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Research Paper

Facile three-component reaction for the synthesis of biologically active 2,3-dihydroquinazolin-4(1H)-ones

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Abstract: We have developed an efficient protocol for the synthesis of 2,3-dihydroquinazolin-4(1H)-ones by the reaction of isatoic anhydride, amine and aldehyde mediated by cyanuric chloride (1,3,5 trichloro triazine; TCT) in good to excellent yield. The reaction allows rapid cyclization and provides a new and useful strategy for the construction of N-heterocycles.

Introduction

Nitrogen-containing heterocycles are ubiquitous subunits of a variety of pharmacologically active substances, play a crucial role in the context of drug scaffolds, synthetic organic chemistry, and medicinal chemistry as well as material sciences [1, 2]. 2,3-dihydroquinazolin-4(1*H*)-one are omnipresent and have been referred to as “core structures” in the synthesis of drug molecules, and natural products [3, 4]. Quinazolinones are excellent reservoir of bioactive substances. Several bio-active natural products such as febrifugine, trypanthrine and rutaecarpine contain quinazolinone moieties with potential antimalarial and antimicrobial activity [5-7]. Quinazolinone derivatives acts as powerful inhibitors of various enzymes, and these enzymes include epidermal growth factor (EGF) receptors of tyrosine kinase, monoamine oxidase, aldose reductase, tumor necrosis factor α, thymidylate synthase and cellular phosphorylation inhibitors [8, 9]. Furthermore, they show various biological and pharmacological activities including antihypertensive [10], anticancer [11], CNS depressant [12], antimicrobial [13], antifungal [14], antiviral [15], antitubercular [16] and antimalarial agents [17]. Numerous protocols have been developed for the synthesis of 2,3-dihydroquinazolinones [18]. However, these methods suffer from one or more disadvantages such as harsh reaction conditions, low yields, strongly acidic conditions, high catalyst loading, expensive methods and tedious work-up conditions. In our ongoing interest of 1,3,5 trichloro triazine (TCT) in medicinal chemistry [19] and in synthetic chemistry [20, 21] herein, for the first time we report highly efficient TCT-catalyzed three-component one-pot reaction, involving isatoic anhydride, amino

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components and aldehydes for the synthesis of quinazolinone analogues (Scheme 1).

Results and Discussion

Initially, we examined the model cyclocondensation reaction of isatoic anhydride (**1**), benzaldehyde (**2a**) and ammonium acetate (Scheme-1) at 60°C under various conditions and the results are summarized in Table 1. It was found that 10 mol% of TCT efficiently catalyzed the reaction. The reaction was initially carried out in CH_3CN at heating; the expected product **3a** was obtained in 90% yield (Table 1, entry 1). The use of other solvents such as DCM, THF, DMSO and water were examined but did not improve the product yield (Table 1, entries 2–5). When the same reaction was conducted using TCT at room temperature the product was obtained in moderate yield (50%) and reaction requires longer reaction time, may be due to the poor solubility of starting substrates. In order to study the scope of reaction, we condensed isatoic anhydride (**1**) with ammonium acetate and commercially available aromatic and heteroaromatic aldehydes (**2a-l**) having electron donating and electron withdrawing substituents to form a series of dihydroquinazolinones (**3a-l**) (Table-2). We observed that there was not any significant impact on the reaction rate with the electronic effects. Moreover to access the feasibility of TCT catalyzed 3-component approach, we have synthesized 2,3-disubstituted quinazolinones (**3m-o**) with aniline. The structure of dihydroquinazolinones was confirmed by IR, NMR and MASS spectrometry.

Conclusion

In summary, herein we have demonstrated a most concise, efficient, mild and facile protocol for the one-pot synthesis of dihydroquinazolinones. Furthermore the moderate reaction conditions and absence of any cocatalyst make this an environment friendly methodology amenable for scale-up.

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Experimental Section

General Procedure 1: Synthesis of 2,3-Dihydroquinazolin-4(1*H*)-ones (3a-o).
Cyanuric chloride (0.07 mmol, 10 mol%) was added to a solution of isatoic anhydride **(1)** (0.61 mmol), ammonium acetate (0.62 mmol) or aniline (0.59 mmol) and desired aldehydes (1eq.) in acetonitrile (5 ml). The mixture was stirred at 60°C for the specified period of time as indicated in **Table 2**. The progress of the reaction was monitored by TLC. After completion, solvent was evaporated at reduced pressure. The corresponding solid products were obtained in quantitative yield through column chromatography by using 100-200 mesh silica gels.

2-phenyl-2,3-dihydroquinazolin-4(1*H*)-one (3a):
White solid; Yield (90%). Mp: 218-220 ºC ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.96 (d, *J* = 8.1 Hz, 1H) 7.58-7.26 (m, 6H), 6.94 (t, *J* = 7.2 Hz, 1H), 6.69 (d, *J* = 8.0 Hz, 1H), 5.90 (s, 1H), 5.82 (s, 1H, NH), 4.41 (s, 1H, NH). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 169.5, 152.9, 145.8, 138.4, 133.8, 133.3, 132.6, 132.0, 122.6, 119.8, 119.5, 72.5; IR (KBr) 3296, 3190, 3070, 1656, 1606 cm^{-1}. Mass 224.00; HRMS (ESI): calcd for [$C_{14}H_{12}N_2O + H^+$] 225.1022; found 225.1017.

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2-p-tolyl-2,3-dihydroquinazolin-4(1*H*)-one (3b):

White solid. Yield: (80%). Mp: 232-234 ºC. ^{1}H NMR (DMSOd_6, 300 MHz): δ 8.18 (s, 1H, NH), 7.62 (d, *J* = 7.5 Hz, 1H), 7.38 (d, *J* = 7.9 Hz, 2H), 7.26-7.17 (m, 3H), 7.02 (bs, 1H, NH), 6.75 (d, *J* = 8.0 Hz, 1H), 6.69 (t, *J* = 7.4 Hz, 1H), 5.71 (s, 1H), 2.29 (s, 3H). ^{13}C NMR (DMSOd_6, 50 MHz): δ 164.4, 148.2, 138.9, 138.2, 133.8, 129.2, 127.7, 127.0, 117.6, 115.2, 114.8, 66.7, 21.0; IR (KBr) 3313, 3196, 3061, 1662, 1610 cm^{-1}; Mass 238.00; HRMS (ESI): calcd for [$C_{15}H_{14}N_2O$ + H^+] 239.1179; found 239.1177.

2-(4'-isopropylphenyl)-2,3-dihydroquinazolin-4(1*H*)-one (3c):

White solid: Yield (85%). Mp: 162-164 ºC; ^{1}H NMR (DMSOd_6, 300 MHz) δ 8.21 (s, 1H), 7.64 (dd, J_1 = 7.6 Hz, J_2 = 1.2 Hz, 1H), 7.44 (d, *J* = 8.1 Hz, 2H), 7.29-7.25 (m, 3H), 7.05 (s, 1H), 6.76-6.68 (m, 2H), 5.73 (s, 1H), 2.95 (m, 1H), 1.22 (d, *J* = 6.9 Hz, 6H); ^{13}C NMR (DMSOd_6, 50 MHz) δ 164.1, 149.3, 148.4, 139.5, 133.7, 127.8, 127.4, 126.7, 117.5, 115.4, 114.8, 67.0, 33.7, 24.3; IR (KBr) 3292, 3191, 3021, 1658, 1610 cm^{-1}; Mass 266.00; HRMS (ESI) calcd for [$C_{17}H_{18}N_2O$ + H^+] 267.1492; found 267.1489.

2-(4'-chlorophenyl)-2,3-dihydroquinazolin-4(1*H*)-one (3d):

White solid; Yield (75%). Mp. 204-206 ºC ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.97 (d, *J* = 7.8 Hz, 1H), 7.57 (d, *J* = 8.4 Hz, 2H), 7.45 (d, *J* = 8.4 Hz, 2H),7.39 (t, *J* = 7.2 Hz, 1H), 6.96 (t, *J* = 7.8 Hz, 1H), 6.70 (d, *J* = 8.1 Hz, 1H), 5.91 (s, 1H), 5.81 (s, 1H, NH), 4.38 (s, 1H, NH); ^{13}C NMR ($CDCl_3$+DMSOd_6 50 MHz) δ 169.4, 152.5, 144.1, 139.3, 138.4, 133.6, 133.4, 132.6, 123.0, 119.9, 119.5, 72.1; IR (KBr) 3318, 3190, 3075, 1659, 1609 cm^{-1}; Mass 258.00; HRMS (ESI) calcd for [$C_{14}H_{11}ClN_2O$ + H^+] 259.0633; found 259.0625

2-(4'-methoxyphenyl)-2,3-dihydroquinazolin-4(1*H*)-one (3e):

White solid; Yield (80%). Mp. 188-190 ºC. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.86 (d, *J* = 7.8 Hz, 1H), 7.43 (d, *J* = 8.7 Hz, 2H), 7.26 (t, *J* =7.8 Hz, 1H), 6.87-6.77 (m, 3H), 6.57 (d, *J* = 8.1 Hz, 1H), 5.75 (s, 1H), 5.63 (bs, 1H, NH), 4.24 (bs, 1H, NH), 3.74 (s, 3H); ^{13}C NMR ($CDCl_3$+ CD_3OD 50 MHz) δ 170.4, 152.4, 138.5, 135.5, 132.9, 132.4, 123.1, 119.1, 118.9, 118.4, 72.7, 59.5; IR (KBr) 3299, 3109, 3021, 1659, 1610 cm^{-1}; Mass 254.00; HRMS (ESI) calcd for [$C_{15}H_{14}N_2O_2$ + H^+] 255.1128; found 255.1125.

2-(4'-(methylthio)phenyl)-2,3-dihydroquinazolin-4(1*H*)-one (3f):

White solid; Yield (80%). Mp. 178-180 ºC; ^{1}H NMR ($CDCl_3$+DMSOd_6, 300 MHz) δ 7.84 (d, *J* = 7.7 Hz, 1H), 7.57-7.50 (m, 2H), 7.29-7.27 (m, 3H), 7.01 (s, 1H, NH), 6.82-6.75 (m, 2H), 6.01 (s, 1H, NH), 5.83 (s, 1H), 2.51 (s, 3H); ^{13}C NMR ($CDCl_3$+ DMSOd_6, 50 MHz) δ 163.7, 147.5, 138.5, 137.4, 132.8, 127.7, 127.0, 125.3, 116.9, 114.5, 114.1, 66.3, 14.6; ; IR (KBr) 3298, 3189, 3063, 1657, 1610 cm^{-1}; Mass 270.00; HRMS (ESI) calcd for [$C_{15}H_{14}N_2OS$ + H^+] 271.0900; found 271.0893.

2-(3'-bromophenyl)-2,3-dihydroquinazolin-4(1*H*)-one (3g):

White solid; Yield (70%). Mp. 229-231 ºC; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.94 (d, *J* = 7.8 Hz, 1H), 7.77 (dd, J_1 = 7.8, J_2= 1.2 Hz, 1H),7.62 (dd, J_1 = 7.8Hz, J_2= 1.2 Hz, 1H), 7.41-7.20 (m, 3H), 6.91-6.83 (m, 1H), 6.69 (d, *J* = 8.0 Hz, 1H), 6.30 (s, 1H), 6.09 (s, 1H, NH), 4.67 (s, 1H, NH); ^{13}C NMR ($CDCl_3$, CD_3OD, 50 MHz) δ 170.0, 152.0, 146.4, 138.6, 136.7, 134.6, 132.2, 130.1, 123.0, 119.0, 71.8; IR (KBr) 3276, 3181, 3057, 1655, 1628 cm^{-1}; Mass 302.00; HRMS (ESI) calcd for [$C_{14}H_{11}BrN_2O$ +H^+] 303.0128; found 303.0121.

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2-(2'-fluorophenyl)-2,3-dihydroquinazolin-4(1*H*)-one (3h):
White solid; Yield (70%). Mp. 185-187 ºC; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.73 (dd, J_1 = 7.8 Hz, J_2 = 1.2 Hz, 1H), 7.57 (dt, J_1 = 7.5 Hz, J_2 = 1.4 Hz, 1H), 7.30-7.18 (m, 2H), 7.10-6.97 (m, 2H), 6.75 (t, J = 7.5 Hz, 1H), 6.63 (d, J = 8.1 Hz, 1H), 6.13 (s, 1H); ^{13}C NMR ($CDCl_3$+DMSOd_6, 50 MHz) δ 172.9, 155.2, 141.7, 138.4, 138.2, 135.9, 135.6, 134.9, 132.0, 126.1, 123.4, 123.0, 122.4, 69.0.; IR (KBr) 3371, 3184, 3067, 1656, 1613 cm^{-1}; Mass 242.00; HRMS (ESI) calcd for [$C_{14}H_{11}FN_2O$ + H^+] 243.0928; found 243.0922.

2-(3'-nitrophenyl)-2,3-dihydroquinazolin-4(1*H*)-one (3i):
Yellow solid; Yield (70%). Mp. 210-212 ºC (lit.[39] 216-217 ºC); ^{1}H NMR ($CDCl_3$+DMSOd_6, 300 MHz) δ 8.42 (s, 1H), 8.24 (s, 1H, NH), 8.17 (d, J = 8.1 Hz, 1H), 7.93 (d, J = 7.5, 1H), 7.73 (d, J = 7.5 Hz, 1H), 7.61 (t, J = 7.8 Hz, 1H), 7.27 (d, J = 7.2Hz, 1H), 6.90 (s, 1H, NH), 6.79-6.69 (m, 2H), 5.91 (s, 1H); ^{13}C NMR ($CDCl_3$+DMSOd_6, 50 MHz) δ 169.1, 152.9, 152.0, 148.6, 138.5, 138.0, 134.4, 132.6, 128.2, 126.9, 122.9, 120.0, 119.6, 71.1; IR (KBr) 3280, 3188, 3068, 1658, 1617 cm^{-1}; Mass 269.00; HRMS (ESI) calcd for [$C_{14}H_{11}N_3O_3$ + H^+] 270.0873; found 270.0875.

2-(naphthalen-2'-yl)-2,3-dihydroquinazolin-4(1*H*)-one (3j):
White solid;Yield (65%). Mp. 172-174 ºC; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.58 (s, 1H), 8.05-7.76 (m, 5H), 7.55-7.51 (m, 3H), 7.29 (t, J = 6.9 Hz 1H), 6.81-6.68 (m, 3H), 6.51 (s, 1H); ^{13}C NMR ($CDCl_3$+CD_3OD, 75 MHz) δ 169.9, 153.4, 139.4, 139.3, 138.8, 135.6, 134.6, 133.6, 132.8, 132.1, 131.4, 130.0, 129.2, 122.8, 120.0, 71.6; IR (KBr) 3381, 3126, 3017, 1653, 1616 cm^{-1}; Mass 274.00; HRMS (ESI) calcd for [$C_{18}H_{14}N_2O$ + H^+] 275.1179; found 275.1183.

2-(pyridin-3'-yl)-2,3-dihydroquinazolin-4(1*H*)-one (3k):
Yellow solid; Yield (70%). Mp. 190-192 ºC; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 8.62 (s, 1H), 8.54-8.51 (m, 1H), 7.99-7.93 (m, 1H), 7.80 (dd, J_1 = 7.8 Hz, J_2 = 1.4 Hz, 1H), 7.38-7.22 (m, 2H), 6.84 (t, J = 7.8 Hz, 1H), 6.67 (d, J = 8.0 Hz, 1H), 5.87 (s, 1H); ^{13}C NMR ($CDCl_3$+CD_3OD, 75 MHz) δ 169.6, 153.6, 151.9, 151.5, 143.0, 140.3, 139.6, 138.2, 131.8, 128.0, 122.8, 118.5, 117.7, 69.7; IR (KBr) 3326, 3264, 3068, 1659, 1613 cm^{-1}; Mass 225.00; HRMS (ESI) calcd for [$C_{13}H_{11}N_3O$ + H^+] 226.0975; found 226.0972.

4-(4'-oxo-1',2',3',4'-tetrahydroquinazolin-2'-yl)benzonitrile (3l):
Yellow solid; Yield (70%). Mp. >250 ºC; ^{1}H NMR (DMSOd_6, 300 MHz) δ 8.43 (s, 1H, NH), 7.87 (d, J = 8.1 Hz, 2H), 7.67-7.59 (m, 3H), 7.28 (t, J = 7.4 Hz, 1H), 6.77 (d, J = 8.0 Hz, 2H), 6.71 (t, J = 7.4 Hz, 1H), 5.84 (s, 1H); ^{13}C NMR (DMSOd_6, 75 MHz) δ 168.9, 152.2, 151.9, 138.4, 137.1, 137.0, 133.6, 132.7, 132.5, 123.3, 122.6, 119.9, 119.6, 116.6, 71.1; IR (KBr) 3286, 3178, 3056, 1651, 1613 cm^{-1}; Mass 249.00; HRMS (ESI) calcd for [$C_{15}H_{11}N_3O$ + H^+] 250.0975; found 250.0973.

2,3-diphenyl-2,3-dihydroquinazolin-4(1*H*)-one (3m):
White solid; Yield (78%). Mp. 212-214 ºC ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.04 (d, J = 7.8 Hz, 1H), 7.38-7.19 (m, 11H), 6.92 (t, J = 7.5 Hz, 1H), 6.65 (d, J = 7.8 Hz, 1H), 6.11 (s, 1H), 4.88 (bs, 1H, NH); ^{13}C NMR ($CDCl_3$+CD_3OD, 75 MHz) δ 165.6, 147.8, 142.1, 141.6, 135.8, 130.6, 130.5, 130.2, 128.7, 128.4, 120.5, 117.5, 116.5, 76.2; IR (KBr) 3327, 3261, 3063, 1649, 1610 cm^{-1}; Mass 300.00; HRMS (ESI) calcd for

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[$C_{20}H_{16}N_2O$ + H^+] 301.1335; found 301.1333.

2-(4-isopropylphenyl)-3-phenyl-2,3-dihydroquinazolin-4(1H)-one (3n):
White solid; Yield (70%). Mp. 180-182 ºC ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.08 (d, *J* = 7.7 Hz, 1H), 7.35-7.19 (m, 8H), 7.16 (d, *J* = 7.8 Hz, 2H), 6.94 (t, *J* = 7.5 Hz, 1H), 6.67 (d, *J* = 7.8 Hz, 1H), 6.10 (s, 1H), 4.95 (bs, 1H, NH), 2.92-2.85 (m, 1H), 1.24 (d, *J* = 6.9 Hz, 6H); IR (KBr) 3323, 3258, 3059, 1656, 1621 cm^{-1}; Mass 342.17; HRMS (ESI) calcd for [$C_{23}H_{22}N_2O$ + H^+] 343.1810; found 343.1819.

2-(4-methoxyphenyl)-3-phenyl-2,3-dihydroquinazolin-4(1H)-one (3o):
White solid; Yield (70%). Mp. 190-192 ºC ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.02 (d, *J* = 7.5 Hz, 1H), 7.32-7.17 (m, 8H), 7.14 (d, *J* = 7.5 Hz, 2H), 6.92 (t, *J* = 7.2 Hz, 1H), 6.63 (d, *J* = 7.5 Hz, 1H), 6.12 (s, 1H), 4.82 (bs, 1H, NH), 3.85 (s, 3H); IR (KBr) 3320, 3254, 3052, 1649, 1624 cm^{-1}; Mass 330.13; HRMS (ESI) calcd for [$C_{21}H_{18}N_2O_2$ + H^+] 331.3872; found 331.3869.

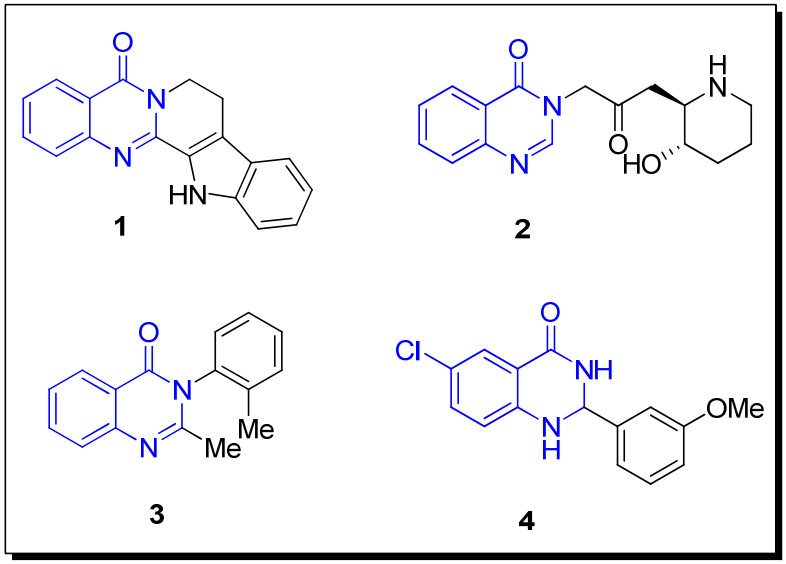
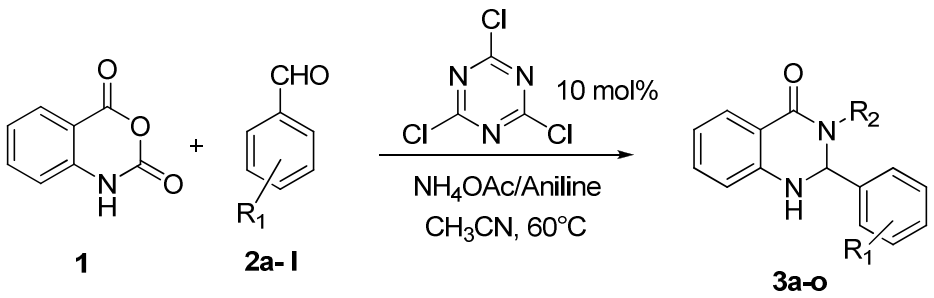


Figure 1. Structures of natural and synthesized bioactive quinazolinones.



Scheme 1. Synthesis of 2,3-dihydroquinazolin-4(1H)-ones.

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Table 1. Screening of the solvents

Entry	Solvent	Time (min)	Yield%
1	Acetonitrile	60	90
2	DCM	120	60
3	THF	150	65
4	DMSO	90	70
5	Water	100	70

Table 2. Scope of the reaction with different aromatic and heteroaromatic aldehydes

Entry	Ar/HetAr aldehyde (R_1)	R_2	Time (min)	Yield (%)
3a	Benzaldehyde (**2a**)	H	60	90
3b	4-Methyl benzaldehyde (**2b**)	H	70	80
3c	4-Isopropyl benzaldehyde (**2c**)	H	60	85
3d	4-Chloro benzaldehyde (**2d**)	H	80	75
3e	4-Methoxy benzaldehyde (**2e**)	H	70	80
3f	4-Thiomethyl benzaldehyde (**2f**)	H	60	80
3g	3-Bromo benzaldehyde (**2g**)	H	90	70
3h	2-Fluoro benzaldehyde (**2h**)	H	80	70
3i	3-Nitro benzaldehyde (**2i**)	H	100	70
3j	2-Naphthaldehyde (**2j**)	H	80	65
3k	Pyridine 3-aldehyde (**2k**)	H	90	70

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3l	4-formylbenzonitrile (**2l**)	H	70	70
3m	Benzaldehyde (**2a**)	Aniline	60	78
3n	4-Isopropyl benzaldehyde (**2c)**	Aniline	80	70
3o	4-Methoxy benzaldehyde (**2e**)	Aniline	80	70

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