A novel approach to polysubstituted 3-aryl-2(1*H*)-pyridinones

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Dedicated in honor of Prof. Donald Cameron on the occasion of his retirement from University of Melbourne

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Abstract

α-Benzotriazolylalkyl ketone **9**, easily prepared from α-chloroacetophenone and benzotriazole, react readily with arylacetamides **7** and aldehydes **8** to give single regioisomers of polysubstituted 3-aryl-2(1*H*)-pyridinones **10** in moderate to good yields.

Keywords: Benzotriazole, arylacetamides, α-chloroacetopheneone, 3-aryl-2(1*H*)-pyridinones

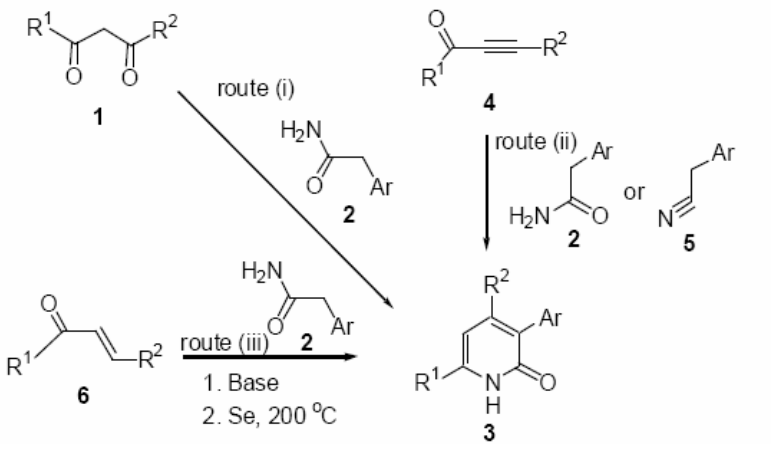
Introduction

2(1*H*)-Pyridinones are well-known building blocks for a variety of biocides. Their derivatives exhibit antiinflammatory [1] and sedative activity[2]. Conjugated tri(heteroaryl)-systems with 2(1*H*)-pyridinone units are cardiotonic or possess phosphodiesterase III inhibiting or antifungal activity[3]. Similarly, conjugated tri(heteroaryl) systems with central 2(1*H*)-pyridinone moieties were reported as NMDA receptor antagonists,[4] and as antibacterials,[5] and anxiolytics and anticonvulsants,[6] as well as platelet antiaggregatory agents.[7] Polyarylsubstituted 2(1*H*)-pyridinones are of special interest due to their anxiolytic activity with improved side-effect profiles.[8] Most recently *O*-substituted 2pyridones were identified as selective COX-2 inhibitors;[9] contrary to diarylbenzenes and other heterocycles with *cis*-stilbene motif, 3,4-diaryl-2-pyridones were as active as the corresponding 2,3-isomers.[10]

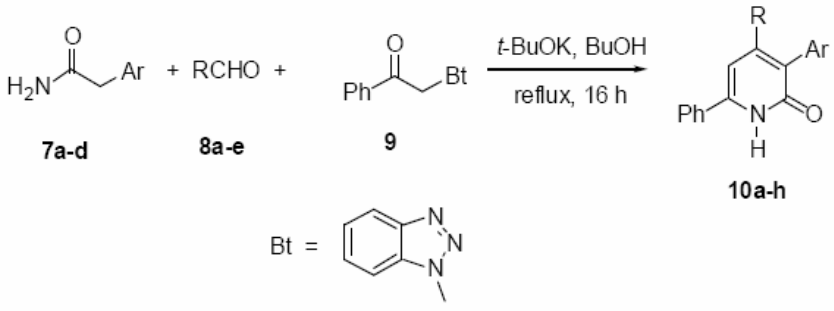
A need exists for improved synthetic approaches to pyridin-2-ones, which provide a high degree of regiospecificity in ring substitution. Numerous 2(1*H*)-pyridinone syntheses involve

variations of [1 + 2 + 3] annulations with ammonia or primary amines as one-atom synthons.[11] Aldehydes are well known as one-carbon synthons for Hantzschtype syntheses of symmetrical 1,4-dihydropyridines from *b*-aminocrotonates[12] and unsymmetrical analogs from *b*-aminocrotonates and ethyl acetoacetate.[13] Their use as one-carbon synthons for one-pot [3 + 2+ 1] 2(1*H*)-pyridinones annulations is an approach which could lead to the desired balance of regioselectivity and diversity.

Common routes to 2-pyridinones substituted with electron withdrawing groups (CN, COOR, $CONR^2$) at C3 utilize the CCN fragment of cyanoacetamide or malononitrile. Fewer general methods exist for preparation of 2-pyridinones substituted with aryl substituents at positions C3 and C6. Reported syntheses of 3-aryl-2-pyridinones (Scheme 1) include (i) reaction of 1,3-diketones **1** with 2-arylacetamides **2** (yields of **3** around 40%);[14] (ii) Michael addition of arylacetamides or arylacetonitrile **5**[16] to 1,3-diaryl-2-propyne-1-ones **4** affording products with limited diversity (3,4,6-triaryl substituted pyridinones **3** in yields about 20%); (iii) Michael addition of 2-arylacetamides **2** to 1,3-diaryl-2-propene-1-ones **6**, followed by cyclization and high-temperature oxidative aromatization of intermediate dihydropyridinones with selenium (yields of **3** of about 76-94%),[15] (iv) our recent reactions of 2-(benzotriazol-1-yl)acylamides with *a,b*-unsaturated ketones with regioselective formation of 4,6-substituted pyridine-2-ones regioselectively (yields are 31-92%).[17] We now report a novel regiospecific 3,4,6-triaryl-2(1*H*)-pyridinone synthesis *via* one-step [1 + 2 + 3] reactions of arylacetamides **7**, aldehydes **8** and α-benzotriazolyl ketone **9** (Scheme 2).



Scheme 1



Scheme 2

Results and Discussion

Arylacetamides **7** are readily available from the corresponding arylacetyl chlorides and ammonia or primary amines according to a known procedure.[18] α-Benzotriazolylalkyl ketone **9** was prepared by reacting α-chloroacetophenone with benzotriazole in refluxing toluene for 72 hours.[19] Subsequent one-pot reaction of **7**, **8**, and **9** in refluxing *n*-butanol in the presence of potassium *t*-butoxide led to 3,4,6-triaryl-2(1*H*)-pyridinones **10** in yields of 48-74% (Table 1).

Table 1. Polysubstituted 2(1*H*)-pyridinones **10**

Entry	Ar	R	Yield, %
10a	Ph	*p*-MeC_6H_4	48
10b	Ph	*p*-$MeOC_6H_4$	71
10c	1-Naphthyl	*p*-MeC_6H_4	63
10d	*p*-Cl-C_6H_4	*p*-MeC_6H_4	69
10e	Ph	*p*-BrC_6H_4	55
10f	*p*-$MeOC_6H_4$	*p*-$MeOC_6H_4$	74
10g	Ph	Ph	53
10h	Ph	2-Furyl	62

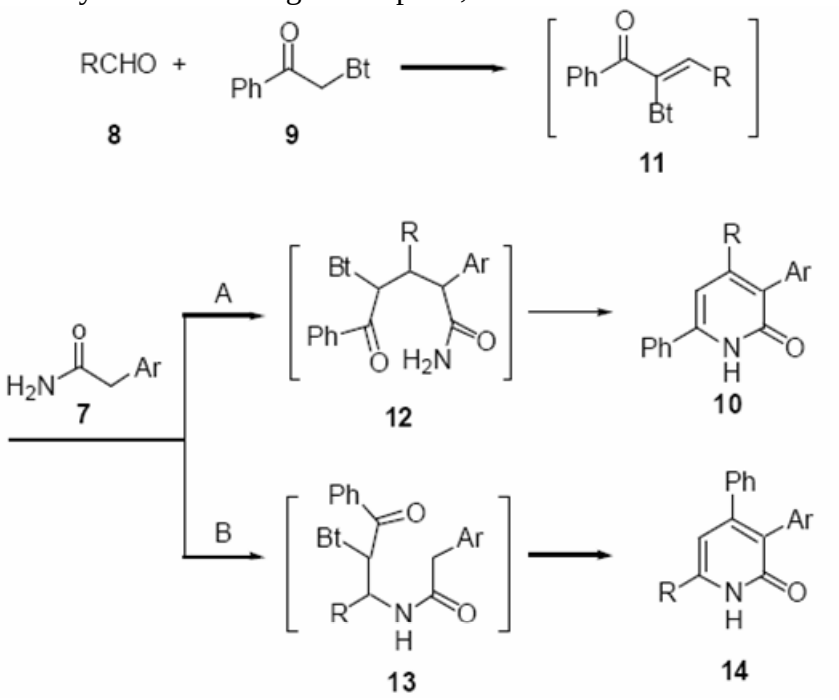
The suggested reaction mechanism is shown in Scheme 3. Aldehydes **8** and α-benzotriazolylalkyl ketone **9** generated *a,b*-unsaturated ketones **11**, which were isolated recently in our group and utilized for heterocyclizations with 1,2-dinucleophiles.[20] In the present case, intermediates **11** were formed *in situ* under basic conditions and subsequently reacted with arylacetamides **7** to produce polysubstituted pyridinones **10**. Compared to previous routes, which use selenium as an oxidant, or use strong basic conditions[12], our present route employs easily accessible starting materials, a one-step reaction, and a simple work-up procedure and affords reasonable yields. The benzotriazole moiety both stabilizes the anion formed and promotes the aromatization of the heterocycle on the elimination step, thus further demonstrating the utility of benzotriazole in organic synthesis.

Two isomeric products **10** and **14** could have arisen from two possible pathways A or B as shown in Scheme 3. However, pathway A, which includes Michael addition of the anion of arylacetamide **7** to the unsaturated ketone **11** to give thermodynamically more stable intermediate **12**, is more favorable. This opens the route to *regiospecific* pyridone ring annulation, and indeed only products of type **10** were isolated, although traces of **14a** were detected from the NMR spectra of **10a**.

Products **10a**, **10e** and **10g** were identified by comparing the melting points with those published for the authentic compounds. The structures of novel compounds **10b-d**, **10f** were established by both spectroscopic and elemental analysis or HRMS, and confirmed by comparisons of their the NMR spectra with those of the known compounds **10a**, **10e** and **10g**. The NMR spectra of **10** show a singlet in the region 6.60-7.04ppm and a broad signal in the

region 11.90-13.43ppm which can be assigned to the proton at C(5) and the NH proton, respectively.

Definitive proof of structure was provided by the X-ray of the trifluoroacetate of **10h**. (Figure 1) This is the first X-ray study of a 3,4,6-trisubstituted 2(1*H*)-pyridinone. Interestingly, the phenyl group in position 3 is out of conjugation with both pyridone ring, and 4 and 6 (hetero)aryl substituents. Perpendicular position of the 3-phenyl to the plane of the pyridone ring could influence the selectivity of their binding to receptors, such as GABA-A.[8]



Scheme 3

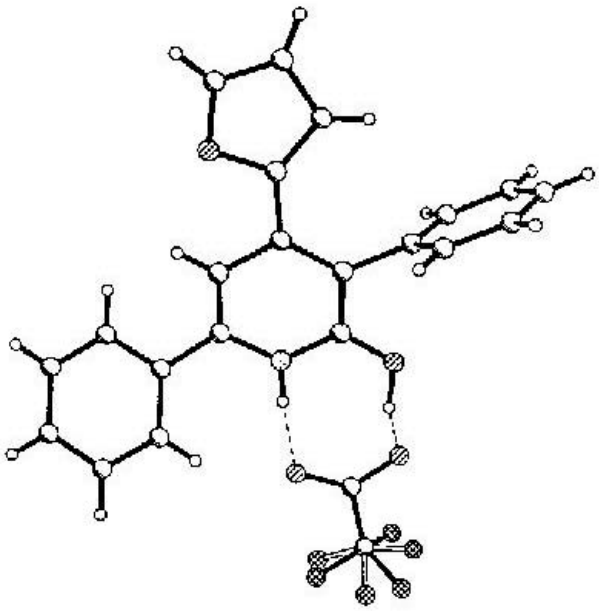


Figure 1

In summary, [1+2+3] annulation reactions of arylacetamides **7**, aldehydes **8** and α-benzotriazolylalkyl ketone **9** under basic conditions provide an efficient one-pot method for the regioselective preparation of 3,4,6-triaryl-2(1*H*)-pyridinones in good yields.

Experimental Section

General Procedures. Melting points were determined using a Bristoline hot-stage microscope and are uncorrected. ^{1}H spectra were recorded at 300 MHz in $CDCl_3$, except for compound **10d**, which was done in $CDCl_3$ containing 5% (v/v) of TFA, and for compounds **10e-g**, which were done in DMSO-d_6. ^{13}C NMR spectra were recorded at 75 MHz in the same solvents. Elemental analyses were performed on a Carlo Erba-1106 instrument.

General procedure for the preparation of 3-aryl-2(1*H*)-pyridinones 10a-h. A mixture of the corresponding *a*-benzotriazolylalkyl ketone **9** (2 mmol), arylacetamide **7** (2 mmol), aldehyde **8** (2 mmol), and potassium *tert*-butoxide (0.45g, 4 mmol) in *n*-butanol (20 mL) was stirred under reflux for 16 h. On cooling, 4 N aqueous HCl solution was added to the reaction mixture until neutralization, and the precipitated crude product was collected by filtration, washed consecutively with water, methanol, and ether, and then air dried. Recrystallization from methanol/ethanol gave **10a-h** as white or pale yellow solids from trifluoroacetic acid/methanol.

4-(4-Methylphenyl)-3,6-diphenyl-2(1*H*)-pyridinone (10a). colorless flakes, mp 271–273 °C (lit. mp 272–273 °C)[12]; ^{1}H NMR δ 2.25 (s, 3H), 6.66 (s, 1H), 7.04 (dd, *J* = 14.1, 8.1 Hz, 4H), 7.14–7.22 (m, 5H), 7.32–7.43 (m, 3H), 7.84 (d, *J* = 7.2 Hz, 2H), 12.86 (bs, 1H); ^{13}C NMR δ 21.2, 107.7, 126.6, 127.5, 128.8, 129.0, 129.7, 131.0, 133.2, 135.4, 136.7, 137.6, 144.6, 151.7, 164.6.

4-(4-Methoxyphenyl)-3,6-diphenyl-2(1*H*)-pyridinone (10b). pale yellow prisms, mp 231–232 °C; ^{1}H NMR δ 3.76 (s, 3H), 6.65(s, 1H), 6.74 (d, *J* = 8.6 Hz, 2H), 7.10 (d, *J* = 8.6 Hz, 2H), 7.20–7.26 (m, 5H), 7.34–7.44 (m, 3H), 7.83 (d, *J* = 7.2 Hz, 2H), 12.56 (br s, 1H); ^{13}C NMR δ 55.2, 107.7, 113.5, 126.6, 126.7, 127.3, 127.6, 129.0, 129.8, 130.4, 131.3, 131.9, 133.2, 135.5, 144.5, 151.3, 159.2, 164.5. Anal. Calcd for $C_{24}H_{19}NO_2$: N, 3.96. Found: N, 3.86.

4-(4-Methylphenyl)-3-(1-naphthyl)-6-phenyl-2(1*H*)-pyridinone (10c). beige needles,mp 262–264 °C; ^{1}H NMR δ 2.18 (s, 3H), 6.70 (s, 1H), 6.84–6.98 (m, 6H), 7.12 (d, *J* = 6.9 Hz, 1H), 7.22 (t, *J* = 7.2 Hz, 1H), 7.32 (t, *J* = 7.5 Hz, 1H), 7.39–7.51 (m, 2H), 7.63 (d, *J* = 7.5 Hz, 2H), 7.78 (d, *J* = 7.1 Hz, 1H), 7.87–7.94 (m, 2H), 12.75 (br s, 1H); ^{13}C NMR δ 21.1, 107.2, 125.5, 125.9, 126.3, 126.5, 126.7, 127.6, 128.1, 128.2, 128.6, 128.8, 129.6, 132.9, 133.0, 133.4, 134.2, 136.5, 1237.6, 145.2, 153.4. Anal. Calcd for $C_{28}H_{21}NO$: C, 86.78; H, 5.47; N, 3.62. Found: C, 86.36; H, 5.83; N, 3.61.

3-(4-Chlorophenyl)-4-(4-methylphenyl)-6-phenyl-2(1*H*)-pyridinone (10d). colorless flakes, mp 315-316 °C; ^{1}H NMR δ 2.35 (s, 3H), 7.00–7.20 (m, 6H), 7.22–7.39 (m, 3H), 7.55–7.68 (m, 3H), 7.70–7.76 (m, 2H), 13.43 (br s, 1H); ^{13}C NMR δ 21.2, 103.5, 116.4, 124.1, 127.1, 128.9,

129.0, 129.6, 129.8, 129.9, 130.8, 132.1, 133.6, 135.0, 140.3, 147.0, 159.2, 160.8. Anal. Calcd for $C_{24}H_{18}ClNO$: C, 77.51; H, 4.89; N, 3.77. Found: C, 77.31; H, 4.80; N, 4.23.

4-(4-Bromophenyl)-3,6-diphenyl-2(1*H*)-pyridinone (10e).[12] colorless flakes, mp 310–311 °C (lit. mp 312–313 °C)[12]; ^{1}H NMR (DMSO) δ 6.67 (s, 1H), 7.09–7.26 (m, 7H), 7.43 (d, *J* = 8.1 Hz, 2H), 7.46–7.72 (m, 3H), 7.85–7.H), 12.01 (br s, 1H); ^{13}C NMR (DMSO) δ 121.1, 126.7, 126.9, 127.5, 128.8, 129.8, 131.0, 131.1, 133.7, 135.4, 138.5, 149.3, 162.5.

3,4-Bis(4-methoxyphenyl)-6-phenyl-2(1*H*)-pyridinone (10f). pale yellow prisms, mp 234–236 °C; ^{1}H NMR (DMSO) δ 3.71 (s, 6H), 6.60 (s, 1H), 6.76 (t, *J* = 6.6 Hz, 4H), 7.01 (d, *J* = 8.7 Hz, 2H), 7.09 (d, *J* = 8.7 Hz, 2H), 7.45–7.47 (m, 3H), 7.84–7.87 (m, 2H), 12.32 (br s, 1H); ^{13}C NMR (DMSO) δ 54.9, 55.0, 107.1, 112.9, 113.4, 126.7, 128.4, 128.7, 129.3, 130.3, 131.9, 132.2, 149.4, 157.6, 158.5. Anal. Calcd for $C_{25}H_{21}NO_3$: C, 78.30; H, 5.53; N, 3.65. Found: C, 78.29; H, 5.38; N, 3.38.

3,4,6-Triphenyl-2(1*H*)-pyridinone (10g). colorless flakes, mp 310–311 °C (lit mp 311–312 °C)[12] ^{1}H NMR (DMSO) δ 6.67 (s, 1H), 7.07–7.26 (m, 10H), 7.46–7.52 (m, 3H), 7.84–7.89 (m, 2H), 11.90 (br s, 1H); ^{13}C NMR (DMSO) δ 107.4, 126.5, 126.9, 127.4, 127.6, 128.0, 128.8, 128.9, 129.7, 131.0, 133.7, 135.7, 139.3, 145.7, 150.5, 162.6.

4-(2-Furyl)-3,6-diphenyl-2(1*H*)-pyridinone (10h). brown prism, mp 127-129 ^{o}C NMR ($CDCl_3$) δ 5.63 (d, *J* = 3.5Hz, 1H), 6.35 (dd, *J* = 3.6, 1.2Hz, 1H), 7.29–7.32 (m, 2H), 7.55–7.62 (m, 7H), 7.75–7.78(m, 2H), 7.84 (s, 1H), 13.24 (bs, 1H) ^{13}C NMR ($CDCl_3$) δ 108.6, 120.1, 121.2, 127.1, 129.4, 129.6, 129.8, 131.3, 131.8, 132.2, 145.0, 145.6, 147.0, 148.1, 160.5.

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