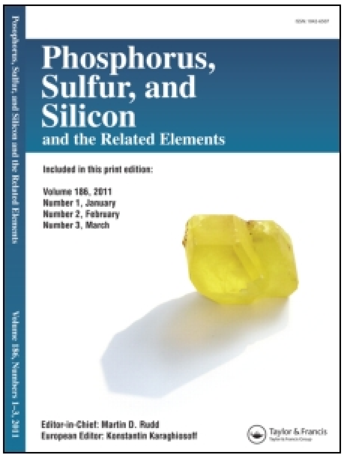

Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

SYNTHETIC REACTIONS OF COUMARIN-3-(4-AMINOSULFONYL)-CARBANILIDE DERIVATIVES WITH REACTIVE METHYLENE COMPOUNDS

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To cite this Article El-saghier, Ahmed M. M. and Al-afaleq, El-Jazi I.(1998) 'SYNTHETIC REACTIONS OF COUMARIN-3-(4-AMINOSULFONYL)-CARBANILIDE DERIVATIVES WITH REACTIVE METHYLENE COMPOUNDS', Phosphorus, Sulfur, and Silicon and the Related Elements, 139: 1, 67 — 75

To link to this Article: DOI: 10.1080/10426509808035678

URL: http://dx.doi.org/10.1080/10426509808035678

Phosphorus, Sulfur and Silicon, 1998, Vol. 139, pp. 67-75
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SYNTHETIC REACTIONS OF COUMARIN-3-(4-AMINOSULFONYL)-CARBANILIDE DERIVATIVES WITH REACTIVE METHYLENE COMPOUNDS

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(Received 30 September, 1997; In final form 13 November, 1997)

Coumarin and benzo[f]coumarin-3-(4-aminosulfonyl)carbanilide derivatives 3a,b react with malononitrile or ethyl cyanoacetate to afford pyrido[3,4-c]- and pyrido[3,4-c]-benzo-[f]coumarin derivatives **4a-d**. Compounds **4a-d** were also prepared by treatment of arylidenemalononitrile or arylidenecyanoester derivatives **1a-d** with ethyl 2-[4-aminosulfonyl carbanilide]acetate **2**. **3a,b** Derivatives were also allowed to react with a variety of active methylenes having an α-cyano or α-keto group to give pyrido[3,4-c]- and pyrido[3,4-c]-benzo[f]coumarin derivatives **5a,b-11a,b** through a nucleophilic addition and cyclization.

Keywords: Pyrido-Coumarin Derivatives; Suflanilamides; Active Methylenes

INTRODUCTION

The reported antibacterial [1-5] and the antibiotic novobiocin [6,7] of many heterocyclic compounds containing the coumarin moiety has prompted us to use a coumarin and benzo[f]coumarin-3-(4-aminosulfonyl)carbanilide derivative as a building block for the synthesis of polyfused heterocycles containing pyrido[3,4-c]- and pyrido[3,4-c]-benzo[f]coumarin derivatives.

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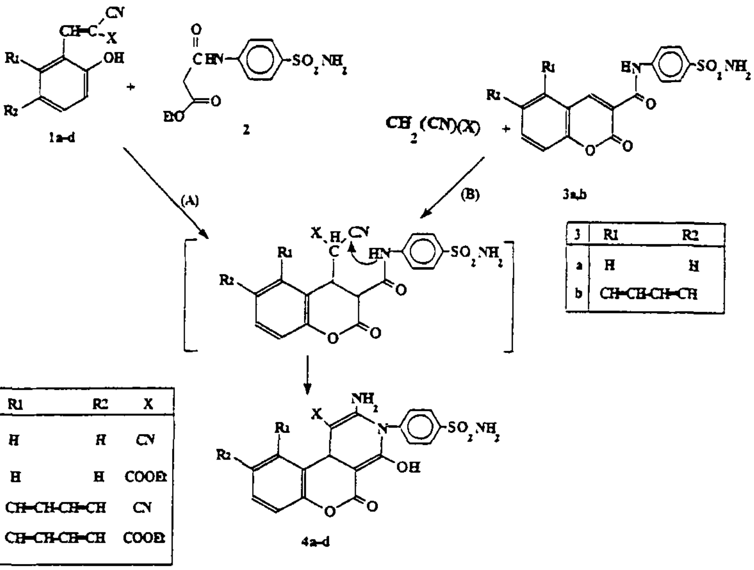
RESULTS AND DISCUSSION

In an extension of our studies on the addition of active methylenes having an α-cyano or α-keto group at the ethylenic double bond in heterocyclic synthesis [8–11], we report here the synthesis of some new pyrido[3,4-c]- and pyrido[3,4-c]-benzo[f]coumarin derivatives starting with coumarin-3-(4-aminosulfonyl)-carbanilide derivatives **3a,b**. Compound **3a** and **3b** were prepared in a one-pot-reaction by cyclocondensation of ethyl 2-[4-aminosulfonyl-carbanilide)acetate **2** with salicylaldehyde and 2-hydroxy-1-naphthaldehyde respectively[5].

Coumarin-3-(4-aminosulfonyl)carbanilide **3a** and benzo[f]coumarin-3-(4-aminosulfonyl)carbanilide **3b** were then allowed to react with malononitrile or ethyl cyanoacetate in refluxing butanol in the presence of a piperidine base where; 2-amino-3-[N(4-aminosulfonyl)phenyl]-1-0-hydro-4-hydroxypyrido[3,4-c]coumarin-1-carbonitrile **4a**, ethyl 2-amino-3-[N(4-aminosulfonyl)phenyl]-10b-hydro-4-hydroxypyrido[3,4-c]coumarin-1-carboxylate **4b**, 2-amino-3-[N(4-aminosulfonyl)-phenyl]-12c-hydro-4-hydroxypyrido[3,4-c]-benzo[f]coumarin-1-carbonitrile **4c** and ethyl 2- amino-3-[N(4-aminosulfonyl)phenyl]-13c-hydro-4-hydroxypyrido[3,4-c]- benzo[f]coumarin-l-carbonitrile **4d** were precipitated after heating for about 2–3 hrs. The reaction pathway was assumed to go through a nucleophilic addition of the formed carbanion at the ethylenic bond followed by cyclization.

Compounds **4a-d** were also prepared in a one-pot reaction by treatment of arylidenemalononitrile or arylidenecyanoester **1a-d** derivatives[12] with ethyl 2-(4-aminosulfonylcarbanilide)acetate **2** in refluxing butanol containing piperidine as a catalyst. This proposed mechanism was confirmed by a three-step reaction through a nucleophilic attack of -OH group at the carbonyl group with EtOH elimination followed by a nucleophilic addition of the formed carbanion at the ethylenic bond and cyclization by a nucleophilic attack of -NH group at the cyano group.

Compound **3a** or **3b** was also allowed to react with a variety ofactive methylene compounds including ; acetylacetone, ethyl acetoacetate, cyanoacetamide, cyanoacetohydrazide, 3-methyl-1-phenylpyrazol-5-one, cyclopentanone and cyclohexanone in refluxing butanol containing piperidine base where in each reaction a nucleophilic addition of the formed carbanion at the ethylenic bond followed by cyclization to give the desired pyrido-coumarin heterocycles namely; 3-[N(4-aminosulfonyl)phenyl]-1-acetyl-10b-hydro-4-hydroxypyrido[3,4-c]coumarin **5a**, 3-[N(4-



1,4	R1	R2	X
a	H	H	CN
b	H	H	COOEt
c	CH=CH-CH=CH		CN
d	CH=CH-CH=CH		COOEt

3	R1	R2
a	H	H
b	CH=CH-CH=CH	

aminosulfonyl)phenyl]-1-acetyl-12c-hydro-4-hydroxypyrido[3,4-c]-benzo[f]coumarin **5b**, 3-[N(4-aminosulfonyl)phenyl]-1-acetyl-2,4-dihydroxy-10b-hydropyrido[3,4-c]coumarin **6a**, 3-[N(4-aminosulfonyl)phenyl]-1-acetyl-2,4-dihydroxy-12c-hydropyrido[3,4-c]-benzo[f]coumarin **6b**, 2-amino-3-[(4-amino-sulfonyl)phenyl]-1-carboxamido-10b-hydro-4-hydroxypyrido[3,4-c]coumarin **7a**, 2-amino-3-[N(4-aminosulfonyl)phenyl]-1-carboxamido-12c-hydero-4-hydroxypyrido [3,4-c]-benzo[f]coumarin **7b**, 4-[N(4-aminosulfonyl)phenyl]-11b-hydro-5-hydroxypyrazolo[3,4-b]-pyrido[3,4-c]coumarin-1(2H,3H)-one **8a**, 4-[N(4-aminosulfonyl)phenyl]-13c-hydro-5-hydroxypyrazolo [3,4-b]pyrido[3,4-c]-benzo-[f]coumarin-1(2H,3H)-one **8b**, 4-[N(4-aminosulfonyl)phenyl]-11b-hydro-5-hydroxy-1-methyl-3-phenylpyrazolo [3,4-b]pyrido[3,4-c]coumarin **9a**, 4-[N(4-aminosulfonyl)phenyl]-13c-hydro-5-hydroxy-1-methyl-3-phenylpyrazolo[3,4-b]-pyrido[3,4-c]-benzo[f]coumarin **9b**, 4-[N(4-aminosulfonyl)phenyl)-1H-5-hydroxy-2,3,11b-trihydrocyclopenta[1,2-b]pyrido[3,4-c]coumarin **10a**, 4-[N(4-aminosulfonyl)phenyl]- 1H-5-hydroxy-2,3,13c-trihydrocyclopenta[1,2-b]pyrido[3,4-c]-benzo[f]coumarin **10b**, 5-[N(4-aminosulfonyl)phenyl]-6-hydroxy-1,2,3,4,12b-pentahydrobenzo[1,2-b]pyrido[3,4-c]coumarin **11a** and 5-[N(4-aminosulfonyl)-phenyl]-6-hydroxy-1,2,3,4.14c-pentahydrobenzo[1,2-b]pyrido[3,4-c] -benzo[f]-coumarin **11b**.

In the case of reaction of compounds **3a,b** with cyanoacetohydrazide a clear evolution of NH_3 gas was observed and the analytical and spectral data (cf. Table I) of the obtained products revealed that a fused pyrazolone ring was formed most probably via a nucleophilic attack of the $-NHNH_2$ group at the $C-NH_2$ linkage of the γ -pyridine nucleus followed by cyclization into compounds **8a** and **8b**.

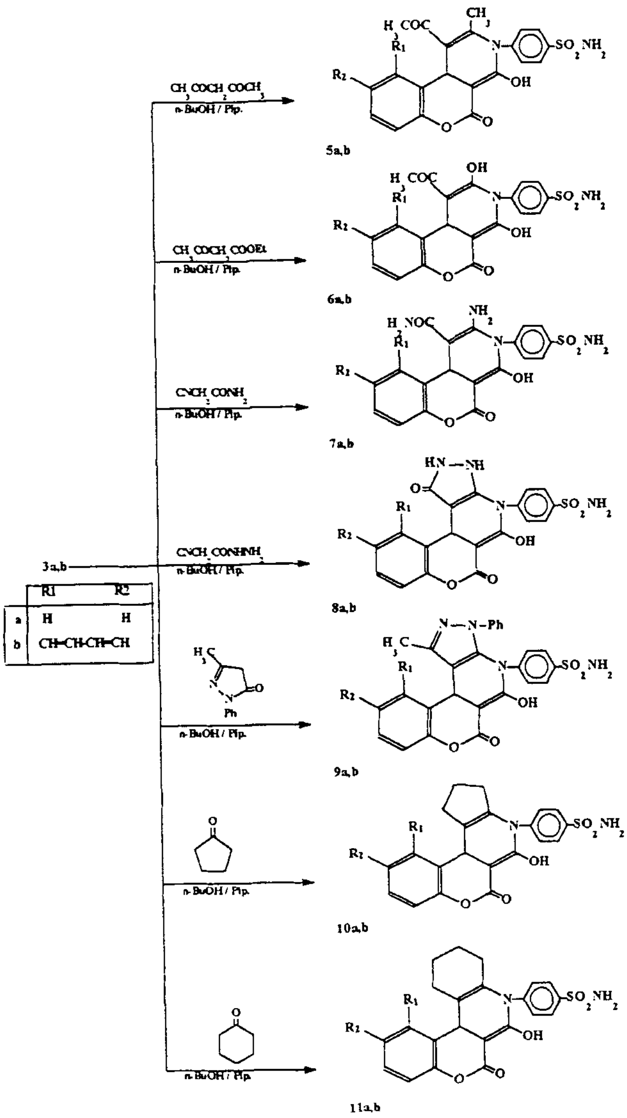


TABLE I Analytical and Spectral Data of the Reported New Compounds

Product	*Yield (%)*	*M. p. (°C)*[a]	*Mol. Form.*[b] *Mol. Wt.*	*IR (KBr)*[c]	*^1H NMR*[d] ***DMSO-d_6***
4a	81	347	$C_{19}H_{14}N_4SO_5$ 410	3450(OH), 3360,3261,3250 (2NH_2), 2199(CN), 1699 (C=O L), 1350,1180(SO_2)	9.20(s,1H,OH), 8.20–7.40(m,8H, arom.), 7.25(br s,2H,SO_2NH_2), 6.80(br s,2H, NH_2), 4.93(s,1H,γ-pyridine).
4b	76	326	$C_{21}H_{19}N_3$ SO_7 457	3470(OH), 3365,3372,3250 (2NH_2), 1720(C=O), 1690 (C=O L), 1350, 1180(SO_2).	9,40(s,1H,OH), 8.50–8.20(m,8H,arom.), 7.20(br s,2H,SO_2NH_2),6.80(br s, 2H, NH_2), 4.90(s,1H,γ-pyridine), 3.60–3.20 (q,2H,CH_2), 1.70–1.30(t,3H,CH_3).
4c	85	340	$C_{23}H_{16}N_4SO_5$ 460	3490(OH), 3365,3223,2242 (2NH_2), 2203(CN), 1700 (C=O L), 1327,1151(SO_2).	9.60(s,1H,OH), 8.50–7.30(m,8H,arom.), 7.10(br s,2H,SO_2NH_2), 6.80(br s,2H,NH_2), 4.50(s,1H,γ -Pyridine).
4d	78	336	$C_{25}H_{21}N_3SO_7$ 507	3490(OH), 3370,3330,2251 (2NH_2), 1717(C=-O), 1685 (C=O L), 1325,1145(SO_2).	9.55(s,1H,OH), 8.70–7.30(m,10H,arom.), 7.25(br s,2H,SO_2NH_2), 6.80(br s,2H,NH_2), 5.10(s,1H,γ-pyridine), 3.60- 3.20(q,2H, CH_2), 1.70–1.30(t,3H,CH_3).
5a	66	>360	$C_{21}H_{18}N_2SO_6$ 426	3475(OH), 3360,3261(NH_2), 1680(C=O L), 1660(C=O), 1350,1180(SO_2).	9.50(s1H,OH), 8.30–7.60(m,8H,arom.), 7.30(br s,2H,SO_2NH_2), 4.93(s,1H,γ- pyridine), 2.40(s,3H,$COCH_3$), 2.20(s,3H, CH_3).
5b	73	335	$C_{25}H_{20}N_2SO_6$ 476	3500(OH), 3360,3260(NH_2), 1690(C=O L), 1670(C=O), 1340, 1180(SO_2).	9.60(s,1H,OH), 8.60–7.60(m,8H,atom.), 7.20(br s,2H,SO_2NH_2), 4.90(s,1H,γ- pyridine), 2.40(s,3H,$COCH_3$), 2.20(s,3H, CH_3).
6a	68	317	$C_{20}H_{16}N_2SO_7$ 428	3500,3460(2OH), 3360,3260 (NH_2), 1690(C=O L), 1650 (C=O), 1350,1180(SO_2).	9.60,9.40(d,2H,2OH), 8.60–7.90(m,8H, atom.), 7.25(br s,2H,SO_2NH_2), 5.25(s,1H, γ-pyridine), 2.40(s,3H, $COCH_3$).
6b	70	309	$C_{24}H_{18}N_2SO_7$ 478	3500,(OH), 3360,320(NH_2), 1700(C=O L), 1670 (C=O), 1350,1180(SO_2).	9.60,9.40(d,2H,2OH), 8.70–7.80(m,10H, arom.), 7.25(br s,2H,SO_2NH_2), 5.10(s,1H, γ-pyridine), 2.40(s,3H, $COCH_3$).
7a	65	>360	$C_{19}H_{16}N_4SO_6$ 428	3490(OH), 3360,3320,3220 (3NH_2), 1690(C=O L), 1650 (C=O), 1350,1180(SO_2).	9.30(s,1H,OH), 8.60–7.80(m,8H,arom.), 7.20(br s,2H,SO_2NH_2), 6.20(br s,2H,NH_2), 5.70(brs,2H,$CONH_2$,4.93(s, 1H,γ-pyrid-ine).

Product	Yield (%)	M. p. (°C)[a]	Mol. Form.[b] Mol. Wt.	IR (KBr)[c]	^1H NMR[d] DMSO-d_6
7b	67	352	$C_{23}H_{18}N_4SO_6$ 478	3490(OH), 3360,3320,3220 (3NH_2), 1690(C=O L), 1650 (C=O 1350,1180(SO_2).	9.30(s,1H,OH), 8.70–7.80(m,10H,arom.), 7.25(br s,2H,SO_2NH_2), 6.20(br s,2H, NH_2), 5.70(brs,2H,CONH2),4.93(s,1H,γ- pyridine).
8a	55	297	$C_{19}H_{14}N_4SO_6$ 426	3500(OH), 3450,3400(NH), 3300, 3220 (NH_2), 1690(C=O L), 1660 (C=O), 1350,1180 (SO_2).	9.80(d,2H,2NH), 9.30(s,1H,OH), 8.50-7.80 (m,8H,arom.), 7.20 (br s,2H, SO_2NH_2), 4.93(s,1H,γ-pyrid-ine).
8b	62	305	$C_{23}H_{16}N_4SO_6$ 476	3500(OH), 3450,3400(NH), 3320,3220 (NH_2, 1690(C=O L), 1660 (C=O), 1350,1180 (SO_2).	9.80(d,2H,2NH), 9.30(s,1H,OH), 8.60-7.80(m,10H,arom.), 7.20(br s,2H, SO_2NH_2), 4.93(s,1H,γ-pyridine).
9a	74	311	$C_{26}H_{20}N_4SO_5$ 500	3500(OH), 3350,3250 (NH_2), 1690(C=O L), 1350,1180 (SO_2).	9.20(s,1H,OH), 8.70–8.00(m,13H,arom.), 7.25(br s,2H,SO_2NH_2), 4.93(s,1H,γ-pyridine), 2.30(s,3H,CH_3).
9b	75	300	$C_{30}H_{22}N_4SO_5$ 551	3500(OH), 3350,3250 (NH_2), 1690(C=O L), 1350,1180 (SO_2).	9.30(s,1H,OH), 8.70–7.80(m,15H,arom.), 7.25(br s,2H,SO_2NH_2), 4.93(s,1H,γ-pyridine), 2.30(s,3H,CH_3).
10a	78	>360	$C_{21}H_{18}N_2SO_5$ 410	3480(OH), 3350,3240(NH_2), 2980(CH_{aliph}), 1690(C=O L), 1350, 1180(SO_2).	9.30(s,1H,OH), 8.60–8.00(m,8H,atom.), 7.25(br s,2H,SO_2NH_2), 4.93(s,1H,γ- pyridine), 2.20–1.60(m,6H, $CH_{2\,Cyclic.}$).
10b	80	327	$C_{25}H_{20}N_2SO_5$ 460	3490(OH), 3360,3250 (NH_2), 2970($CH_{aliph.}$), 1690(C=O L), 1350, 1180(SO_2).	9.30(s,1H,OH), 8.60–7.80(m,10H,arom.), 7.25(br s,2H,SO_2NH_2), 4.93(s,1H,γ-pyridine), 2.20–1.60(m,6H, $CH_{2Cyclic.}$).
11a	65	355[d]	$C_{22}H_{20}N_2SO_5$ 424	3500(OH), 3350,3240 (NH_2), 2980($CH_{aliph.}$), 1700(C=O L), 11350,1 180(SO_2).	9.30(s,1H,OH), 8.70–8.00(m,8H,arom.), 7.25(br s,2H, SO_2NH_2), 4.93(s,1H,γ-pyridine), 2.40–1.60(m,8H, $CH_{2\,Cyclic.}$).
11b	69	343	$C_{26}H_{22}N_2SO_5$ 474	3500(OH), 3350,3250 (NH_2), 2980($CH_{aliph.}$), 1690(C=O L), 1350,1180(SO_2).	9.30(s,1H,OH), 8.70–7.90(m,10H,atom.), 7.25(br s,2H,SO_2NH_2), 4.93(s,1H,γ-pyridine), 2.40–1.60(m,8H, $CH_{2Cyclic.}$).

[a] Not Corrected. [b] Satisfactory microanalysis obtained: C ± 0.4, H ±0.3, N ±0.3%. [c]Measured on a Nicolet 710 FT-IR Spectrometer.
[d] Measured on Varian EM 360A Specrometer using TMS as internal standard. L (C=O for coumarin).

EXPERIMENTAL

All melting points were determined on a Kofler melting points apparatus and were uncorrected. IR spectra were obtained on a Nicolet 710 FT-IR specrometer. ^{1}H-NMR spectra were recorded on a Varian EM 360 A at 60 MHz using TMS as an internal standered. The elemental analyses were carried out on an elemental analyzer model 240C.

Synthesis of Pyrido[3,4-c] and Pyrido[3,4-c]-benzo[f]coumarin Derivatives 4a-d

General Procedure

Method A

A mixture of compound 2 (0.01 mol) was added to a stirred suspension of (0.01 mol) of arylidene derivatives **1a**, **1b**, **1c** or **1d** in 50 ml of n-butanol containing lml of piperidine. The reaction mixture was refluxed over different periods of time and then allowed to cool, the resulting solid was collected by filteration and recrystallized from the proper solvent.

Compound 4a: The reaction mixture was refluxed for 2hrs, the solid product was filtered off and recrystallized from DMF as white crystals.

Compound 4b: The reaction mixture was refluxed for 3hrs, the solid product was filtered off and recrystallized from DMF and n-BuOH (2:1) mixture as white crystals.

Compound 4c: The reaction mixture was refluxed for 2.5 hrs, the precipitated solid was filtered off and recrystallized from DMF as yellow crystals.

Compound 4d: The reaction mixture was refluxed for 3hrs, the precipitated solid was filtered off and recrystallized from DMF as yellow crystals.

Method B

A mixture of compound **3a** or **3b** (0.01 mol) was added to a stirred solution of malononitrile or ethylcyanoacetate in 30 ml n-butanol, 10 ml dimethylformamide and 1ml piperidine. The reaction mixture was refluxed for 3hrs and concentrated to its half – volume. On cooling, the precipitated solid was filtered off and recrystallized from the proper solvent.

Synthesis of Pyrido[3,4-c]coumarin and Pyrido[3,4-c]-benzo[f]coumarin derivatives 5a,b-11a,b

General Procedure

A mixture of compound 3a or 3b (0.01 mol) was added to a stirred suspension of (0.01 mol) of the appropriate active methylene reagent including acetylacetone, ethylacetoacetate, cyanoacetamide, cyanoacetohydrazide, 3-methyl-1-phenylpyrazol-5-one, cyclopentanone or cyclohexanone in 30 ml n-BuOH, 10 ml DMF containing 1ml piperidine. The reaction mixture was refluxed over different periods of time, concentrated to its half-volume and left to cool. The obtained solid was collected by filtration, and recrystallized from the appropriate solvent.

Compound ***5a***: The reaction mixture was refluxed for 5 hrs, the solid product was filtered off and recrystallyzed from MeCN as white crystals.

Compound ***5b***: The reaction mixture was refluxed for 6hrs, the solid product was filtered off and recrystallized from MeCN as yellow crystals.

Compound ***6a***: The reaction mixture was refluxed for 5 hrs, the solid product was filtered off and recrystallized from dioxan as white crystals.

Compound ***6b***: The reaction mixture was refluxed for 5 hrs, the solid product was filtered off and recrystallized from dioxan as pale yellow crystals.

Compound ***7a***: The reaction mixture was refluxed for 3hrs, the solid product was filtered off and recrystallized from DMF as white crystals.

Compound ***7b***: The reaction mixture was refluxed for 3hrs, the solid product was filtered off and recrystallized from DMF as pale yellow crystals.

Compound ***8a***: The reaction mixture was refluxed for 4hrs, the solid product was filtered off and recrystallized from benzene as white crystals.

Compound ***8b***: The reaction mixture was refluxed for 4hrs, the solid product was filtered off and recrystallized from benzene as pale yellow crystals.

Compound ***9a***: The reaction mixture was refluxed for 3hrs, the solid product was filtered off and recrystallized from DMF as white crystals.

Compound ***9b***: The reaction mixture was refluxed for 3hrs, the solid product was filtered off and recrystallized from DMF as white crystals.

Compound ***10a***: The reaction mixture was refluxed for 5 hrs, the solid product was filtered off and recrystallized from dioxan as white crystals.

*Compound **10b***: The reaction mixture was refluxed for 5 hrs, the solid product was filtered off and recrystallized from dioxan as orange crystals.

*Compound **11a***: The reaction mixture was refluxed for 6hrs, the solid product was filtered off and recrystallized from DMF as white crystals.

*Compound **11b***: The reaction mixture was refluxed for 6hrs, the solid product was filtered off and recrystallized from DMF as orange crystals.

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