 167.0 (C=O). HRMS [CI$^+$]: Anal. Calcd for $C_{19}H_{20}NO_3$: 310.1365. Found: 310.1448. **8b**; Yield: 272 mg, 87% (*E*/*Z* isomers ratio 87:13) as a green oil. (*E*)-isomer; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.45 (s, 6H, CH_3O), 4.0 (d, J = 5.2 Hz, 2H, CH_2N), 4.69 (t, J = 5.2 Hz, 1H, $CH(OCH_3)_2$), 6.66 (s, 1H, CH), 7.27–7.45 (m, 6H, H_{arom}), 7.70–7.75 (m, 1H, H_{arom}), 7.83–7.87 (m, 1H, H_{arom}). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 42.3, 54.8, 102.7, 109.9, 123.2, 123.5, 129.1, 129.6, 130.2, 131.1, 131.8, 133.9, 134.0, 135.2, 137.2, 167.0 (C=O). HRMS [CI$^+$]: Anal. Calcd for $C_{19}H_{19}NO_3Cl$: 344.0975. Found: 344.1060. **8c**; Yield: 252 mg, 82% (*E*/*Z* isomers ratio >98:2) as a green oil. (*E*)-isomer; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.44 (s, 6H, CH_3O), 3.87 (s, 3H, CH_3O), 4.03 (d, J = 5.2 Hz, 2H, CH_2N), 4.71 (t, J = 5.2 Hz, 1H, $CH(OCH_3)_2$), 6.69 (s, 1H, CH), 6.95–6.98 (m, 2H, H_{arom}), 7.28–7.42 (m, 5H, H_{arom}), 7.83–7.86 (m, 1H, H_{arom}). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 42.3, 54.7, 55.5, 102.7, 111.4, 114.3, 123.2, 123.3, 127.7, 129.1, 130.2, 131.0, 131.2, 131.7, 135.5, 136.2, 159.6 (C=O). HRMS [CI$^+$]: Anal. Calcd for $C_{20}H_{22}NO_4$: 340.1471. Found: 340.1561.