Brønsted Acid-Catalyzed Alkynylation of Benzhydrol

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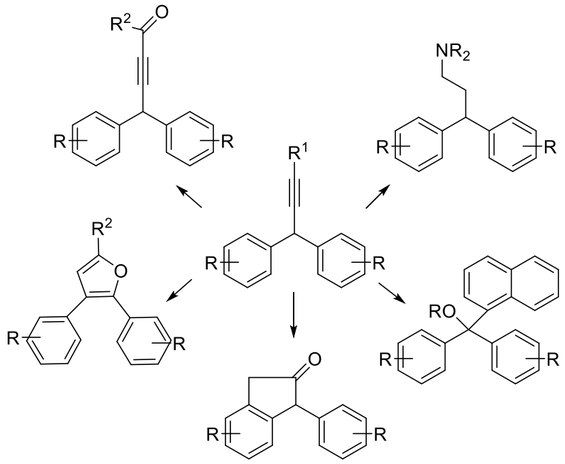
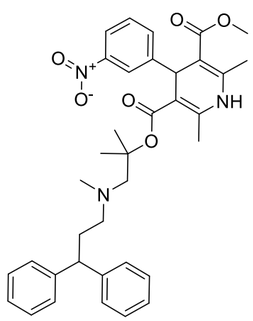
Introduction

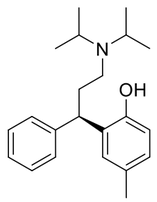
A Brønsted acid-catalyzed carbon-carbon bond forming methodology was developed for the preparation of alkyne-functionalized benzhydrols. This transformation has the advantage of short reaction times. The particularly appealing features of this reaction are the mild reaction conditions and the absence of transition metals, which are commonly toxic and highly unstable.[1] Internal alkyne units are frequently used as intermediates for the preparation of pharmaceuticals[2] and natural products[3], and there is a need for the rapid preparation of internal alkynes in drug design when screening the bioactivity of potential drug candidates[4].



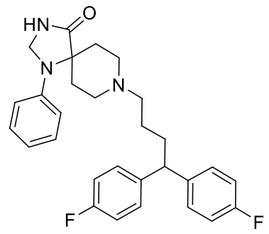
Drugs with Benzhydrol Moiety



Zanidip©
Lercanidipine
Antihypertensive drug

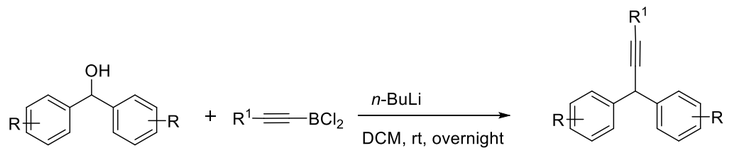


Detrusitol©
Tolterodine
Antimuscarinic drug for the treatment of urinary incontinence

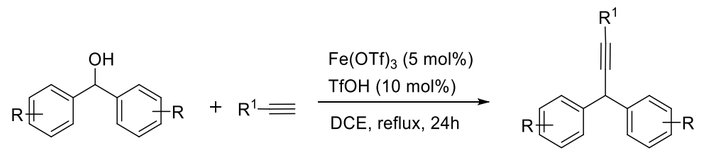


Imap©
Fluspirilene
Antipsychotic drug for the treatment of chronic schizophrenia

Current Methods

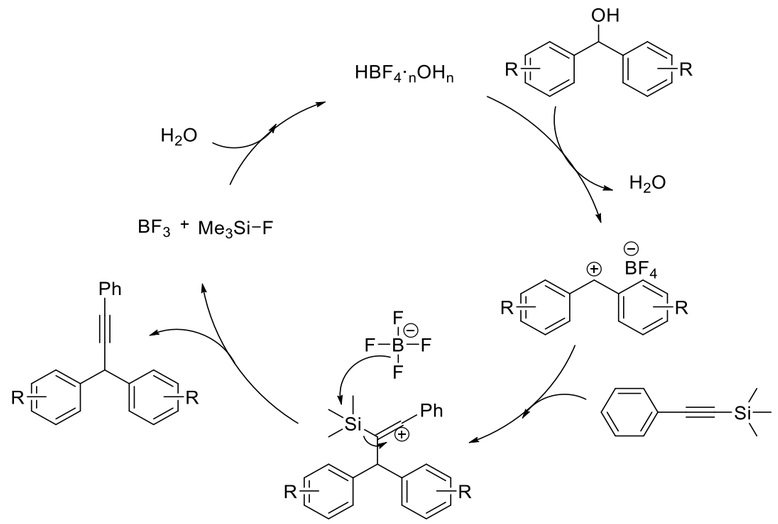


Drawbacks:
1. The exposure of both starting materials to n-BuLi, which forms an unstable haloborane intermediate.
2. Narrow substrate scope

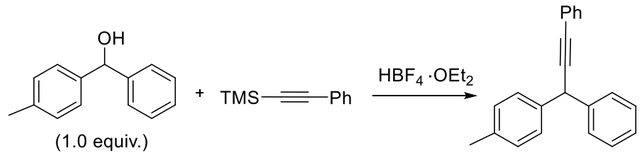


Drawbacks:
1. The inherent toxicity associated with the transition metal.
2. Reaction must be performed under inert gas.
3. Limited to terminal alkyne.

Proposed Mechanism



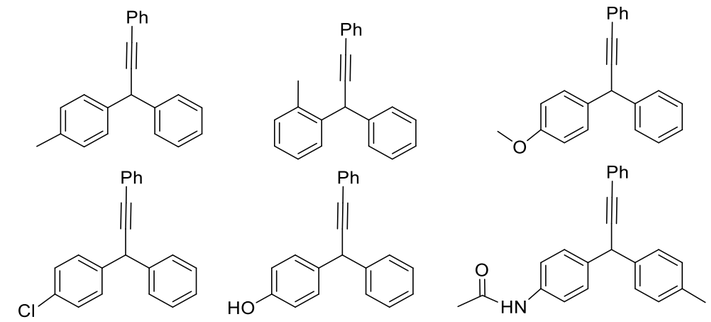
Optimization of Reaction Conditions



Entry	Solvent	Phenyl Acetylene (equiv.)	Acid (equiv.)	Temp. (°C)	[Reaction] (mmol/mL)	Time (min.)	Yield
1	CH_3CN	1.2	0.4	60	0.36	20	N/A
2	Toluene	1.2	0.4	60	0.36	20	26%
3	DCE	1.2	0.4	60	0.36	20	34%
4	DCE	1.2	0.4	50	0.36	20	31%
5	DCE	1.2	0.4	60	0.36	20	23%
6	DCE	1.2	0.4	70	0.36	20	19%
7	DCE	1.1	0.5	50	0.36	20	48%
8	DCE	1.1	0.5	50	0.25	20	55%
9	DCE	1.1	0.5	50	0.15	40	56%
10	DCE	1.2	0.5	50	0.15	20	31%
11	DCE	1.6	0.5	50	0.15	40	60%
12	DCE	2.0	0.5	50	0.15	40	73%

Future Work

Investigation of the reaction scope:



References

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