

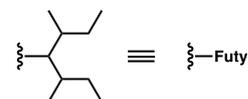


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# Methyl Ethyl Butyl Fytyl

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Everyone who has spent more than a year in the field of organic chemistry has heard the refrain: methyl ethyl butyl futile. This joke underlines the point of diminishing returns which is reached when making analogues of the same molecule. Because of this joke, the versatile chemistry of the futyl group has been overshadowed. This review highlights some examples in the history and applications of the futyl group.



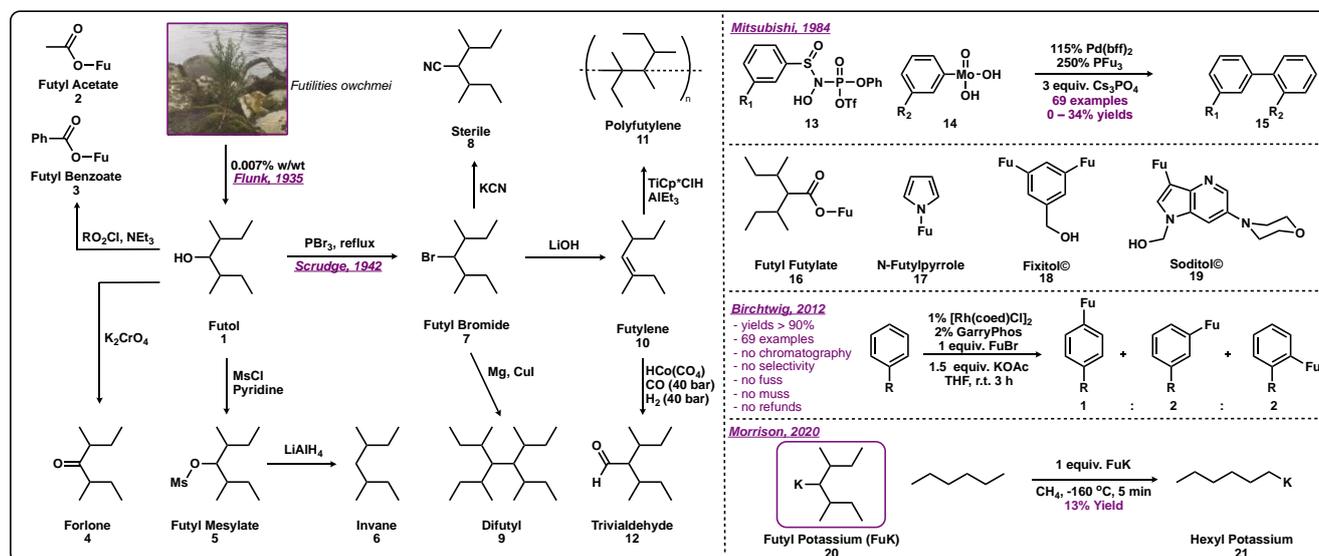
The IUPAC brown book defines the futyl group as a (di-sec-butyl)methyl fragment, which is abbreviated as Fu.<sup>1</sup> The floppy, aliphatic nature of the Fu group gives its compounds a slimy character when compared to its sleeker isopropyl and tert-butyl cousins. The first recorded example of a futyl molecule was the isolation of futol (**1**) from the plant *Futilitus owchmii* by Erasmus Flunk in 1935.<sup>2</sup> The yield (0.007% w/wt) was so low, one wonders why he bothered, but having spent a decade working as an accountant, we can assume he was well accustomed to pointless tasks. Flunk prepared a number of futyl esters from futol, such as futyl acetate (**2**, a solvent) and futyl benzoate (**3**, which is completely insolvent).

Flunk's futyl chemistry was cut short by his untimely death in a cheese-slicing accident in 1942. His student, Herbert Scudge, inherited his legacy. Scudge performed several functional group transformations on futol, beginning with oxidation to forlone (**4**).<sup>3</sup> Reaction of **1** with MsCl yielded futyl mesylate (**5**), which could be reduced to invane (**6**). Bromination of futol gave futyl bromide (**7**), though forceful conditions were needed to convince futol to react. Futyl bromide is a common entry point to futyl chemistry. By reacting futyl bromide with cyanide, Scudge obtained Sterile (**8**), a useful contraceptive often abbreviated to FuCN. In an attempt to perform a cuprate addition, Scudge inadvertently synthesised difutyl (**9**, also called FuFu or Fu<sub>2</sub>). Futyl bromide can also be eliminated with LiOH to yield futylene (**10**). Polymerisation of **10** yields polyfutylene (**11**), while hydroformylation gave trivaldehyde (**12**) in ironically low yield.

At this stage, Scudge's futyl chemistry was curtailed, as despite the prodigious nature of his work, nobody would fund him. Scudge left academia to become an art critic and table dancer in 1953. Futyl chemistry was left largely untouched for several decades until Mitsubishi and co-workers prepared trifutylphosphine as a ligand for use in the coupling of aryl thiahydroxylaminophenoxyphosphoryltriflates (**13**) and phenylmoronic acids (**14**).<sup>4</sup> With ligand loadings as low as 250 mol%, Mitsubishi was able to achieve a catalyst turnover of up to 7.

In 1990, Lasquisha and Alapisha held a competition to publish the synthesis of the most useless compound in a scientific journal. Alapisha struck first by esterifying futol and futylic acid to make futyl futylate (**16**), which was published in AIR.<sup>5</sup> However, Lasquisha was proclaimed the victor for publishing the synthesis of N-futylpyrrole (**17**).<sup>6</sup> In this striking example of gilding the lily, Lasquisha suggested that pyrrole would still win the competition, even without the futyl group.

Futyl chemistry got its first taste of popularity in 2001 when the pharmaceutical giant Smerk brought their drug Fixitol<sup>®</sup> to market.<sup>7</sup> Fixitol, a highly futylated molecule, was originally intended to treat restless-breast syndrome, however clinical trials found that the molecule mitigated the mood swings associated with bipolar disorder in post-grads. Further studies indicated that the highly lipophilic nature of futyl groups were aiding transport across the blood-brain barrier.<sup>8</sup> Smerk's competitors weren't far behind, and Jøhansson and Jøhansson



released Soditol<sup>®</sup> (19) a year later. The success of Fixitol led to a rush for new futyl drugs. This in turn led to a search for futylation methodology, as Scrudge's original futylation conditions were hampered by low tolerance (like most things from the 50's).

The first such example was reported by Cupid Stunt from the University of Llanbobbll, Old South Wales.<sup>9</sup> Stunt developed a procedure for the palladium-catalysed futylation of phenylmoronic acids. The appeal of this reaction lies in the availability of moronic acids (they seem to be everywhere these days). This work was followed up by Barabbas with an atom-transfer-radical-futylation,<sup>10</sup> and by Nebuchadnezzar with the hydrofutylation of alkenes.<sup>11</sup> More recently, Johan Birchtwig reported the rhodium-catalysed directionless C-H futylation of arenes.<sup>12</sup> This protocol exhibits the high yields, simple purification, and complete lack of selectivity characteristic of directionless C-H activations. While this would be a most useful reaction, no one else can afford to try it until the rhodium market settles down again.

The pinnacle of futyl chemistry was reached in 2020 when the Morrison lab prepared futyl potassium (20, FuK) by refluxing futyl bromide in potassium metal.<sup>13</sup> Often referred to as an "uberbase", FuK is capable of deprotonating hexane, making it somewhat difficult to handle. Despite this handicap, FuK is now commercially available from both Smegma-Aldrich and DuCont Chemical.<sup>14</sup>

## Conclusions and Outlook

It can be expected that plenty more futyl chemistry will be published, but nobody will notice. After all, what would be the point?

## About the Author

Demeritus Professor Günther Schlöck was born in the small Austrian town of Fucking in 1905. He received his BSc from the back of a serial box in 1925, and commenced his doctoral work with Herr Doktor Professor Claus Graf von der Plonk at the Universität von Wankendorf. There he worked on the chemistry of purine and conducted the first synthesis of 2-purylarsole. He undertook postdoctoral work with Victor Grignard in 1927, but drew the short straw and had to work with strontium instead of magnesium. In 1938, Schlöck moved to ETH in Zurich to study the chemistry of gold. Positions at Oxford, Cambridge, UC Berkeley, and Oxford again saw him through to his current position as the Fritz Haber Chair of Chemistry at the University of West Failure.

## Conflicts of Interest

Günther Schlöck is the Imperial Editor in Chief of The Journal of Immaterial Science. That didn't stop reviewer two from being an arsehole, though.

## Declaration of Funding

This work was funded by the proceeds of crime.

## Acknowledgements

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