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REVIEW article

A comprehensive analysis of disclosed synthetic strategies in prior arts from 1970-2012 (Part I) regarding synthesizing the renowned drug, Febuxostat, and its related compounds

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Abstract: Febuxostat, a nonpurine selective inhibitor of oxidized and reduced forms of xanthine oxidase. It was approved by the FDA in 2008 (EU) & 2009 (US) for the management of hyperuricemia in patients with gout. This review article provides the exhaustive and systematic review coverage of prior art disclosures on the synthesis of Febuxostat and its related compounds from 1970-2012. In line with this, the prior arts were sourced from various common and renowned search tools like Google Scholar and Google Patents using different search terms/sentences. Additionally, back and cross reference sourcing initiatives had assisted in gathering the complete past scientific disclosures on Febuxostat. During the process, 67 publications (as research articles and filed patents) were collected and the reaction schemes that are specific to each work were elaborated for the better readability of budding researchers. In this article, every disclosure has been given priority from 1970-2012 and hence 41 reaction schemes were framed in a yearly chronology. Meanwhile, the country-wise details of research organizations/institutions/laboratories were included where the disclosed work was executed. This article would certainly assist the researchers in understanding the past developments on the synthesis of Febuxostat and its closely related compounds.

Introduction

Febuxostat (**Fb**) is a renowned Xanthine Oxidase (XO) inhibitor drug used to treat gout (due to high uric acid levels). It is chosen for patients who did not respond to the treatment by the drug, allopurinol [1-5]. It is marketed globally under the brand or trade names like uloric, adenuric, etc. It has the IUPAC nomenclature as 2-(3-cyano-4-isobutoxy phenyl]-4-methyl-1,3-thiazole-5-carboxylic acid having the molecular formula as $C_{16}H_{16}N_2O_3S$ and the molecular mass as 316.38 g/mol (**Figure 1**). The melting point of **Fb** was reported as 206º-208ºC and it is influenced by the solvent used for the final recrystallization of **Fb** [6, 7].

Sourcing the prior arts: Many disclosures are available on the global platform regarding the synthesis of **Fb** and its related moieties in the form of publications by several researchers in various academic journals and patent databases. The available prior arts are too many and hence contents were sequentially crisped within **Table 1**. Additionally, elaborate reaction schemes were also provided for every disclosure which could benefit the global researchers to innovate or invent different strategies to develop **Fb** in the near future.

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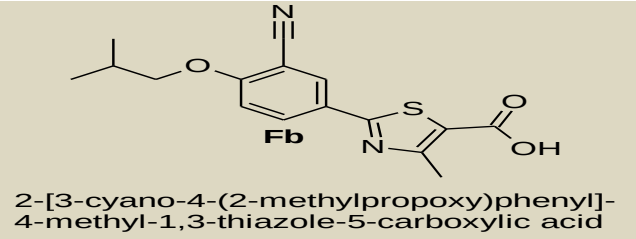

Figure 1: Structure and IUPAC nomenclature of Febuxostat **Fb**

Table 1: Tabulation of the major disclosed aspects in prior arts about the synthesis of **Fb** and its related scaffolds

Entry	Inventor/s or innovator/s	Disclosed data in brief	Synthetic route hint	Ref.
1	Bernard	Compounds like **5**, **6** & **7** were prepared from **1**.	Scheme 1	[8]
2	Mikhail	Thioamides were prepared by reacting alkyl, aryl, heterocyclic nitriles, or phenylacetonitriles with H_2S.	Scheme 2	[9]
2	Hasegawa & Komoriya	**Fb** was prepared from **8** in a four-step process.	Scheme 3	[10]
3	Shiro et al.	Numerous compounds were reported, **20** was prepared from **15** in a five-step process, **Fb** was isolated from **21** in a six-step process, **31** & **32** were prepared from **18** and formylation t**o 33** was also done to get **34** & **35**.	Scheme 4a, 4b, 4c & 4d	[11]
4	Hasegawa	**Fb** was prepared from **8** in a modified four-step process.	Scheme 5	[12]
5	Watanabe et al.	**Fb** was prepared from **7** in a four-step process.	Scheme 6a & 6b	[13]
6	Minojima & Hiramatsu	**14** was synthesized from **38** and also from **42** in a five-step each process. Also, **14** was isolated through one/two-step process from **30**.	Scheme 7a, 7b & 7c	[14]
7	Torii & Minojima	**34** was prepared from **47** in four-step process.	Scheme 8	[15]
8	Tanabe et al.	**7** was isolated in a single-step process from **38**. Moreover, a few thioamides were also synthesized from the respective nitriles.	Scheme 9	[16]
9	Matsumoto et al.	Forms of **Fb** like A, C, D & G were isolated and characterized.	NA	[17]
10	Koichi et al.	Forms of **Fb** such as A, B, C, D, G and the amorphous type were prepared and characterized.	NA	[18]
11	Watanabe et al.	Synthesized **Fb** from **7** in a four-step process and also the modified/improved pathway was disclosed to synthesize **14** from **7**.	Scheme 10a & 10b	[19]
12	Robbins	Prepared **1** & **7** from **38** in a single-step process.	Scheme 11	[20]
13	Qiang et al.	Forms of **Fb** like I, II, A, B & D were prepared and characterized.	NA	[21]
14	Qiang et al.	Form III of **Fb** was prepared and characterized.	NA	[22]
15	Wang et al.	**Fb** was synthesized from **38** in a five-step process.	Scheme 12	[23]
16	Canivet et al.	**Fb** was prepared in a single-step process by the condensation of **60** & **61**.	Scheme 13	[24]
17	Sui et al.	**36** was prepared from **38** in a three-step process.	Scheme 14	[25]
18	Wang et al.	**7** was synthesized in a single-step process from **38**.	Scheme 15	[26]
19	Deng & Zhang	Form K of **Fb** was prepared and characterized.	NA	[27]
19	Castaldi et al.	**14** was synthesized in a five-step process starting from **38**.	Scheme 16	[28]
20	Jian & Shen	**14** was prepared in a three-step process starting from **38**.	Scheme 17	[29]
21	Qi et al.	**37** was synthesized in a single-step from **36**.	Scheme 18	[30]
22	Zhu et al.	**Fb** was prepared from **38** in a six-step process.	Scheme 19	[31]
23	Shi & Wang	**Fb** was synthesized from **38** in a six-step process.	Scheme 20	[32]
24	Zhu et al.	Alpha form of **Fb** was prepared and characterized.	NA	[33]
25	Liu et al.	Form Q of **Fb** was synthesized and characterized.	NA	[34]
26	Liu et al.	Form P of **Fb** was synthesized and characterized.	NA	[35]
27	Deng et al.	Form K & L of **Fb** was synthesized and characterized.	NA	[36]
28	Chao et al.	Forms of **Fb** like I, B, D & K were prepared and characterized.	NA	[37]
29	He et al.	Form K of **Fb** was synthesized and characterized.	NA	[38]
30	Luo et al.	Forms of **Fb** like X, Y& Z were synthesized and characterized.	NA	[39]
31	Li et al.	**34** was prepared in a single-step from **7**.	Scheme 21	[40]
32	Baumann et al.	A review artile was presented on the synthetic routes to achieve 5-membered ring heterocyclic drugs.	NA	[41]
33	Birari et al.	**Fb** was prepared in six/seven-step process from **47** & **66**. Also, **Fb** was also synthesized from **7** in a four-step process.	Scheme 22a & 22b	[42]
34	Yamamoto et al.	**Fb** was synthesized from **60** & **61** in a two-step process.	Scheme 23	[43]
35	Yan et al.	**36** was synthesized in single-step process from **7**.	Scheme 24	[44]
36	Zhao et al.	**Fb** was prepared in six-step process starting from **38**.	Scheme 25	[45]
37	Zhou et al.	**14** was synthesized from **7** in a three-step process.	Scheme 26	[46]

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38	Zhou et al.	**36** was prepared from **38** in a three-step process. Additionally, it was synthesized by the condensation of **73** & **74**.	Scheme 27a & 27b	[47]
39	Zhou et al.	Impurities of **Fb** such as A, B & C were isolated and characterized. Also, recrystallization process was disclosed to get **Fb** in high purity.	NA	[48]
40	Zheng et al.	Form A of **Fb** was prepared and characterized.	NA	[49]
41	Anonymous	Form W of **Fb** was synthesized and characterized.	NA	[50]
42	Zhou et al.	Forms of **Fb** like forms H, I & J were prepared and characterized.	NA	[51]
43	Thaimattam et al.	Forms of Fb such as R_1, R_2, R_3, R_4 & R_5 were prepared and characterized.	NA	[52]
44	Satyanarayana et al.	**Fb** was prepared from **16** or **36** or **76** in a multi-step synthesis. Also, form A, B & G and salts **Fb** were synthesized and characterized.	Scheme 28a & 28b	[53]
45	Zou 2011	**Fb** was synthesized from **79** in a seven-step process.	Scheme 29	[54]
46	Hong & Li	**Fb** was prepared from **84** in a four-step process.	Scheme 30	[55]
47	Wu et al.	**Fb** was synthesized from **87** in a multi-step process.	Scheme 31	[56]
48	Zou	**14** was prepared from **38** in a five-step process.	Scheme 32	[57]
49	You & Li	Synthesized some deuterated cyanophenyl thiazoles including deuterated-**Fb**.	NA	[58]
50	Hayashisaka & Iida	Synthesized some thiobenzamides	Scheme 33	[59]
51	He et al.	**Fb** was prepared from **76** in a five-step process.	Scheme 34	[60]
52	Anonymous	**Fb** was synthesized from **38** in a seven-step process.	Scheme 35	[61]
53	Piran & Metsger	Forms of **Fb** like F_1-F_{14} were prepared and characterized.	NA	[62]
54	Zhang	Form M of **Fb** was synthesized and characterized.	NA	[63]
55	Guo & Ji 2012	**1** was prepared from **38**.	Scheme 36	[64]
56	Uemura et al.	Form A of **Fb** was synthesized and characterized.	NA	[65]
57	Wu et al.	Form M of **Fb** was prepared and characterized.	NA	[66]
58	Tombari et al.	Form III of **Fb** was synthesized and characterized.	NA	[67]
59	Luthra et al.	**Fb** was synthesized from 7. Form III of **Fb** was reported.	Scheme 37a & 37b	[68]
60	Metsger et al.	**Fb** was prepared from **36** in a single/three-step process.	Scheme 38	[69]
61	Rajadhyaksha et al.	**Fb** was synthesized from **1** or **107** or **108** in a two/four-step process.	Scheme 39a & 39b	[70]
62	Komiyama et al.	**71** was prepared in a two-step process.	Scheme 40a & 40b	[71]
63	Koushik et al.	Co-crystals of **Fb** like Fb-urea, Fb-nicotinamide and Fb-caffeine were synthesized and characterized.	NA	[72]
64	Salaet-Ferre & Marquillas-Olondriz	Form A of **Fb** was synthesized and characterized.	NA	[73]
65	Satoshi	**1** and **57** were prepared in a single-step from **38** & **39** respectively.	Scheme 41	[74]

Statistical data of prior arts: The entire prior art disclosures were collected by routine/back/cross-referencing methods and were saved in a folder with the year of disclosure as the file name. This process gave an important year-wise statistics of research work data disclosure in the global platform. In line with this, 2011 had recorded 22 research work disclosures as patents or journal publications. Meanwhile, in 2010 the same had reached up to 13 disclosures. In 2012, 12 scientific disclosures were traced from the global platform (**Table 2**).

Table 2: Year-wise statistics of disclosed prior arts

Year of disclosure	Number of disclosures
1970	1
1972	1
1994	1
1997	1
1998	3
1999	2
2000	1
2001	2
2005	1
2008	1
2009	6
2010	13
2011	22
2012	12
1970-2012	**67**

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Nomenclature: In this review article, **114** compounds are featured in the tabulated 41 reaction schemes as raw materials/starting materials and intermediates. The compounds from **1** to **114** were listed in **Table 3** with IUPAC nomenclature. Meanwhile, only compound number was presented in the reaction schemes and it avoids the clumsiness.

Table 3: IUPAC nomenclature of compounds appearing in the reaction schemes as raw materials and intermediates

C. No.	IUPAC Nomenclature
1	4-Hydroxybenzenecarbothioamide
2	Chloroacetaldehyde
3	1-Chloropropan-2-one
4	Ethyl 2-bromo-3-oxobutanoate
5	4-(1,3-Thiazol-2-yl) phenol
6	4-(4-Methyl-1,3-thiazol-2-yl) phenol
7	Ethyl 2-(4-hydroxyphenyl)-4-methyl-1,3-thiazole-5-carboxylate
8	4-Nitrobenzonitrile
9	1-Bromo-2-methylpropane
10	4-(2-Methylpropoxy) benzene-1,3-dicarbonitrile
11	Ethanethioamide
12	3-Cyano-4-(2-methylpropoxy) benzenecarbothioamide
13	Ethyl 2-chloro-3-oxobutanoate
14	Ethyl 2-[3-cyano-4-(2-methylpropoxy)phenyl]-4-methyl-1,3-thiazole-5-carboxylate
15	4-Hydroxy-3-nitrobenzaldehyde
16	4-Hydroxy-3-nitrobenzonitrile
17	4-Hydroxy-3-nitrobenzenecarbothioamide
18	Ethyl 2-(4-hydroxy-3-nitrophenyl)-4-methyl-1,3-thiazole-5-carboxylate
19	Ethyl 4-methyl-2-[4-(2-methylpropoxy)-3-nitrophenyl]-1,3-thiazole-5-carboxylate
20	4-Methyl-2-[4-(2-methylpropoxy)-3-nitrophenyl]-1,3-thiazole-5-carboxylic acid
21	4-Chloro-3-nitrobenzaldehyde
22	4-Chloro-3-nitrobenzonitrile
23	4-Chloro-3-nitrobenzenecarbothioamide
24	Ethyl 2-(4-chloro-3-nitrophenyl)-4-methyl-1,3-thiazole-5-carboxylate
25	2-Methylpropan-1-ol
26	Ethyl 4-methyl-2-[4-(2-methylpropoxy)-3-nitrophenyl]-1,3-thiazole-5-carboxylate
27	Ethyl 2-(3-chloro-4-hydroxyphenyl)-4-methyl-1,3-thiazole-5-carboxylate
28	Ethyl 2-(3-bromo-4-hydroxyphenyl)-4-methyl-1,3-thiazole-5-carboxylate
29	Ethyl 2-[3-chloro-4-(2-methylpropoxy)phenyl]-4-methyl-1,3-thiazole-5-carboxylate
30	Ethyl 2-[3-bromo-4-(2-methylpropoxy)phenyl]-4-methyl-1,3-thiazole-5-carboxylate
31	2-[3-Chloro-4-(2-methylpropoxy)phenyl]-4-methyl-1,3-thiazole-5-carboxylic acid
32	2-[3-Bromo-4-(2-methylpropoxy)phenyl]-4-methyl-1,3-thiazole-5-carboxylic acid
33	Ethyl 4-methyl-2-[4-(2-methylpropoxy)phenyl]-1,3-thiazole-5-carboxylate
34	Ethyl 2-[3-formyl-4-(2-methylpropoxy)phenyl]-4-methyl-1,3-thiazole-5-carboxylate
35	2-[3-Formyl-4-(2-methylpropoxy)phenyl]-4-methyl-1,3-thiazole-5-carboxylic acid
36	Ethyl 2-(3-formyl-4-hydroxyphenyl)-4-methyl-1,3-thiazole-5-carboxylate
37	Ethyl 2-(3-cyano-4-hydroxyphenyl)-4-methyl-1,3-thiazole-5-carboxylate
38	4-Hydroxybenzonitrile
39	4-(2-Methylpropoxy)benzonitrile
40	3-Bromo-4-(2-methylpropoxy)benzonitrile
41	3-Bromo-4-(2-methylpropoxy)benzenecarbothioamide
42	2-Chlorophenol
43	1-Chloro-2-(3-methylbutyl)benzene
44	Ethyl {[3-chloro-4-(2-methylpropoxy)phenyl]carbonothioyl}carbamate
45	3-Chloro-4-(2-methylpropoxy)benzenecarbothioamide
46	Ethyl 2-[3-iodo-4-(2-methylpropoxy)phenyl]-4-methyl-1,3-thiazole-5-carboxylate
47	5-Bromo-2-hydroxybenzaldehyde
48	5-Bromo-2-(2-methylpropoxy)benzaldehyde
49	3-Formyl-4-(2-methylpropoxy)benzonitrile
50	3-Formyl-4-(2-methylpropoxy)benzenecarbothioamide
51	4-Methylbenzonitrile
52	4-Methylbenzenecarbothioamide
53	Benzonitrile

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54	Benzenecarbothioamide
55	4-Bromobenzonitrile
56	4-Bromobenzenecarbothioamide
57	4-(2-Methylpropoxy)benzenecarbothioamide
58	4-Hydroxy-3-iodobenzonitrile
59	3-Iodo-4-(2-methylpropoxy)benzonitrile
60	*tert*-Butyl 4-methyl-1,3-thiazole-5-carboxylate
61	5-Iodo-2-(2-methylpropoxy)benzonitrile
62	3-Bromo-4-hydroxybenzonitrile
63	4-Nitrobenzenecarbothioamide
64	Ethyl 4-methyl-2-(4-nitrophenyl)-1,3-thiazole-5-carboxylate
65	1-Chloro-2-methylpropane
66	Thiourea
67	Ethyl 2-amino-4-methyl-1,3-thiazole-5-carboxylate
68	Ethyl 2-bromo-4-methyl-1,3-thiazole-5-carboxylate
69	5-Bromo-2-(2-methylpropoxy)benzonitrile
70	3-Cyano-4-isobutoxy phenyl boronic acid
71	*tert*-Butyl 2-[3-cyano-4-(2-methylpropoxy)phenyl]-4-methyl-1,3-thiazole-5-carboxylate
72	2-Methylpropan-1-ol
73	4-Methylphenol
74	Propanethioamide
75	Ethyl bromoacetate
76	2,4-Dibromophenol
77	Ethyl 2-{3-[(*E*)-(hydroxyimino)methyl]-4-(2-methylpropoxy)phenyl}-4-methyl-1,3-thiazole-5-carboxylate
78	2-{3-[(*E*)-(Hydroxyimino)methyl]-4-(2-methylpropoxy)phenyl}-4-methyl-1,3-thiazole-5-carboxylic acid
79	4-Hydroxy-3-methylbenzaldehyde
80	4-Hydroxy-3-methylbenzonitrile
81	3-Methyl-4-(2-methylpropoxy)benzonitrile
82	3-Formyl-4-(2-methylpropoxy)benzonitrile
83	3-Formyl-4-(2-methylpropoxy)benzenecarbothioamide
84	2-Fluoro-5-iodobenzonitrile
85	2-(2-methylpropoxy) 5-(tetramethyl dioxaborane) benzonitrile
86	Ethyl 2-bromo-4-methyl-1,3-thiazole-5-carboxylate
87	4-Hydroxybenzaldehyde
88	4-(2-Methylpropoxy)benzaldehyde
89	3-Bromo-4-(2-methylpropoxy)benzaldehyde
90	(*E*)-1-[3-Bromo-4-(2-methylpropoxy)phenyl]-N-hydroxymethanimine
91	Benzonitrile
92	Benzenecarbothioamide
93	4-Methoxybenzonitrile
94	4-Methoxybenzenecarbothioamide
95	4-Chlorobenzonitrile
96	4-Chlorobenzenecarbothioamide
97	4-Bromo-2-methylbenzonitrile
98	4-Bromo-2-methylbenzenecarbothioamide
99	4-Bromo-2-hydroxy-6-methylbenzonitrile
100	4-Bromo-2-hydroxy-6-methylbenzenecarbothioamide
101	2,4-Dibromo-1-(2-methylpropoxy)benzene
102	4-(2-Methylpropoxy)benzamide
103	3-Bromo-4-(2-methylpropoxy)benzamide
104	3-Cyano-4-(2-methylpropoxy)benzamide
105	2-Chloro-N,N-dimethylacetamide
106	2-(4-Hydroxyphenyl)-N,N,4-trimethyl-1,3-thiazole-5-carboxamide
107	2-(3-Formyl-4-hydroxyphenyl)-N,N,4-trimethyl-1,3-thiazole-5-carboxamide
108	2-[3-Formyl-4-(2-methylpropoxy)phenyl]-N,N,4-trimethyl-1,3-thiazole-5-carboxamide
109	2-(3-Cyano-4-hydroxyphenyl)-N,N,4-trimethyl-1,3-thiazole-5-carboxamide
110	2-[3-Cyano-4-(2-methylpropoxy)phenyl]-N,N,4-trimethyl-1,3-thiazole-5-carboxamide
111	2-[3-Formyl-4-(2-methylpropoxy)phenyl]-4-methyl-1,3-thiazole-5-carboxylic acid
112	4-Methyl-1,3-thiazole-5-carboxylic acid
113	2-Methylpropan-2-ol
114	5-Bromo-2-fluorobenzonitrile

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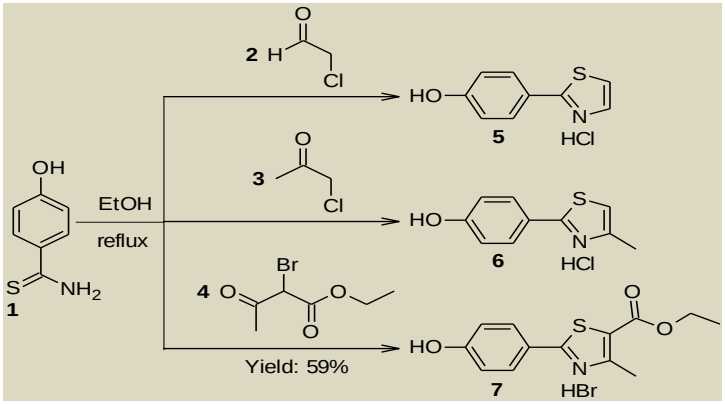
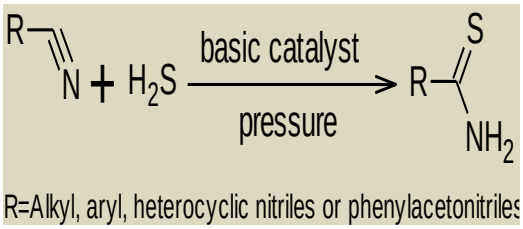
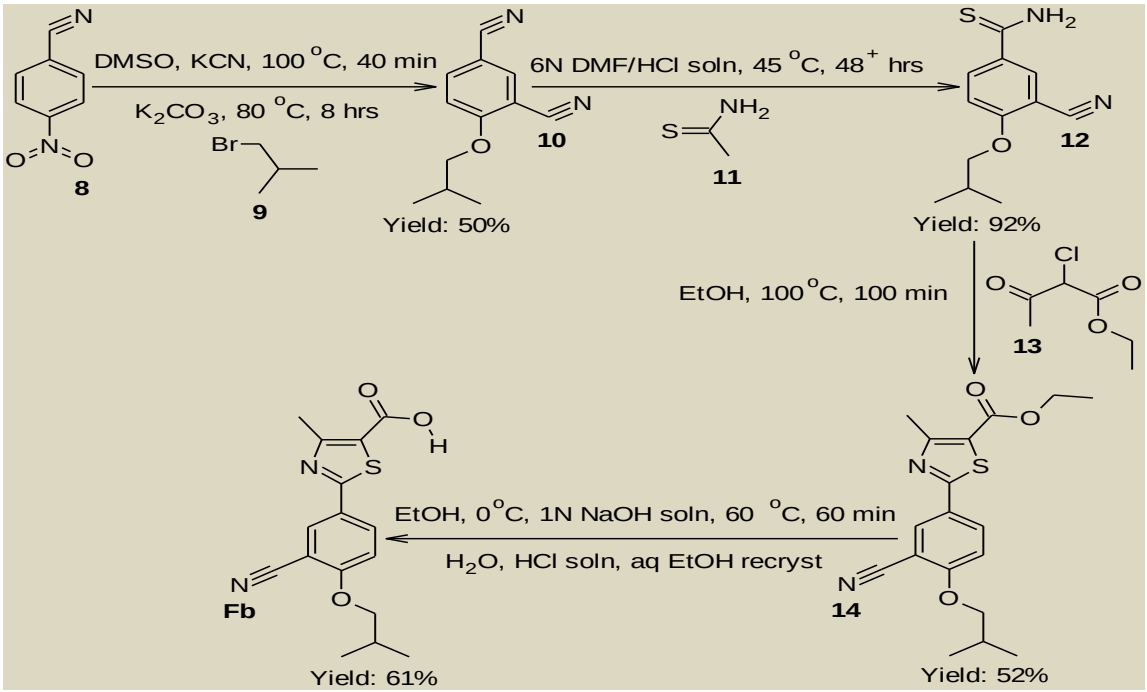
REACTION SCHEMES



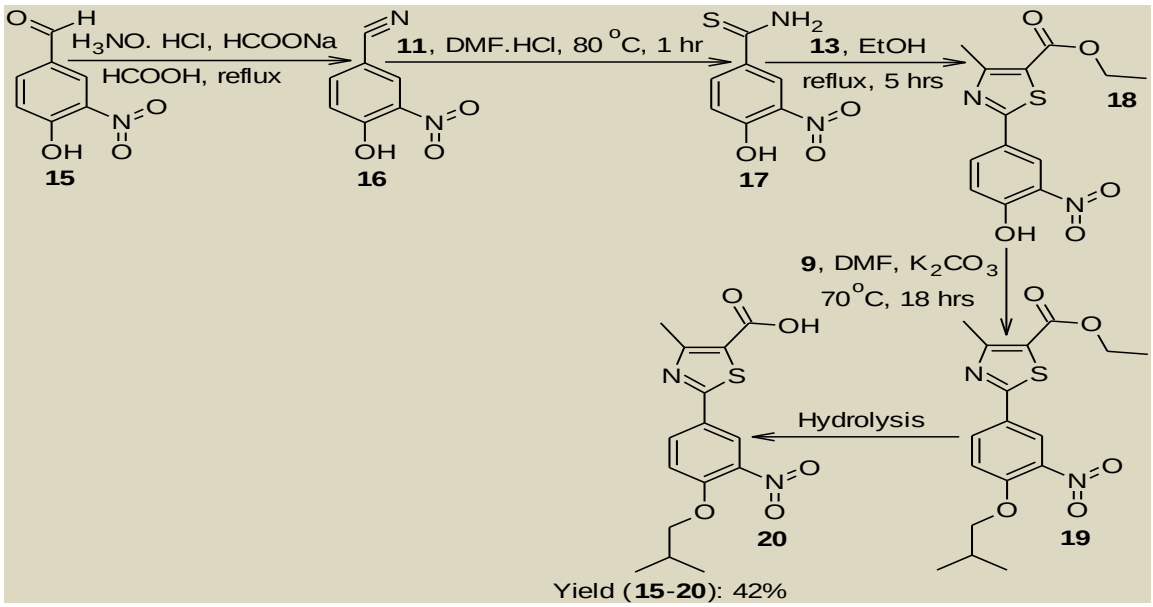
Scheme 1: Synthesis of some thiazolylphenyl derivatives as per the disclosure by Bernard [8]



Scheme 2: Synthesis of thioamides as per the disclosure by Mikhail [9]



Scheme 3: Synthesis of **Fb** from **8** as per the disclosure by Hasegawa & Komoriya [10]



Scheme 4a: Synthesis of **20** from **15** as per the disclosure by Shiro et al. [11]

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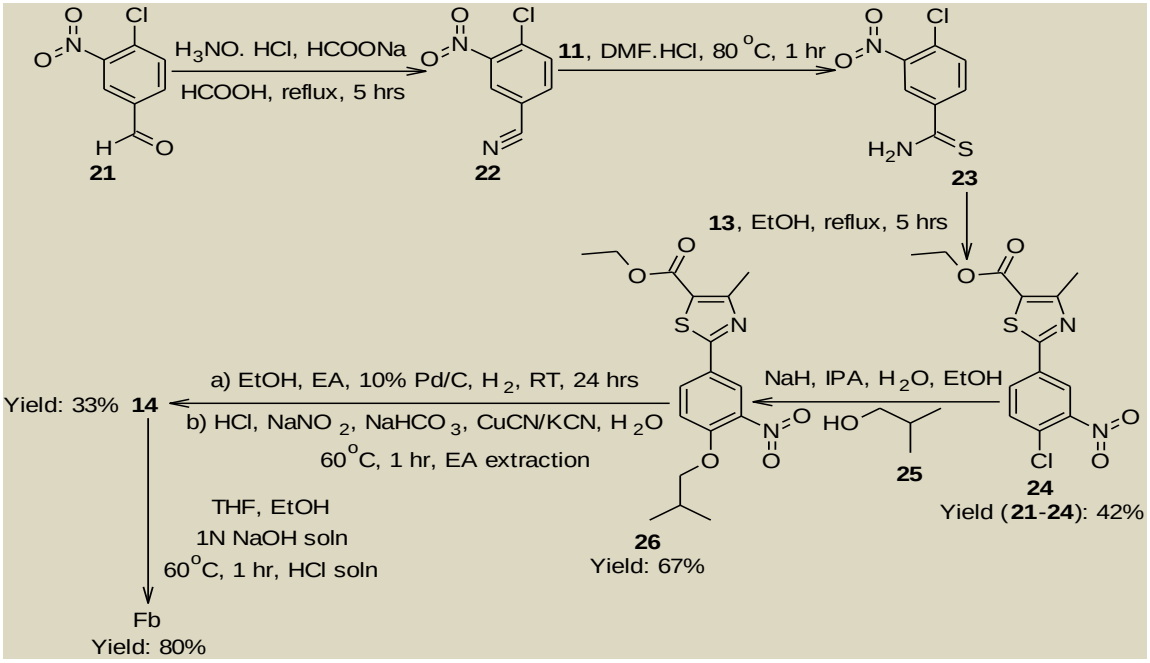
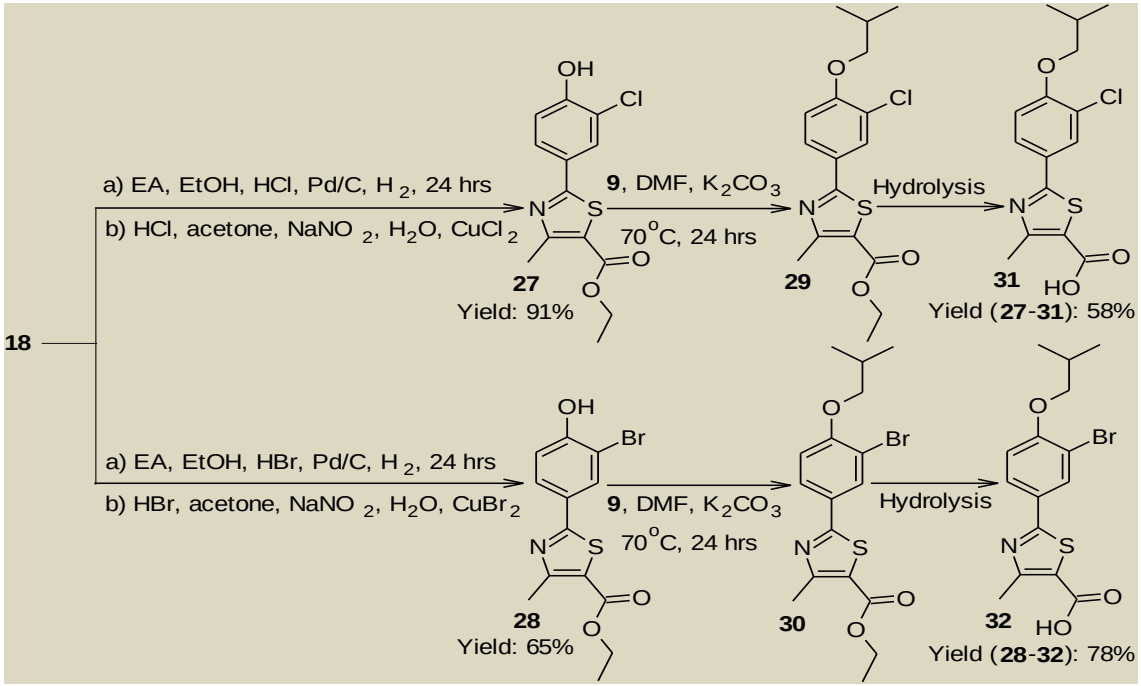
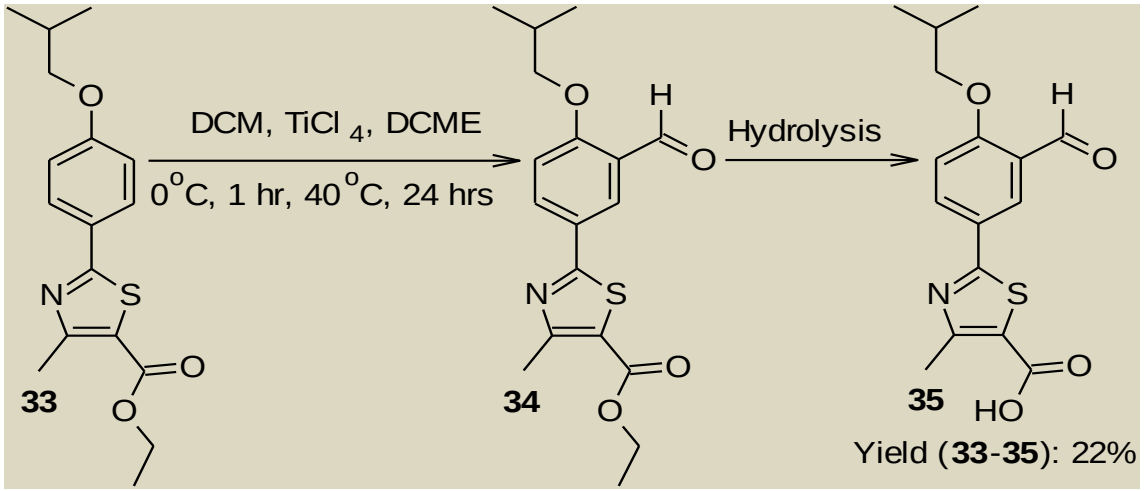


Scheme 4b: Synthesis of **Fb** from **21** as per the disclosure by Shiro et al. [11]



Scheme 4c: Synthesis of **31** and **32** from **18** as per the disclosure by Shiro et al. [11]



Scheme 4d: Synthesis of **35** from **33** as per the disclosure by Shiro et al. [11]

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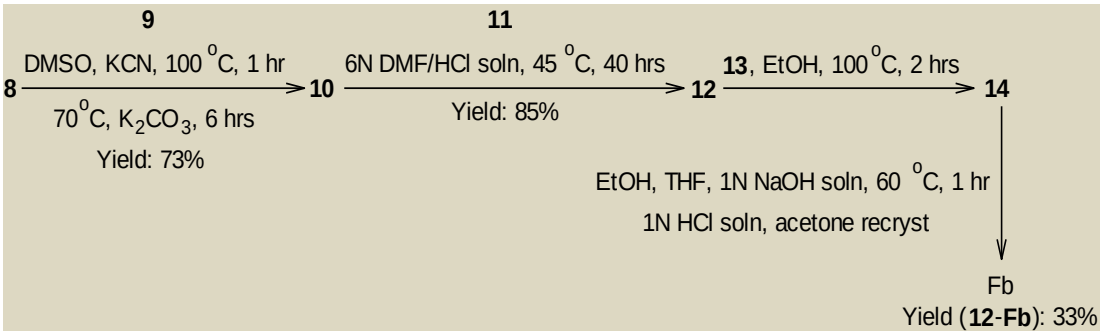
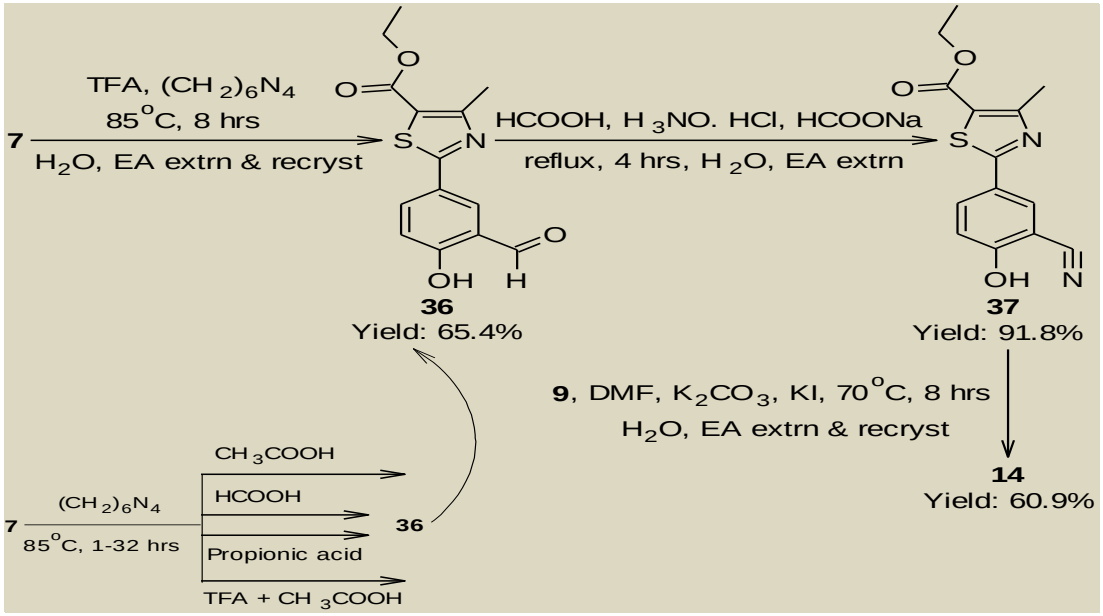
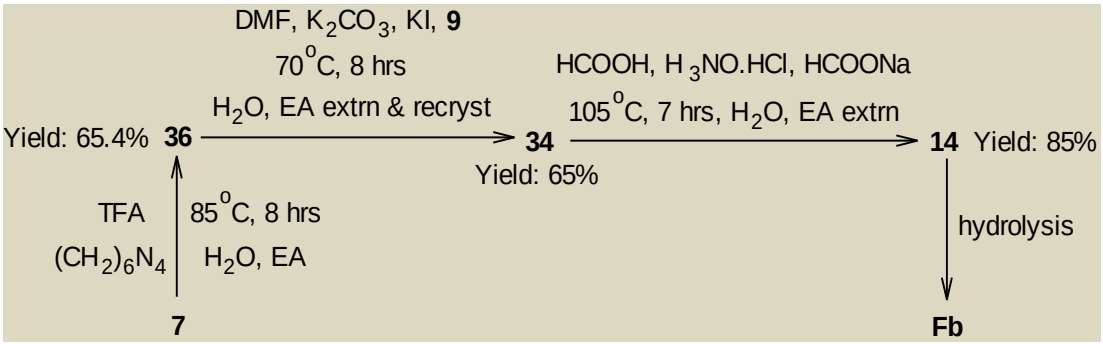


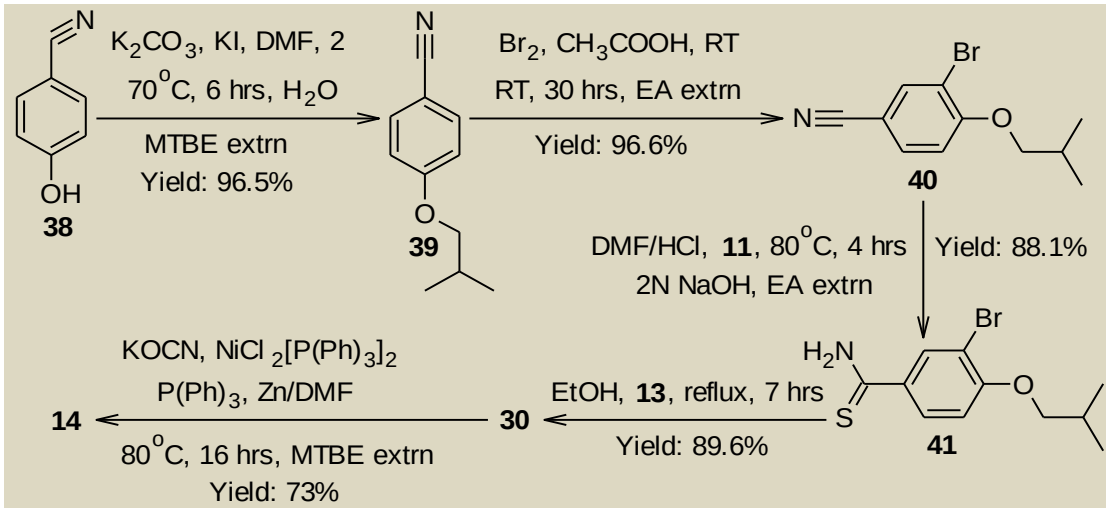
Scheme 5: Synthesis of **Fb** from **8** as per the disclosure by Hasegawa [12]



Scheme 6a: Synthesis of **14** from **7** as per the disclosure by Watanabe et al. [13]



Synthesis of 6b: Synthesis of **Fb** from **7** as per the disclosure by Watanabe et al. [13]



Scheme 7a: Synthesis of **14** from **38** as per the disclosure by Minojima & Hiramatsu [14]

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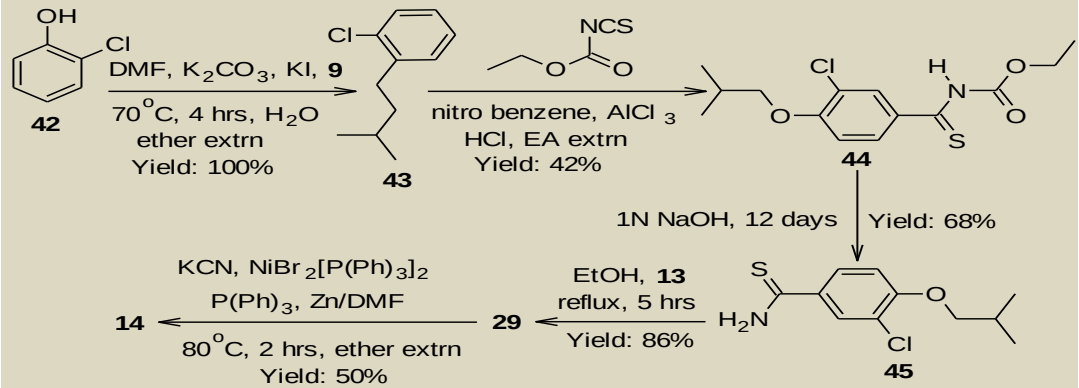
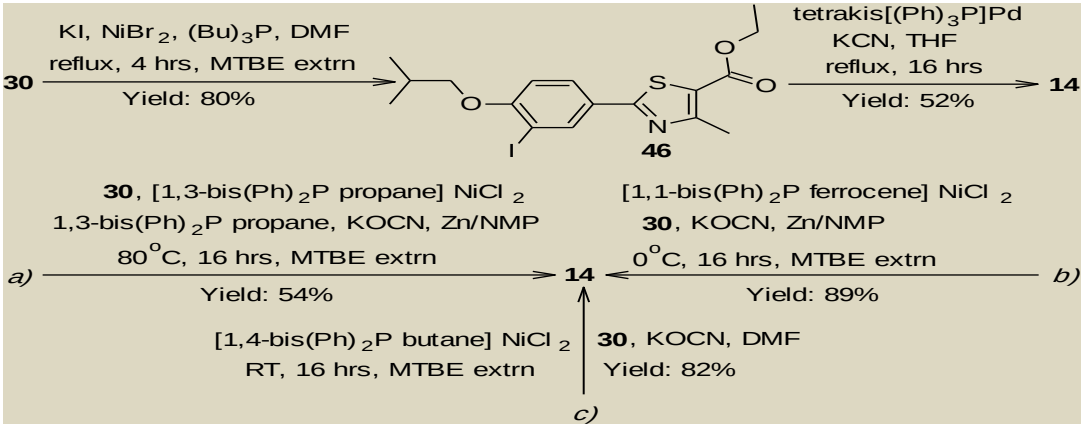
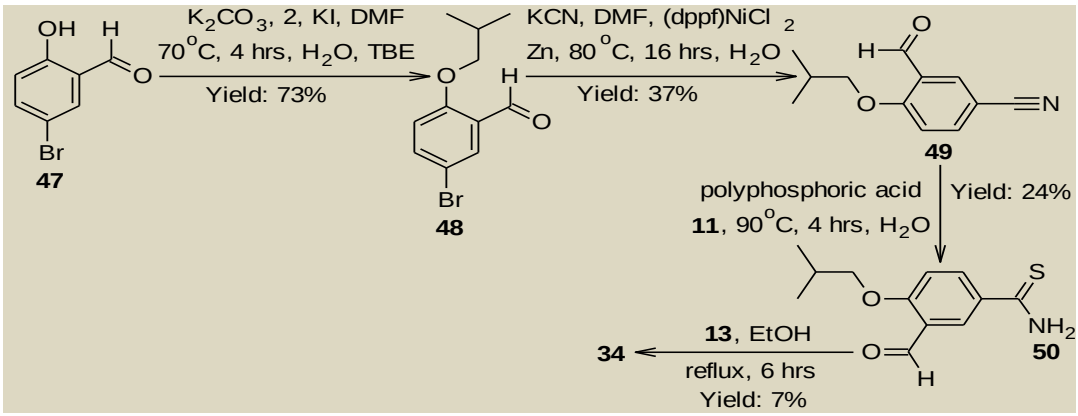


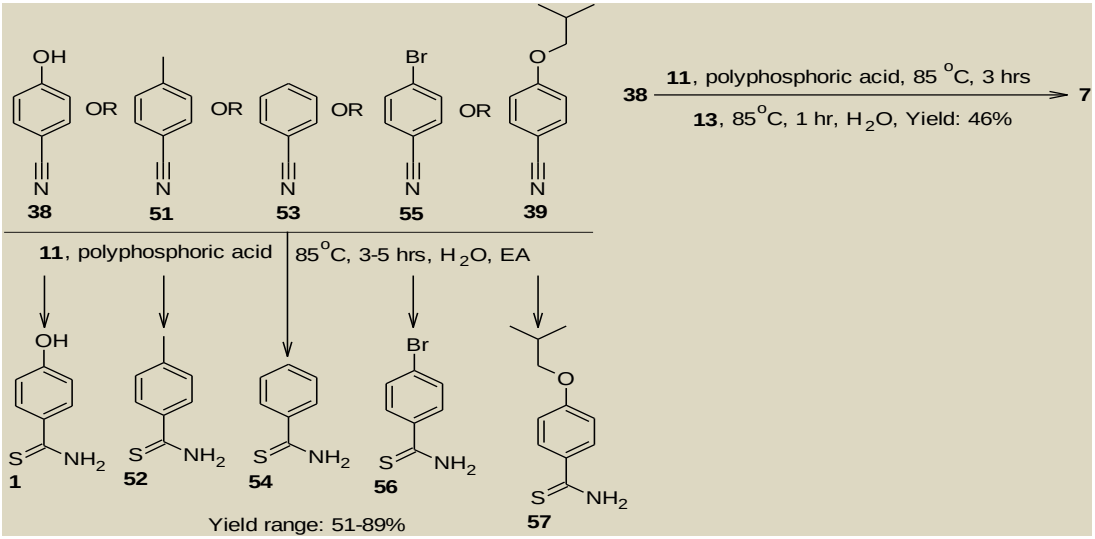
Scheme 7b: Synthesis of **14** from **42** as per the disclosure by Minojima & Hiramatsu [14]



Scheme 7c: Synthesis of **14** from **30** as per the disclosure by Minojima & Hiramatsu [14]



Scheme 8: Synthesis of **34** from **47** as per the disclosure by Torii & Minojima [15]



Scheme 9: Synthesis of various benzothioamides (**1**, **52**, **54**, **56** & **57**) and the one step process to isolate **7** from **38** as per the disclosure by Tanabe et al. [16].

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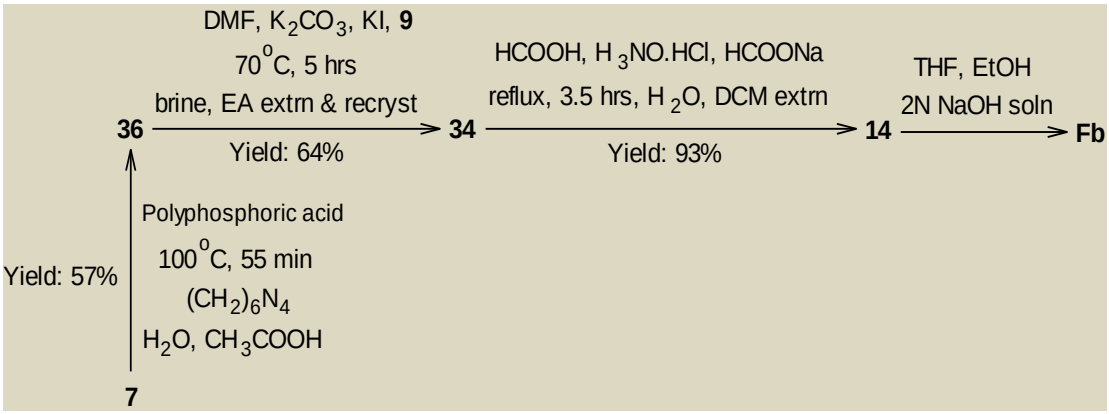
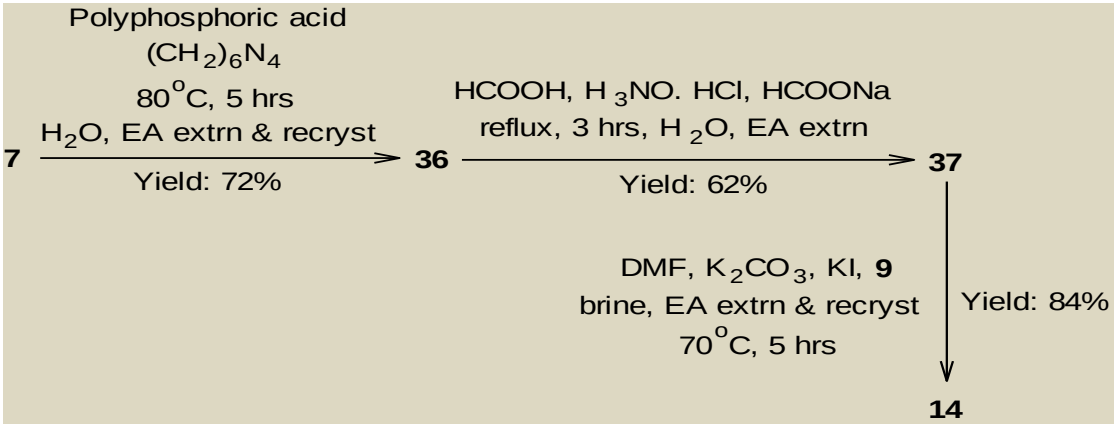
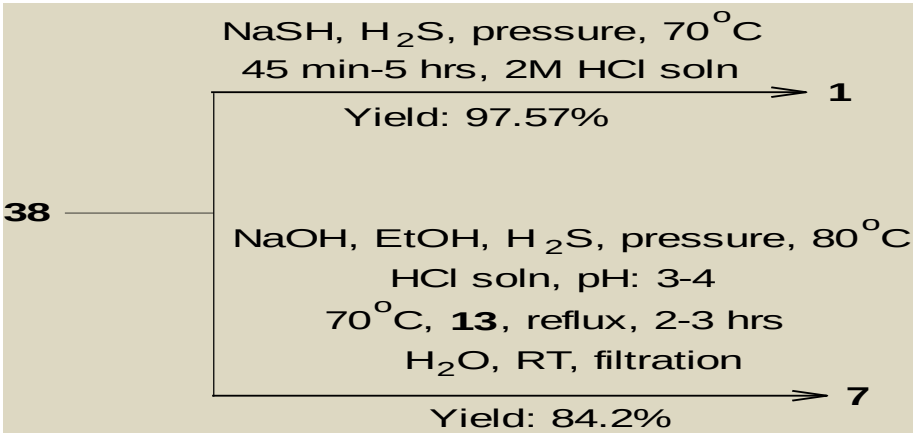


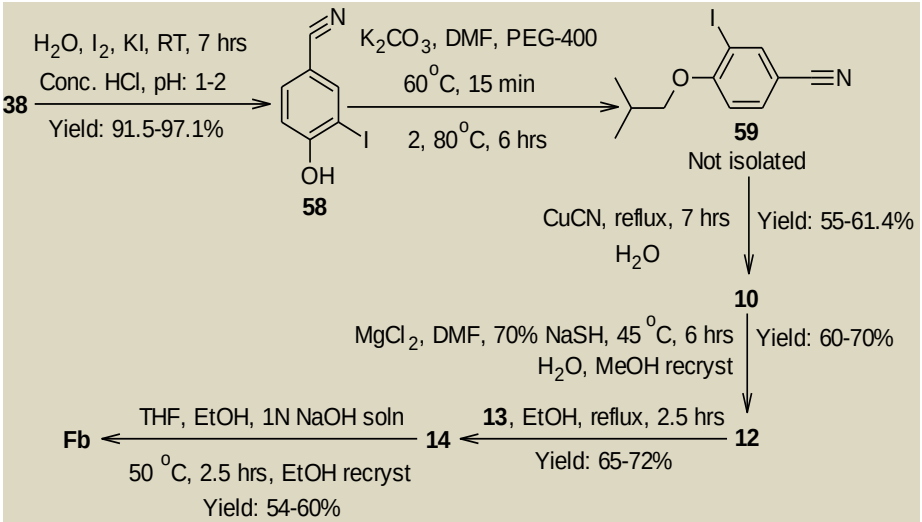
Scheme 10a: Synthesis of **Fb** from **7** as per the disclosure by Watanabe et al. [19]



Scheme 10b: Synthesis of **14** from **7** as per the disclosure by Watanabe et al. [19]



Scheme 11: Synthesis of **1** and **7** from **38** as per the disclosure by Robbins et al. [20]



Scheme 12: Synthesis of **Fb** from **38** as per the disclosure by Wang et al. [23]

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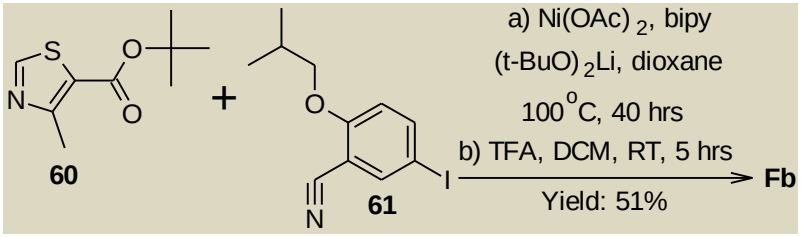
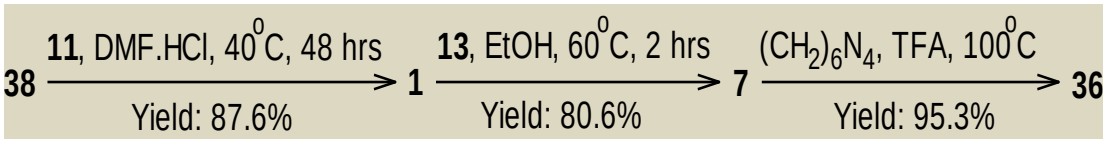
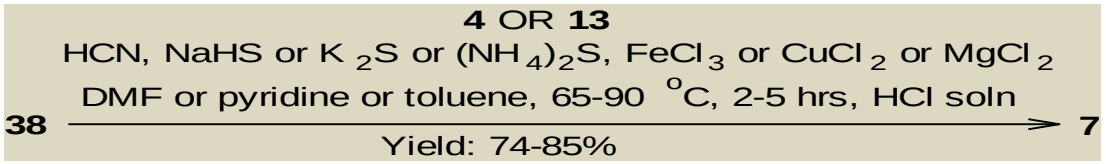


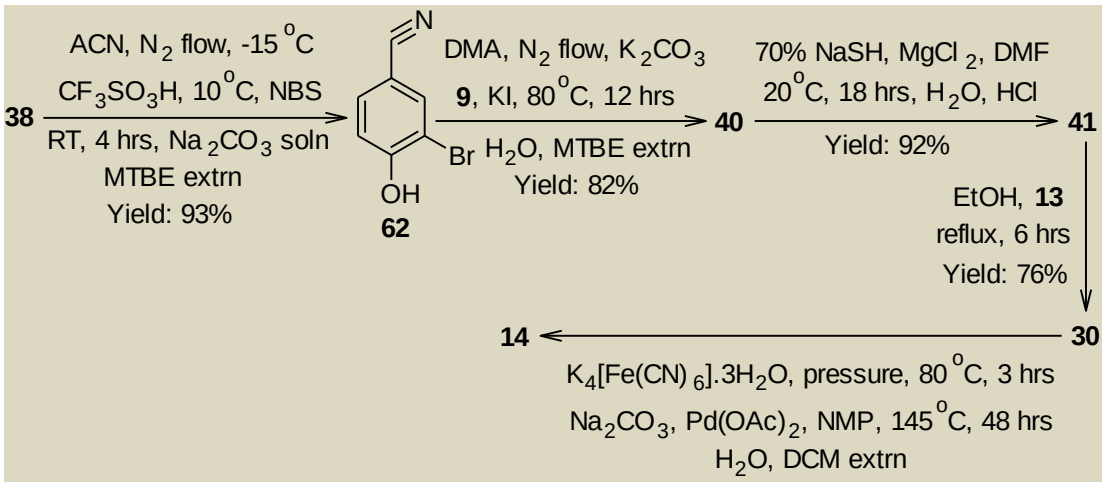
Scheme 13: Synthesis of **Fb** as per the disclosure by Canivet et al. [24]



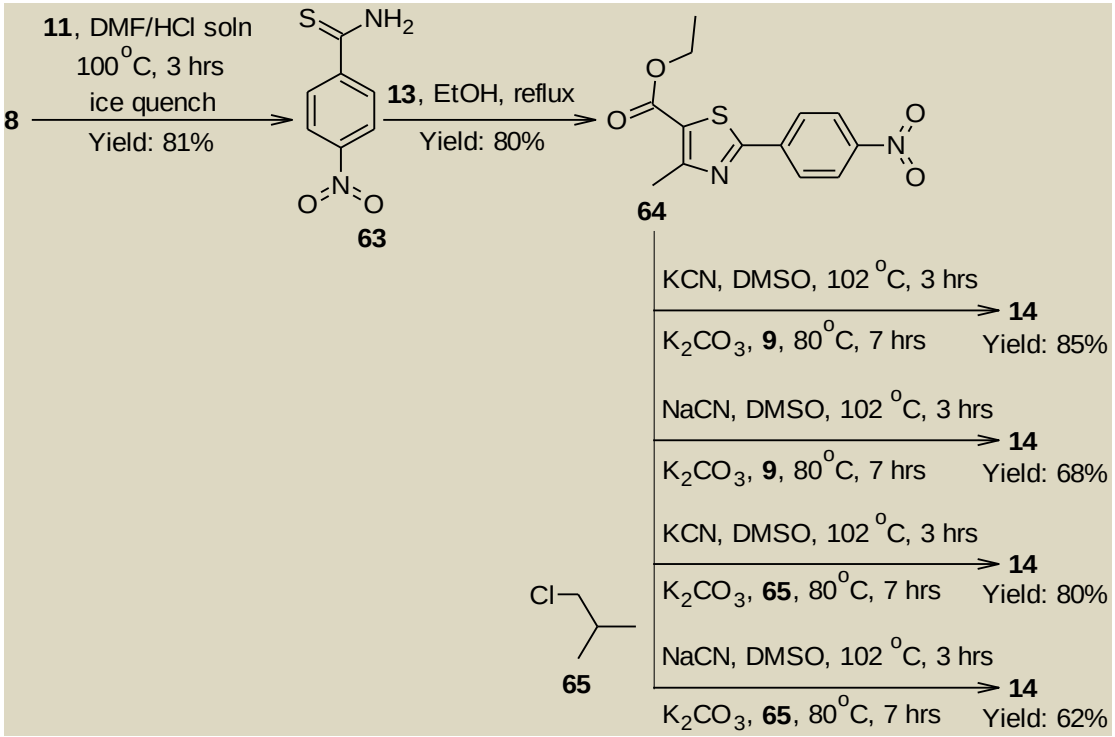
Scheme 14: Synthesis of **36** from **38** as per the disclosure by Sui et al. [25]



Scheme 15: Synthesis of **7** from **38** as per the disclosure by Wang et al. [26]



Scheme 16: Synthesis of **14** from **38** as per the disclosure by Castaldi et al. [28]



Scheme 17: Synthesis of **14** from **8** as per the disclosure by Jian & Shen [29]

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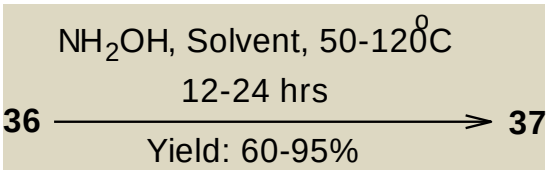
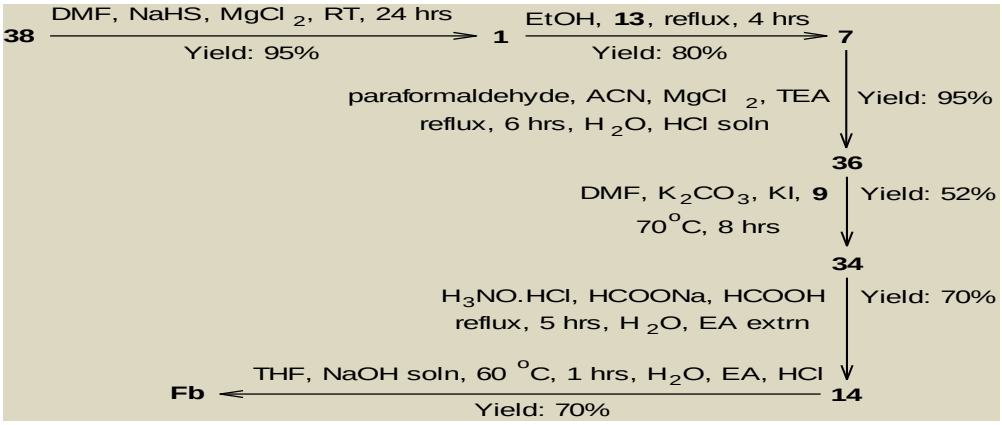
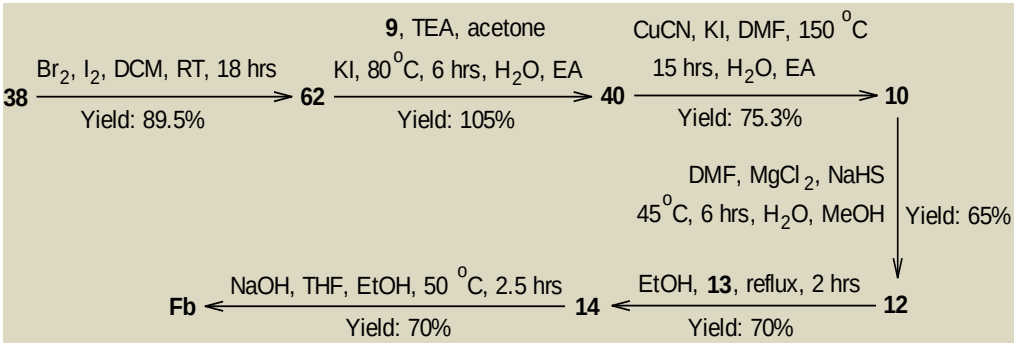


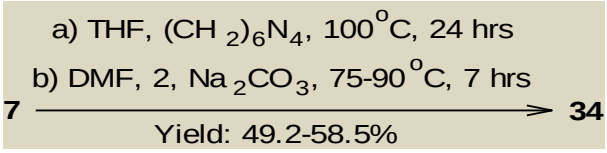
Scheme 18: Synthesis of **37** from **36** as per the disclosure by Qi et al. [30]



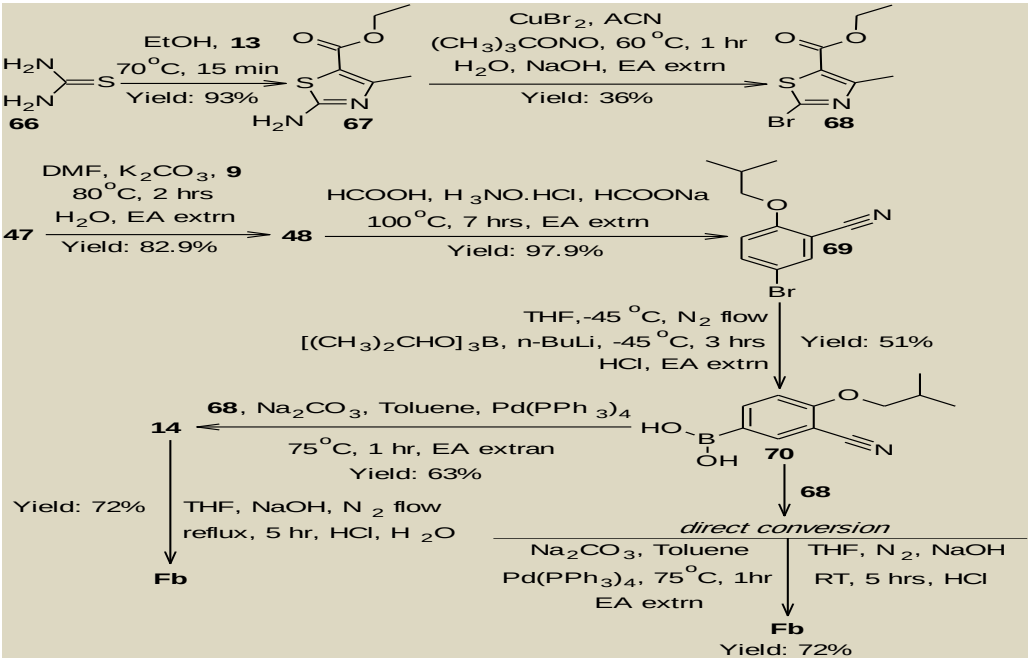
Scheme 19: Synthesis of **Fb** from **38** as per the disclosure by Zhu et al. [31]



Scheme 20: Synthesis of **Fb** from **38** as per the disclosure by Shi & Wang [32]



Scheme 21: Synthesis of **34** from **7** as per the disclosure by Li et al. [40]



Scheme 22a: Synthesis of **Fb** from **47** & **66** as per the disclosure by Birari et al. [42]

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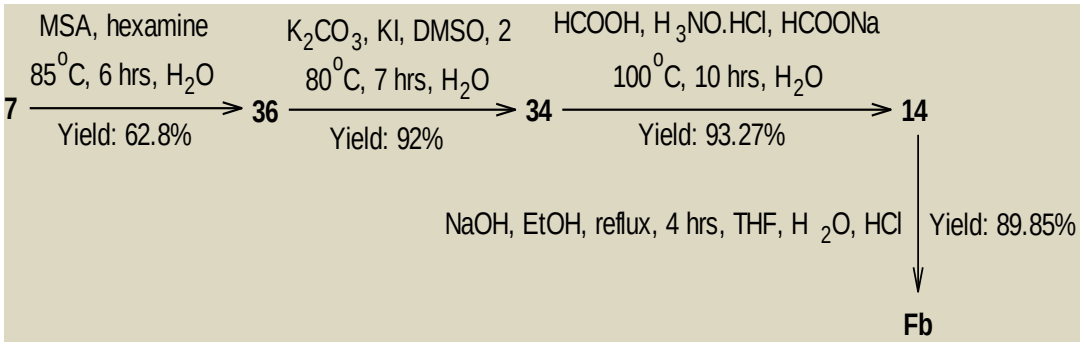
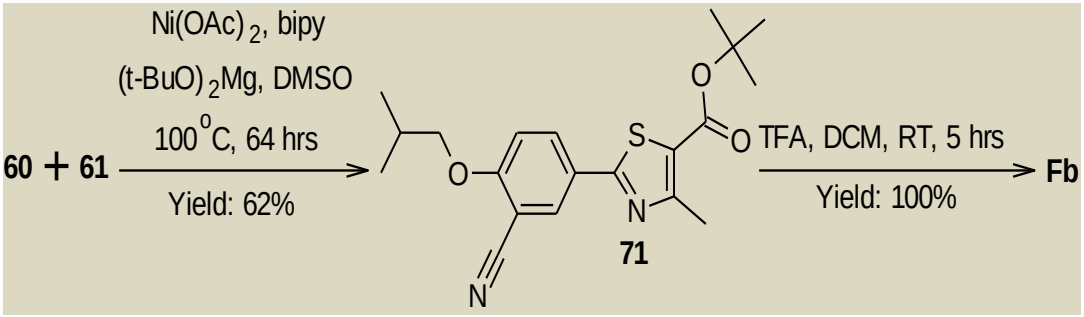
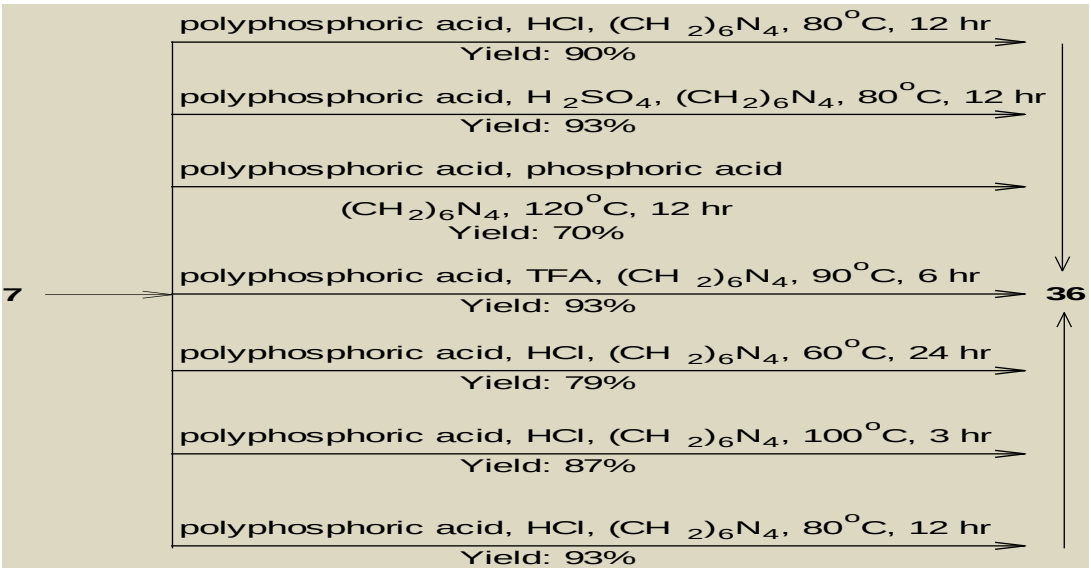


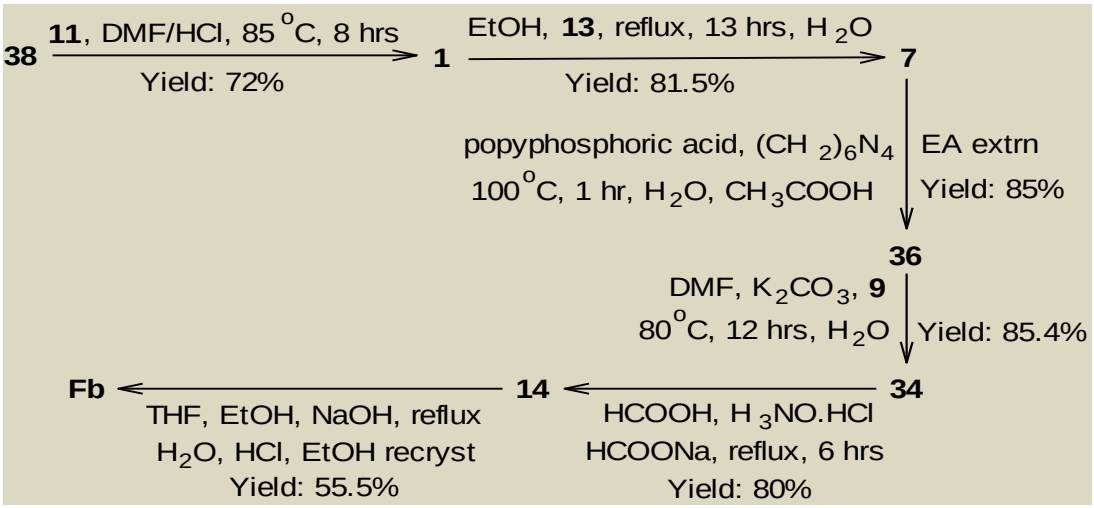
Scheme 22b: Synthesis of **Fb** from **7** as per the disclosure by Birari et al. [42]



Scheme 23: Synthesis of **Fb** from **60** & **61** as per the disclosure by Yamamoto, et al. [43]



Scheme 24: Synthesis of **36** from **7** as per the disclosure by Yan et al. [44]



Scheme 25: Synthesis of **Fb** from **38** as per the disclosure by Zhao et al. [45]

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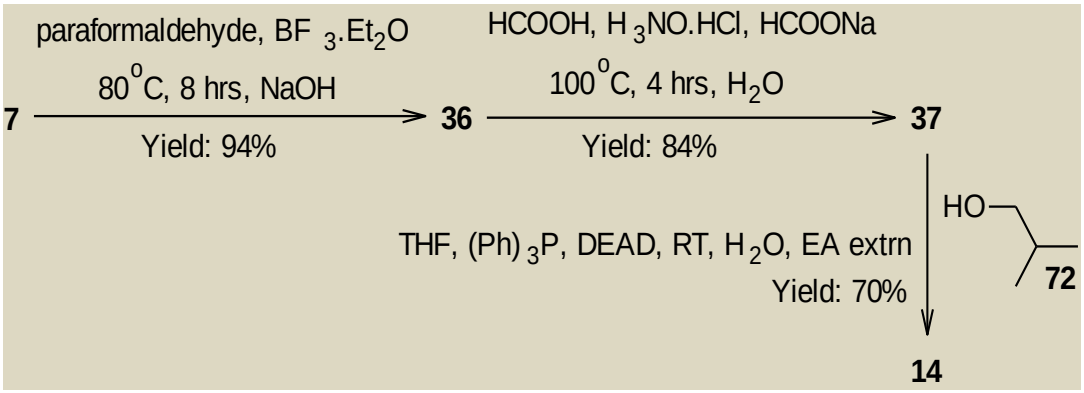
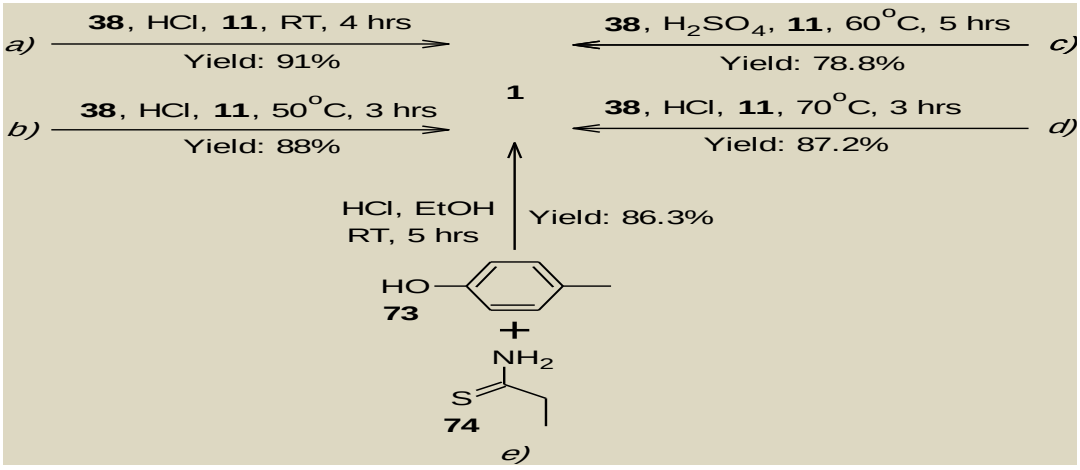
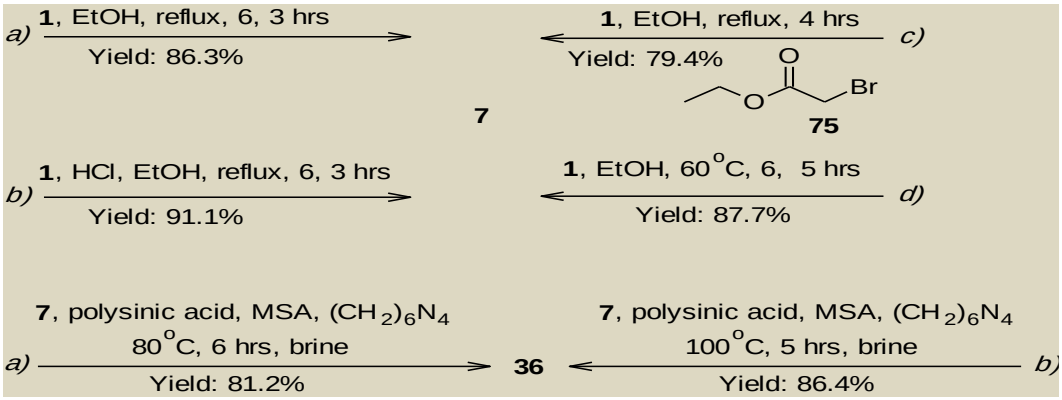


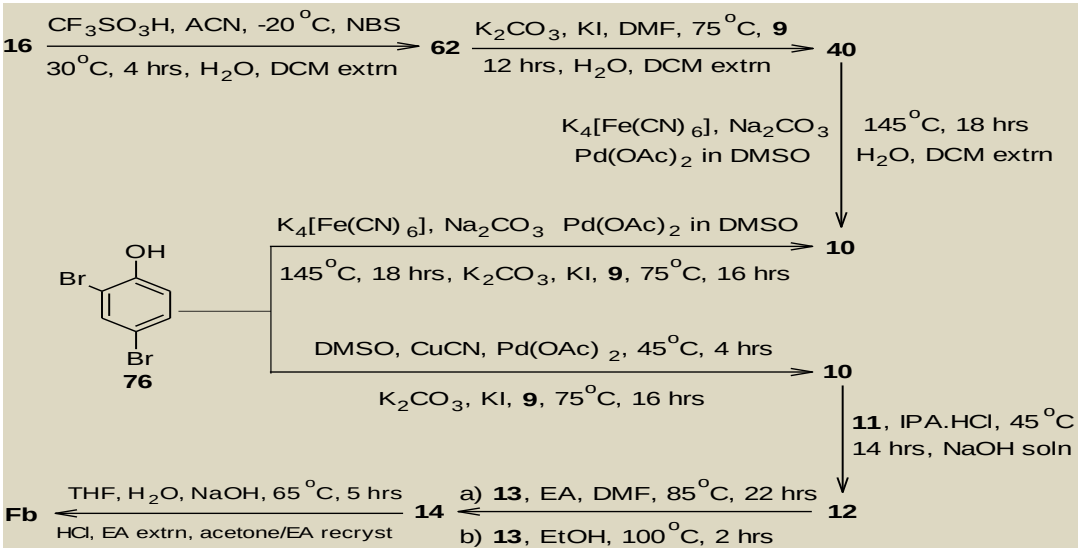
Scheme 26: Synthesis of **14** from **7** as per the disclosure by Zhou et al. [46]



Scheme 27a: Synthesis of **1** as per the disclosure by Zhou et al. [47]



Scheme 27b: Synthesis of **36** from **1** as per the disclosure by Zhou et al. [47]



Scheme 28a: Synthesis of **Fb** as per the disclosure by Satyanarayana et al. [53]

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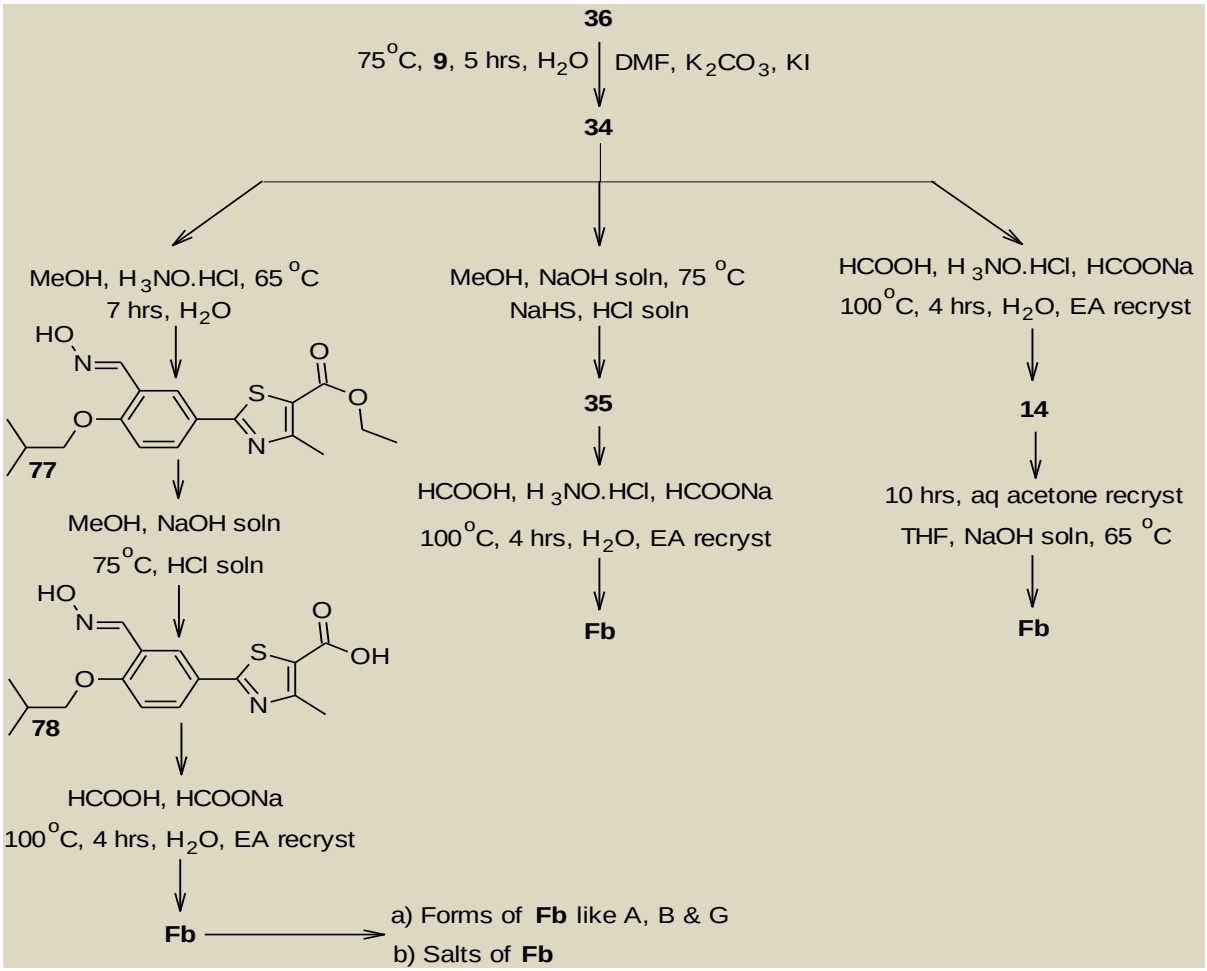
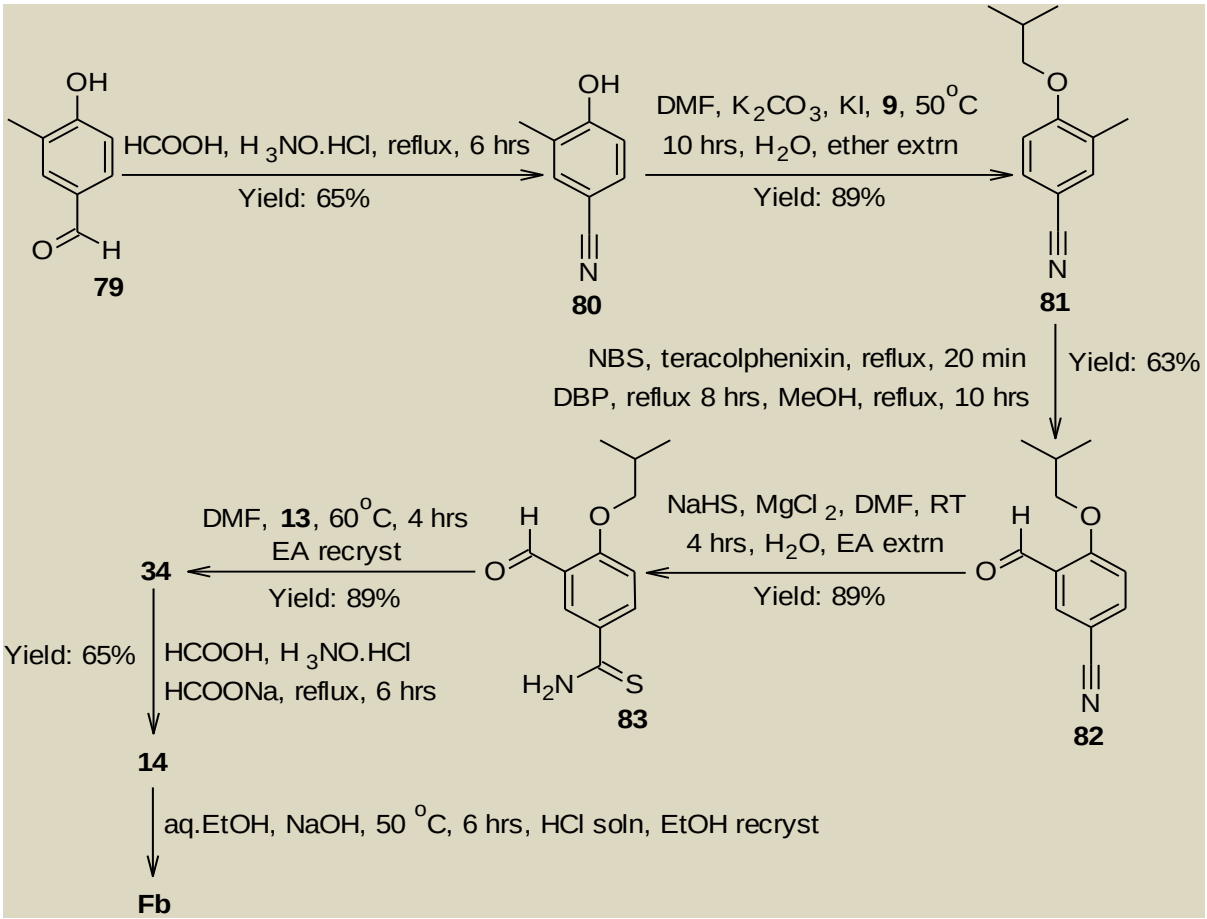


Scheme 28b: Synthesis of **Fb**, its forms and it salts as per the disclosure by Satyanarayana et al. [53]



Scheme 29: Synthesis of **Fb** from **79** as per the disclosure by Zou [54]

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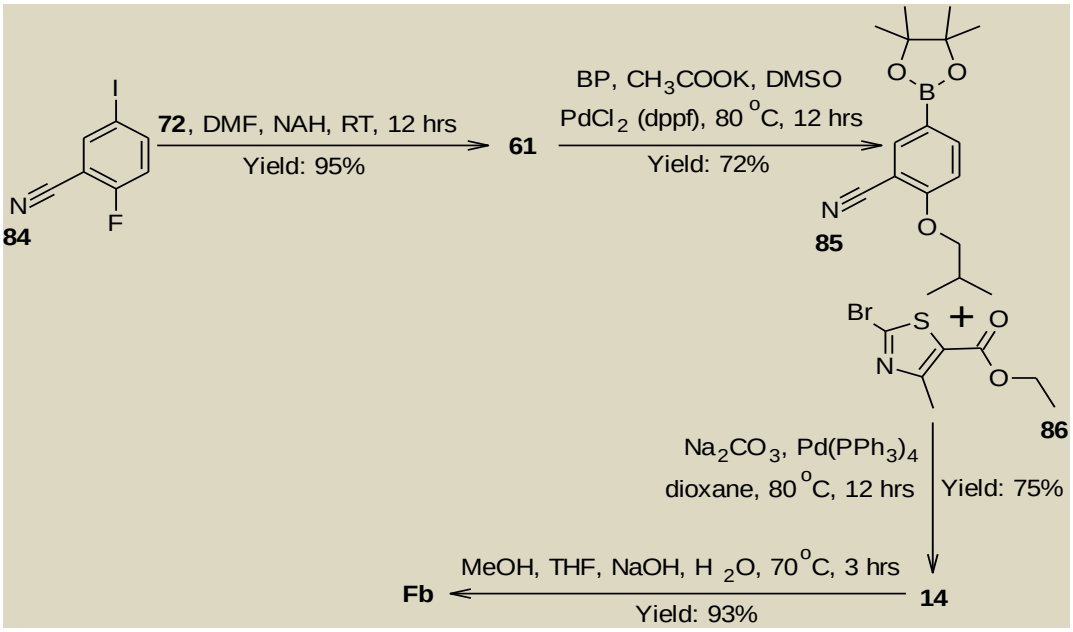
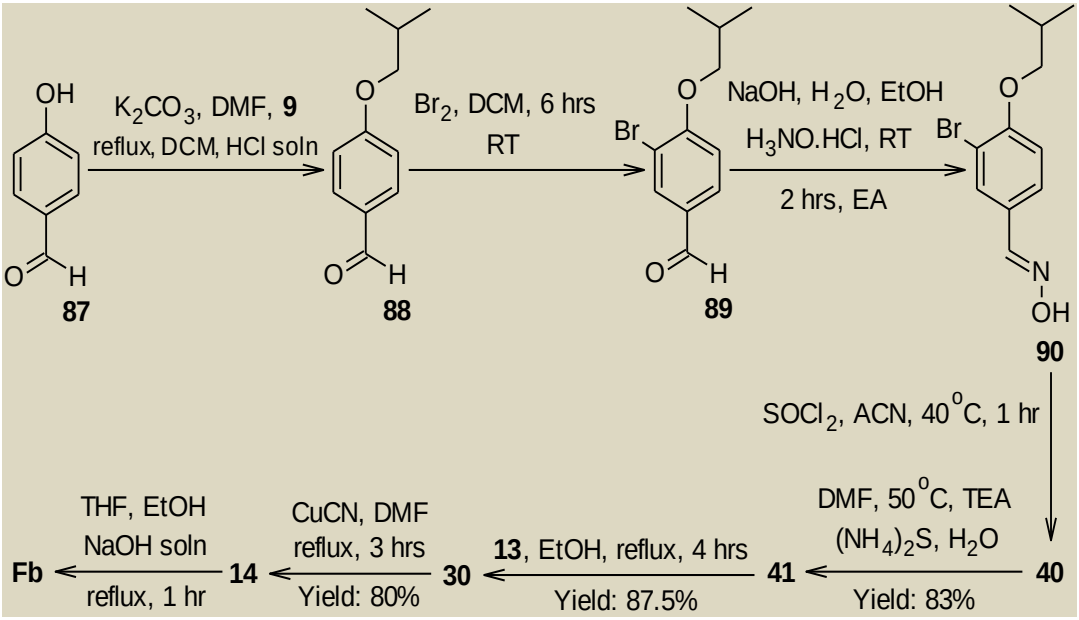
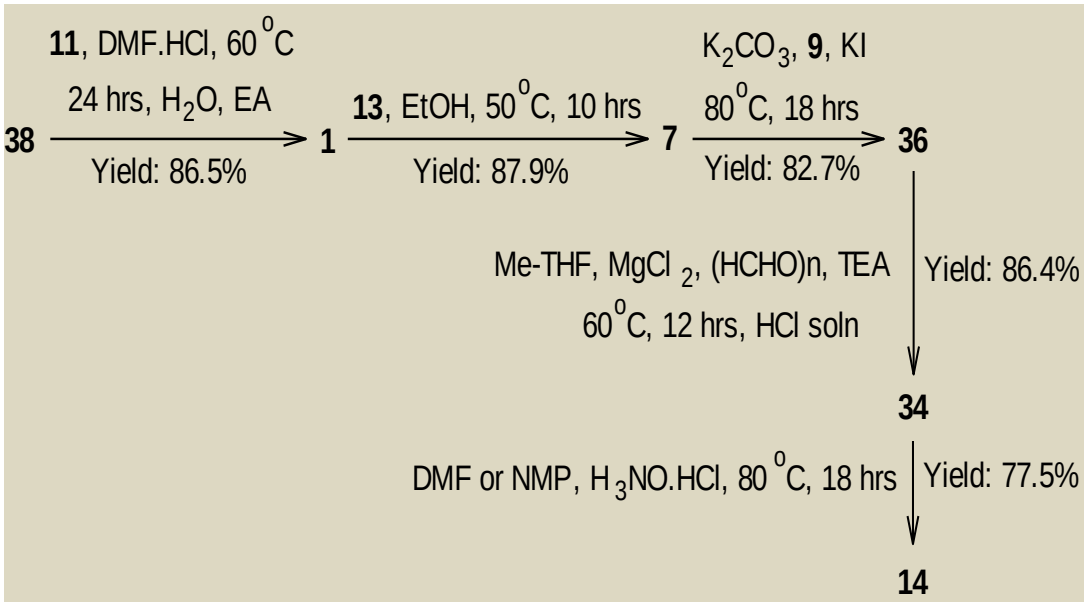


Scheme 30: Synthesis of **Fb** from **84** as per the disclosure by Hong & Li [55]



Scheme 31: Synthesis of **Fb** from **87** as per the disclosure by Wu et al. [56]



Scheme 32: Synthesis of **14** from **38** as per the disclosure by Zou [57]

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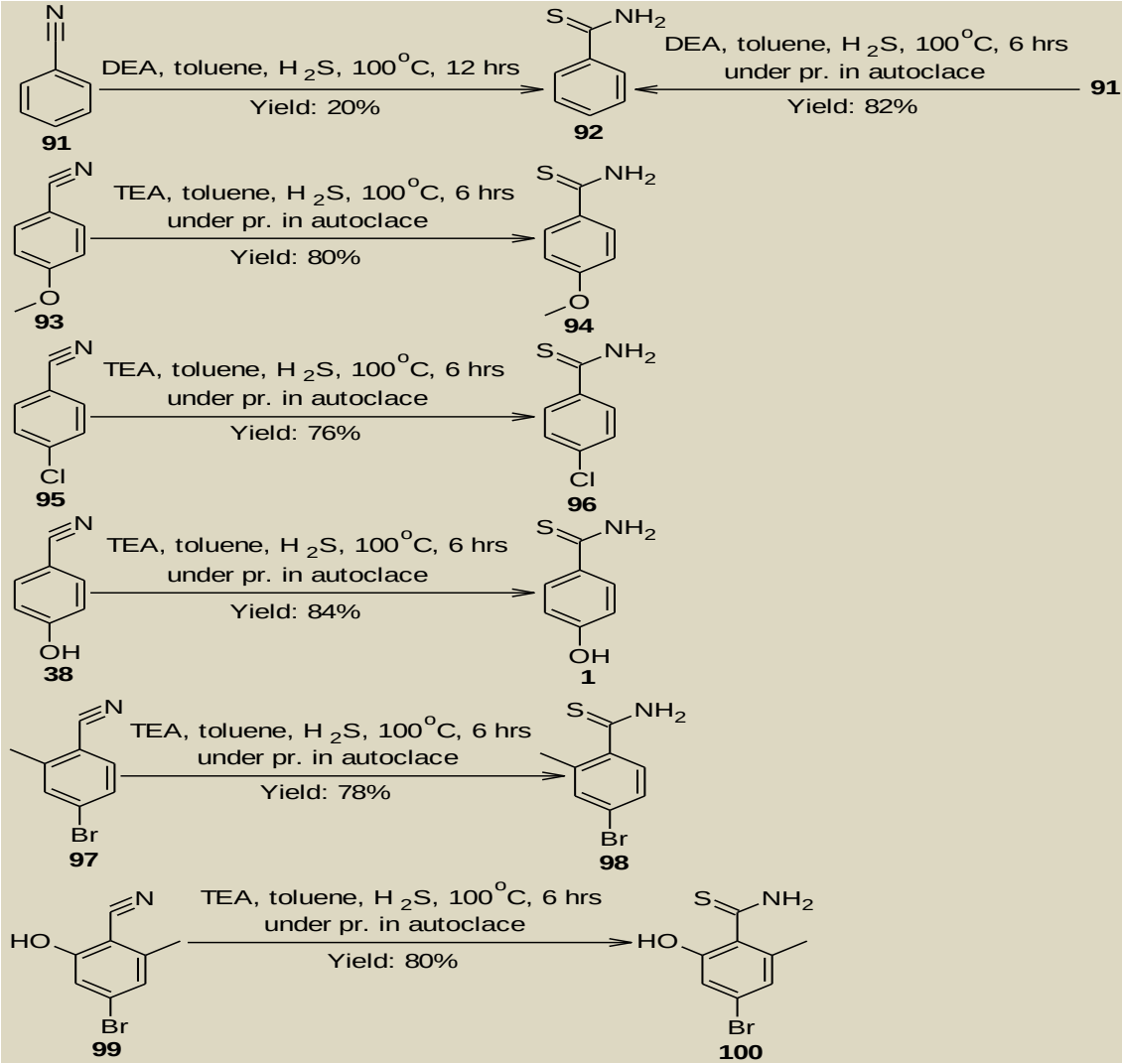
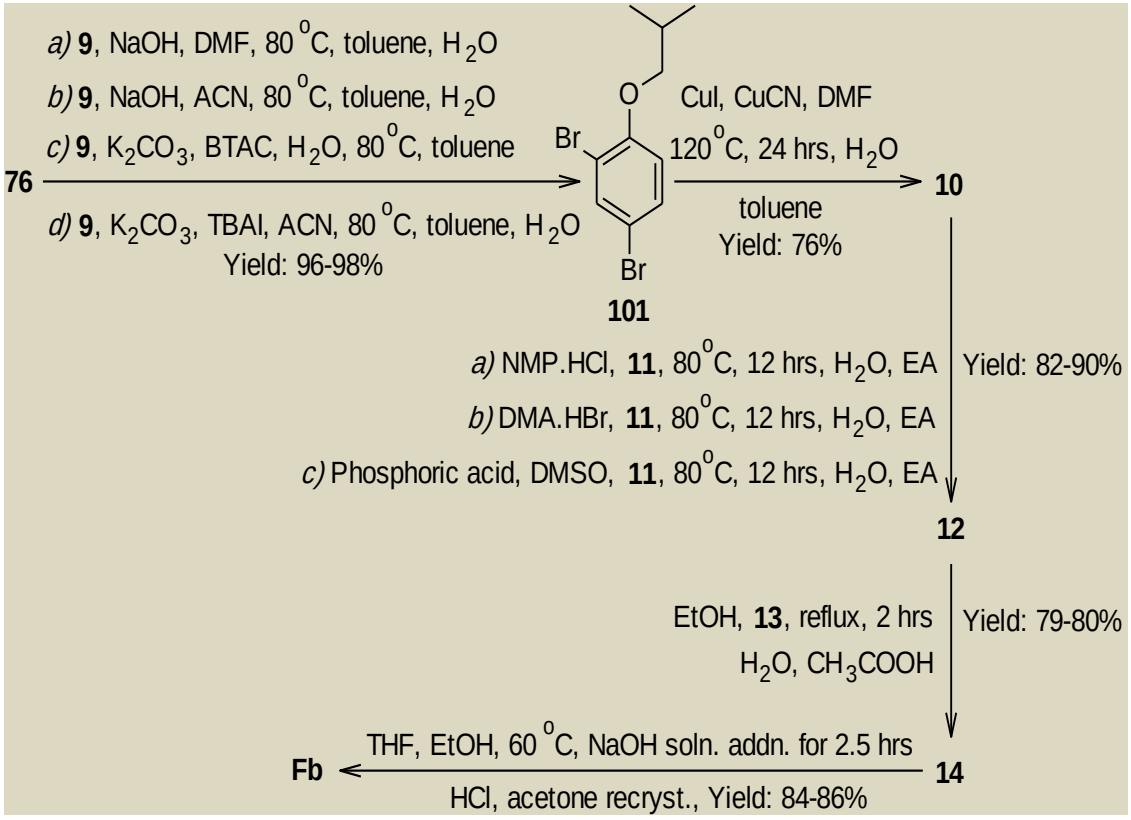


Scheme 33: Synthesis of some thiobenzamides as per the disclosure by Hayashisaka & Iida [59]



Scheme 34: Synthesis of **Fb** from **76** as per the disclosure by He et al. [60]

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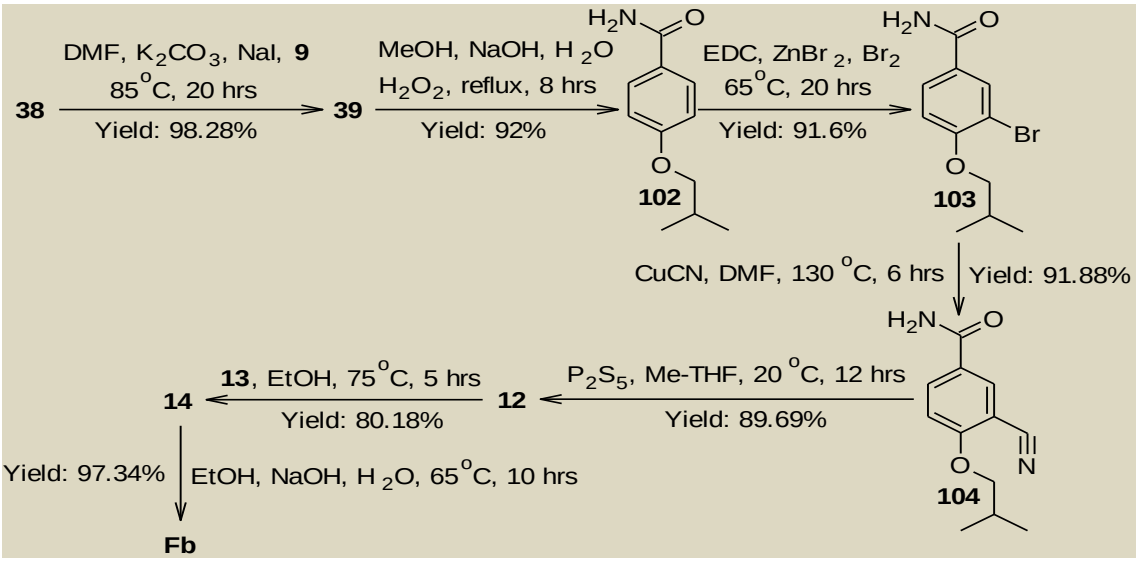
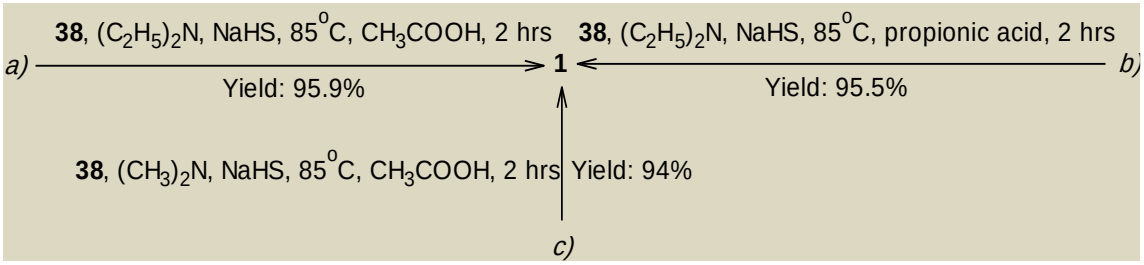
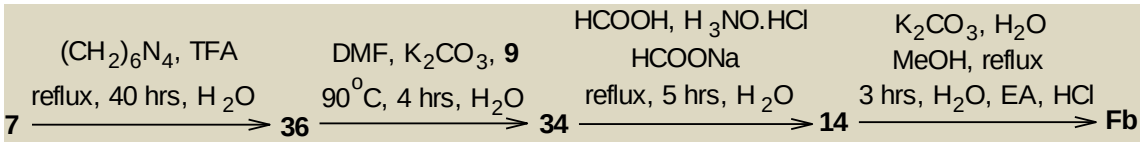


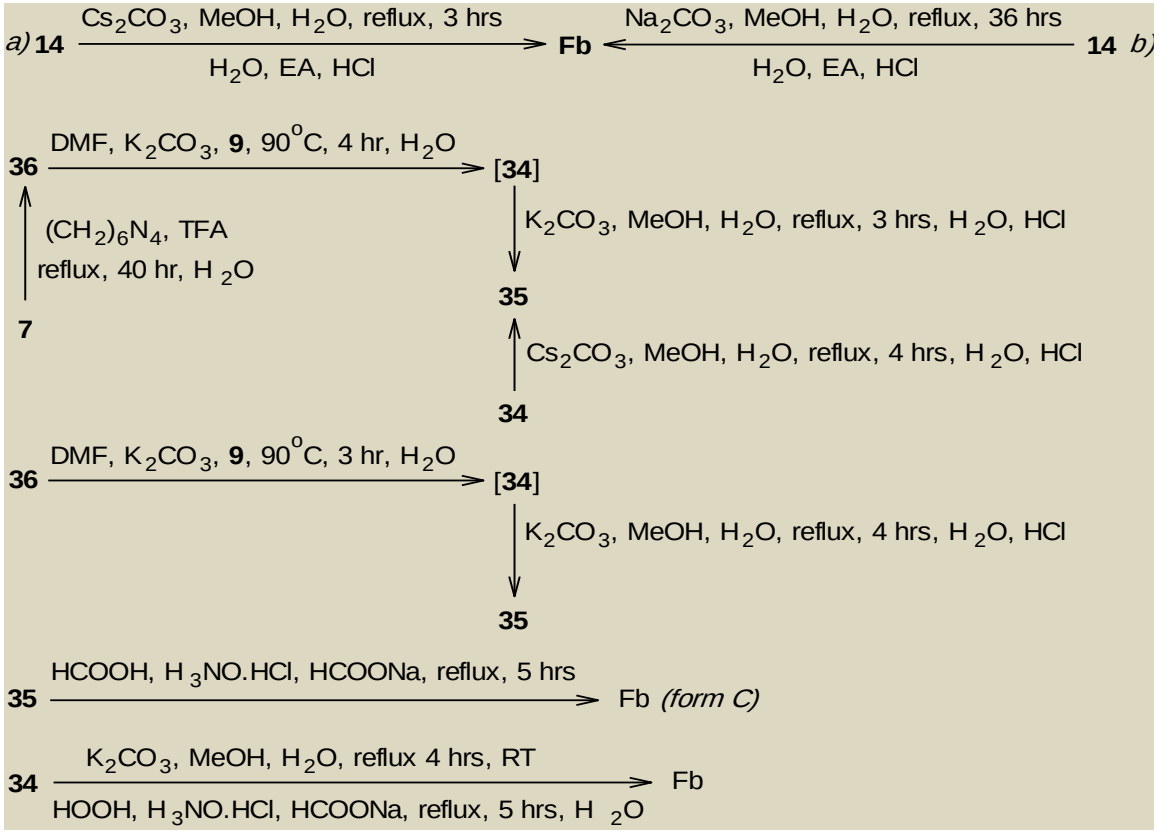
Scheme 35: Synthesis of **Fb** from **38** as per the disclosure by Anonymous [61]



Scheme 36: Synthesis of **1** from **38** as per the disclosure by Guo & Ji [64]



Scheme 37a: Synthesis of **Fb** from **7** as per the disclosure by Luthra et al. [68]



Scheme 37b: Synthesis of **Fb** as per the disclosure by Luthra et al. [68]

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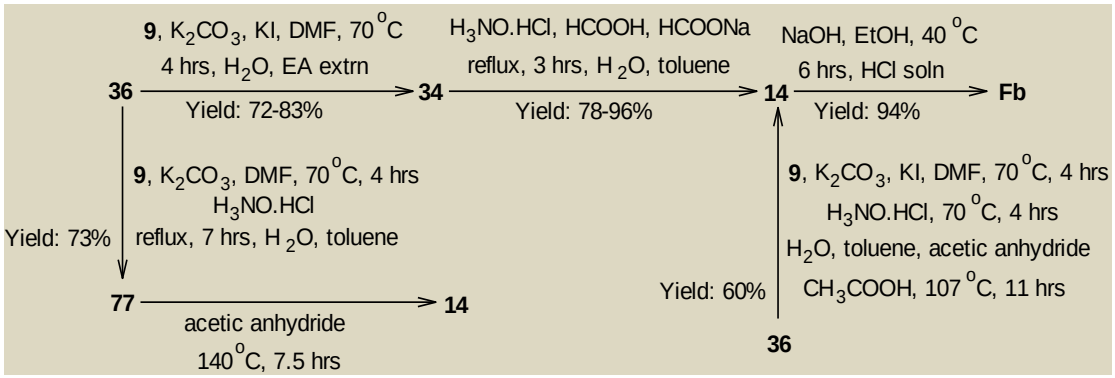
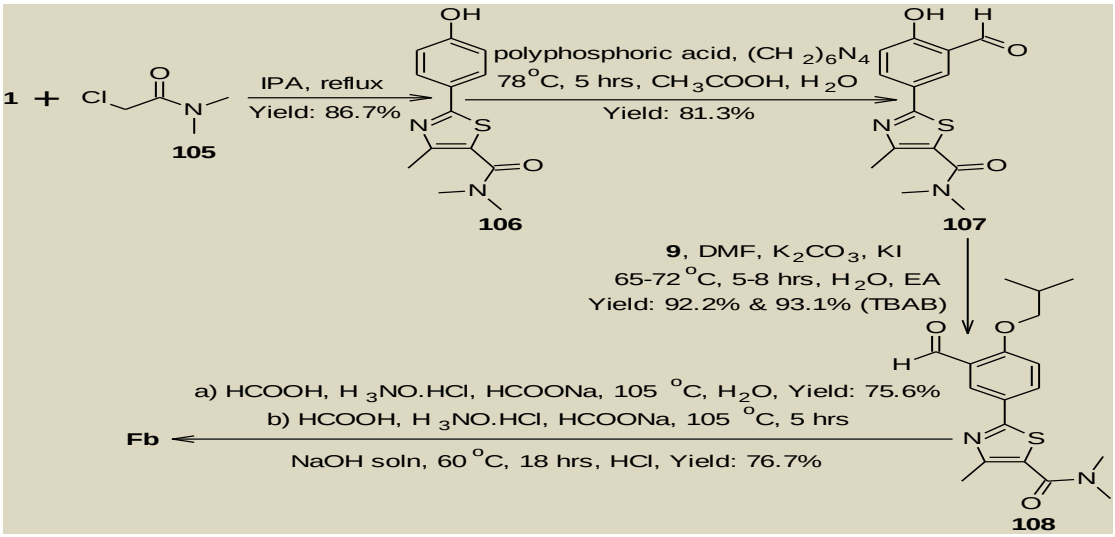
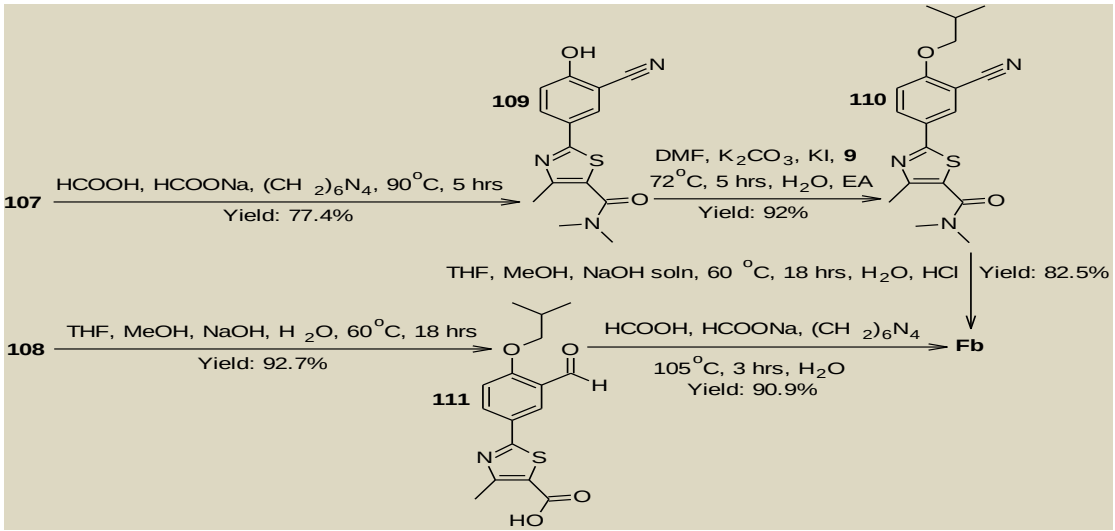


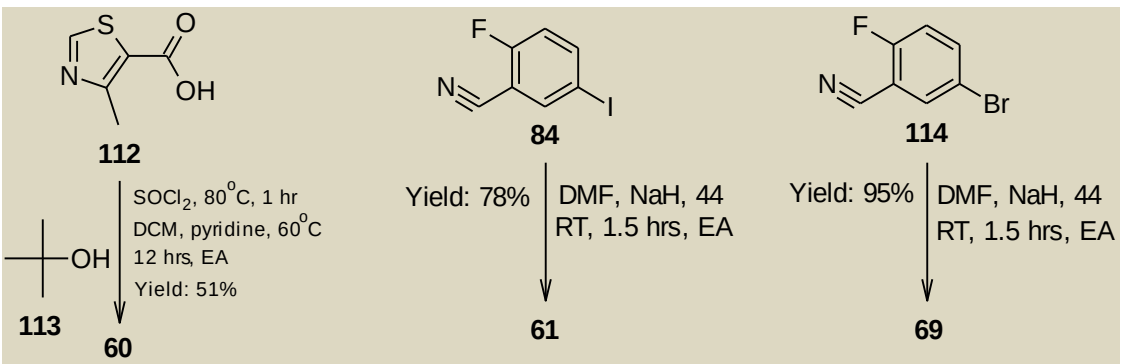
Scheme 38: Synthesis of **Fb** from **36** as per the disclosure by Metsger et al. [69]



Scheme 39a: Synthesis of **Fb** from **1** as per the disclosure by Rajadhyaksha et al. [70]



Scheme 39b: Synthesis of **Fb** from **107** or **108** as per the disclosure by Rajadhyaksha et al. [70]



Scheme 40a: Synthesis of **60**, **61** & **69** as per the disclosure by Komiyama et al. [71]

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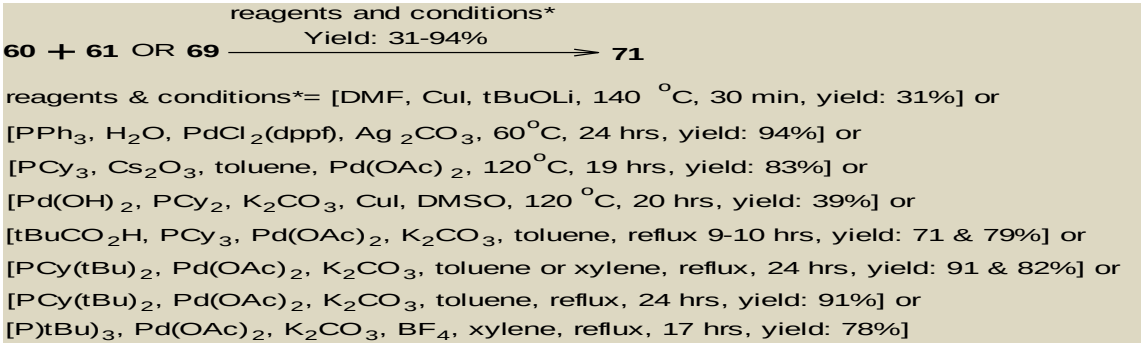
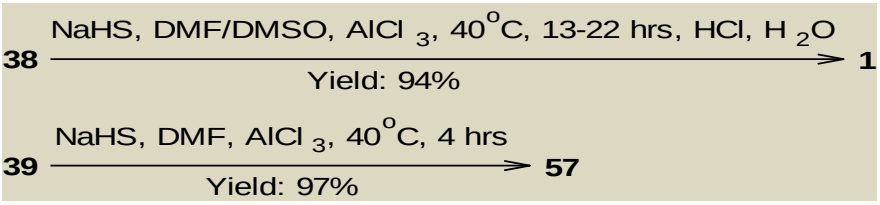


Scheme 40b: Synthesis of **71** as per the disclosure by Komiyama et al. [71]



Scheme 41: Synthesis of **1** & **57** as per the disclosure by Satoshi [74]

Upon summarizing the prior art disclosures in accordance to their region-specific origin, there are nine countries which had facilitated the synthesis and process development of **Fb** and its related compounds through various organizations/institutions/laboratories/individuals etc. Interestingly, USA, Canada, Japan, China, Spain, UK, India, Israel, and Argentina are the countries in which the research work on **Fb** was conducted **Table 4**. Among those countries, Japan and China are the leading contenders behind the development of **Fb** and its associated moieties.

Table 4: Country-wise list of institutions/organizations/laboratories/individuals etc behind the synthesis of **Fb** and its related compounds

Ref.	Research work was executed by or belongs to	Country
[8]	American Cyanamid Co.	USA
[9]	Uniroyal Ltd.	Canada
[10]	Teijin Ltd.	Japan
[11]	Teijin Ltd.	Japan
[12]	Teijin Institute for Bio-Medical Research	Japan
[13]	Teijin K K.	Japan
[14]	Teijin Ltd.	Japan
[15]	Teijin Ltd.	Japan
[16]	Teijin Ltd.	Japan
[17]	Teijin Ltd.	Japan
[18]	Teijin Ltd.	Japan
[19]	Teijin Ltd.	Japan
[20]	Abbott Laboratories	USA
[21]	Shanghai Medical Industry Institute, Zhejiang Huahai Pharmaceutical Co., Ltd.	China
[22]	Shanghai Medical Industry Institute, Zhejiang Huahai Pharmaceutical Co., Ltd.	China
[23]	Kangya Pharmaceutical Industry Co., Ltd. Ningxia, Shenyang Pharmaceutical University	China
[24]	Graduate School of Science, Nagoya University & Japan Science and Technology Agency, Nagoya	Japan
[25]	Shanghai Institute of Pharmaceutical Industry, Zhejiang Huahai Pharmaceutical Co., Ltd.	China
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Conclusion: This review article has the complete collection of prior arts from 1970-2012 regarding the synthesis of **Fb** and its related compounds. This has been substantiated with 41 reaction schemes which are framed based on the disclosures in 67 scientific communications. The reaction schemes are self-explanatory because all the reagents and specific conditions were provided in every reaction scheme with yield (if disclosed). Strategically, **Table 1** provides the hint of key raw materials involved along with the number of process steps involved. **Table 2** provides the year-wise statistics of disclosed prior arts. **Table 3** provides the IUPAC nomenclature of raw materials, reagents, and intermediates which had featured in the reaction schemes. **Table 4** provides the country-specific data of organizations/institutions/laboratories/individuals behind the disclosure of all 67 prior arts till 2012. More importantly, this review work can trigger the pathway for new inventions/innovations to synthesize **Fb** in the near future.

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