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A concise synthesis of *ortho*-substituted aryl-acrylamides—potent activators of soluble guanylyl cyclase

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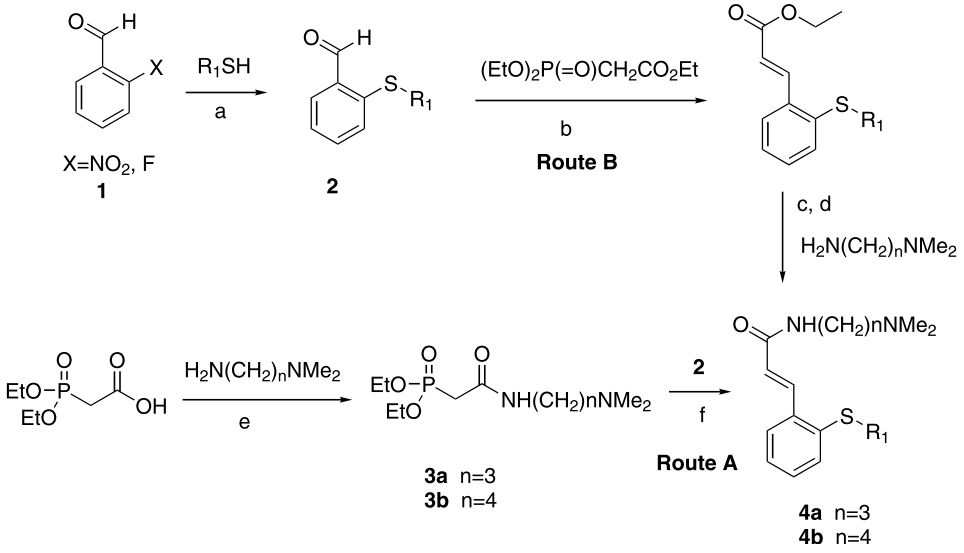
Abstract—Horner–Emmons reaction of phosphonate amides with aldehydes leads to generation of *o*-substituted aryl-acrylamides. These compounds have been shown to be useful to quickly establish structure–activity relationships (SAR) for soluble guanylyl cyclase (sGC) activator drug discovery.

Nitric oxide (NO) plays an important role in a number of physiological processes, acting as an inter- and intracellular mediator. NO stimulates soluble guanylyl cyclase (sGC) to convert guanosine 5′-trisphosphate (GTP) to cyclic guanosine 3′,5′-monophosphate (cGMP) which results in smooth muscle relaxation, inhibition of platelet aggregation and neurotransmission.[1,2] The increase of the cGMP level reduces Ca^{2+} concentration, resulting in cavernosal smooth muscle relaxation and, ultimately, in penile erection. Therefore, activation of sGC provides an alternate treatment of sexual dysfuction.[3] A-350619 has been reported as an novel sGC activator, which can activate sGC in the presence or absence of NO.[4,5]



Scheme 1. *Reagents and conditions*: (a) K_2CO_3, DMF, 50–80°C, 12–16 h (80–100%); (b) NaH, THF, rt, 8–16 h (90–98%); (c) NaOH, EtOH–dioxane, rt, 24 h (95–99%); (d) EDCI, HOBt, CH_3Cl or CH_2Cl_2, rt, 6–8 h (26–50%); (e) *N*-cyclohexylcarbodimide, *N*′-methyl polystyrene (DCC resin), HOBT, DMA/CH_2Cl_2, rt, 18 h, tris-(2-aminoethyl)-amine polystyrene (PS-trisamine); (f) LDA, THF, rt, 1 h (44–82% for two steps).

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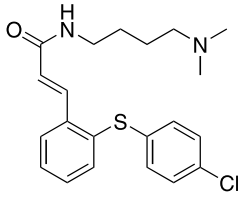


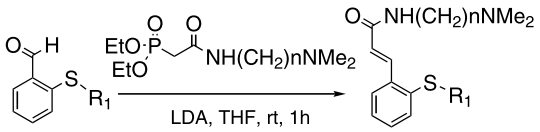
A-350619

In this paper, we report a three-step convergent synthesis of *o*-substituted aryl-acrylamides from *o*-nitrobenzaldehyde or *o*-fluorobenzaldehyde (Scheme 1, Route A). The chemistry exploits the Horner–Emmons reaction with phosphonate amides instead of conventional phosphonate esters (Scheme 1, Route B). This route obviates the need for extra steps to convert the esters into amides. Recently, there has been reports of Horner–Emmons olefination for preparing α,β-unsaturated *N*-methyl-*N*-methoxyamide (Weinreb amide).[6] There has also been several reports of using phosphonate amides to provide α,β-unsaturated amides as synthetic precursors in natural product synthesis.[7] However, generation of phosphonate amides under standard Arbuzov reaction[6–8] does not allow for adequate diversity of the amide side chains, mainly due to the limited availability of the starting material. Our approach took advantage of commercially available diethylphosphonoacetic acid to generate phosphonate amides in almost quantitative yield by a simple modified solid phase peptide coupling procedure. The chemistry is versatile and results in highly efficient generation of *o*-substituted aryl-acrylamide libraries when a large number of aldehydes and amines are employed to quickly establish structure–activity relationships (SAR) for our sGC project.

o-Alkylsulfanylbenzaldehydes and *o*-arylsulfanylbenzaldehydes **2** were synthesized from commercially available 2-nitrobenzaldehyde or 2-fluorobenzaldehyde following the literature procedure.[9] A mixture of 1 equiv. of *o*-fluorobenzaldehyde, 1.1 equiv. of potassium carbonate and 1.1 equiv. of thiol in DMF was heated at 80°C for 16 h. Product **2** was obtained by simple filtration and removal of the solvent. In general, the yields were high (80–100%). The products were easily purified by recrystallization from methanol or used without purification. Phosphonate amides **3a** and **3b** were synthesized from commercially available diethylphosphonoacetic acid by modifying conventional solid phase peptide coupling procedure.[10] 2.5–3.5 equiv. of *N*-cyclohexylcarbodimide, *N*′-methyl polystyrene (DCC resin from Novabiochem) was required to complete the amide formation. Trisamine resin (4–6 equiv. from Argonaut Technology) was used as a scavenger to remove HOBt after the reaction was completed.[11] Products **3a** and **3b** were isolated by simple filtration and were used without further purification.

In the final step, phosphonate amide **3** was treated with 5 equiv. of LDA. After 30 minutes, aldehyde **2** was added and the reaction was completed in 1 hour at room temperature.[12] Only 2.5 equiv. of LDA was required when the reaction was performed on a 1 mmol scale. The reaction was typically carried out on a 0.1 mmol scale for our project. Amides **4a** and **4b** were isolated in 44–82% overall yield in two steps starting from diethylphosphonoacetic acid (Table 1).

Table 1. Yields of products **4** from benzaldehydes **2**

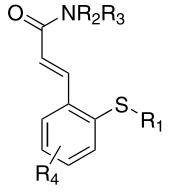


2 **4a** n=3 **4b** n=4

Entry	R_1	**4a** (Yield %)	**4b** (Yield %)
1	Ph	69	65
2	3,5-diCl-Ph	44	n/a*
3	2,6-diCl-Ph	53	n/a*
4	3-Cl-Ph	54	60
5	4-Br-Ph	54	n/a*
6	4-F-Ph	69	49
7	4-Me-Ph	75	n/a*
8	3-Me-Ph	80	74
9	2-Me-Ph	82	73
10	2-*iso*-Pr-Ph	68	n/a*
11	4-*tert*-Bu-Ph	66	n/a*
12	3,4-diMeO-Ph	56	n/a*
13	2-MeO-Ph	75	n/a*
14	3-MeO-Ph	81	73
15	4-MeO-Ph	56	54
16	4-MeS-Ph	60	50
17	2-CF_3-Ph	69	n/a*
18	3,5-diCF_3-Ph	76	n/a*
19	2-Naphthyl	64	54
20	Cyclopentyl	58	51
21	Cyclohexyl	56	45
22	*iso*-Butyl	69	49
23	*iso*-Propyl	71	52

* Compounds were synthesized from Route B (Scheme 1).

In conclusion, we report a short convergent synthesis of *o*-substituted aryl-acrylamides **4** from *o*-nitrobenzaldehyde or *o*-fluorobenzaldehyde in good overall yield. Compounds in Table 1 have shown biological activities (EC_{50} = 2.9–100 μM) as sGC activators.[4] The most potent activator (Table 1, entry 21, **4b**) was identified with EC_{50} = 2.9 μM. Libraries with different R_1, R_2, R_3 and R_4 groups (**5**) were synthesized. Identification of more potent soluble guanylyl cyclase (sGC) activators is in progress, and these results will be reported in the near future.



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10. Compound **3b**: A mixture of diethylphosphonoacetic acid (620 mg, 3.0 mmol), *N*-cyclohexylcarbodimide, *N′*-methyl polystyrene (5.0 g, 9.6 mmol) and HOBt (450 mg, 3.3 mmol) in *N*,*N*-dimethylacetamide/dichloromethane (1:1, 60 mL) was shaken at room temperature for 15 min. 4-(Dimethylamino)butyl amine (570 mg, 4.9 mmol) in *N*,*N*-dimethylacetamide/dichloromethane (1:1, 10 mL) was added and the resulting mixture was shaken at room temperature for 18 h. Trisamine polystyrene (5.0 g, 20 mmol) was added and the resulting mixture was shaken at room temperature for 6 h. The reaction solution was collected by filtration. The resin was washed with dichloromethane (2×10 mL). The combined filtrate was concentrated in vacuo. The residue 0.89 g (100%) was used without purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.37 (t, $J=7$ Hz, 6H), 1.58 (m, 4H), 2.32 (s, 6H), 2.40 (m, 2H), 2.80 (s, 1H), 2.90 (s, 1H), 3.32 (m, 2H), 4.13 (q, $J=7$ Hz, 4H), 7.16 (m, 1H); MS (ESI APCI+) m/z 295 $(M+H)^+$.
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12. **Typical prodedure**: To amide **3a** (28 mg, 0.1 mmol) in anhydrous THF (Aldrich, 1.5 mL) was added LDA (Aldrich, 2.0 M in heptane/THF/ethylbenzne, 0.25 mL, 0.5 mmol) at room temperature. After 30 min, 2-(3-chlorophenylthio)benzaldehyde (20 mg, 0.08 mmol) in anhydrous THF (0.75 mL) was added. The reaction mixture was stirred at room temperature for 1 h and quenched with water (0.3 mL). The reaction mixture was concentrated. The residue was purified by preparative HPLC on a Waters Symmetry C8 column (25×100 mm, 7 μm particle size) using a gradient of 10% to 100% acetonitrile: 0.1% aqueous TFA over about 8 min (10 min run time) at a flow rate of 40 ml/min to provide 21 mg (54%) of the desired product **4a** (Table 1, entry 4) as a trifluoroacetic acid salt. ^{1}H NMR (300 MHz, DMSO-d_6) 1.80 (m, 2H), 2.80 (s, 6H), 3.04 (m, 2H), 3.22 (m, 2H), 6.60 (d, $J=15$ Hz, 1H), 7.10 (m, 2H), 7.35 (m, 2H), 7.50 (m, 3H), 7.79 (d, $J=3$ Hz, 1H), 7.86 (d, $J=15$ Hz, 1H), 8.38 (br s, 1H), 9.42 (br s, 1H); MS (ESI APCI+) m/z 375 $(M+H)^+$.