2-Naphthol as a Nucleophilic Carbon Source in a Catalyst Free, Mannich-Like Multicomponent Reaction

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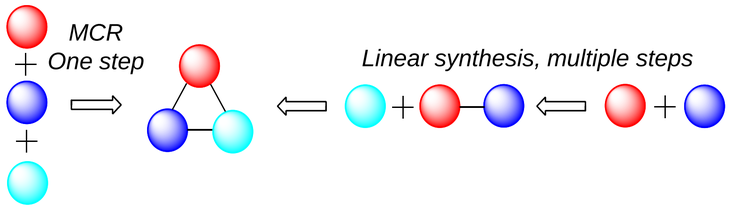
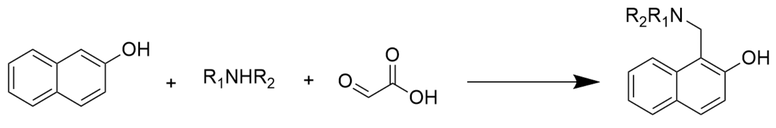
Introduction



- Multicomponent reactions (MCR) combine three or more substrates simultaneously for high atom economy. MCRs offer added advantages such as reduced synthetic operations, maximized functional complexity, and assembly of large compound libraries in shorter period.
- 2-Naphthol derivatives possess anticancer, antibacterial and anti-inflammatory properties.[1-3] Additionally, they exhibit cardiovascular properties such as antihypertensives and calcium channel blockers.[4,5]
- Given the medicinal importance of 2-naphthol derivatives, we developed a 2-naphthol based MCR to expeditiously access various 2-naphthol analouges to uncover new molecules that possess anticancer and antibacterial properties.

Experimental Method

- A mixture of 2-naphthol (1.0 eq), different aliphatic amines (1.25 eq), and glyoxylic acid (1.25 eq) were reacted in DMF at 90 °C to furnish 2-napthol derivatives.
- Various solvents and temperatures were evaluated to determine optimal conditions to complete the MCR transformation.



Scheme 1: Synthesis of 2-naphthol analouges

Results and Discussions

Table 1: Effect of solvent on the formation of 1-methylmorpholine-2-naphthol

S.N	Solvent	Yield (%)
1	DMF	76
2	DMA	73
3	DMSO	35
4	THF	Trace Amount
5	Toluene	Trace Amount
6	EtOH	Trace Amount
7	Dioxane	Trace Amount
8	ACN	No Reaction

Note: The reaction was carried out at 90 °C

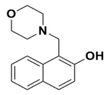
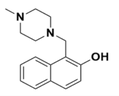
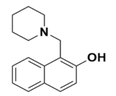
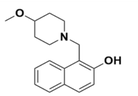
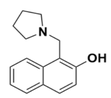
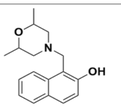
Table: 2 Effect of temperature on the formation of 1-methylmorpholine-2-naphthol

S.N	Temperature (°C)	Yield (%)
1	RT	No reaction
2	90	76
3	120	70
4	150	Trace Amount

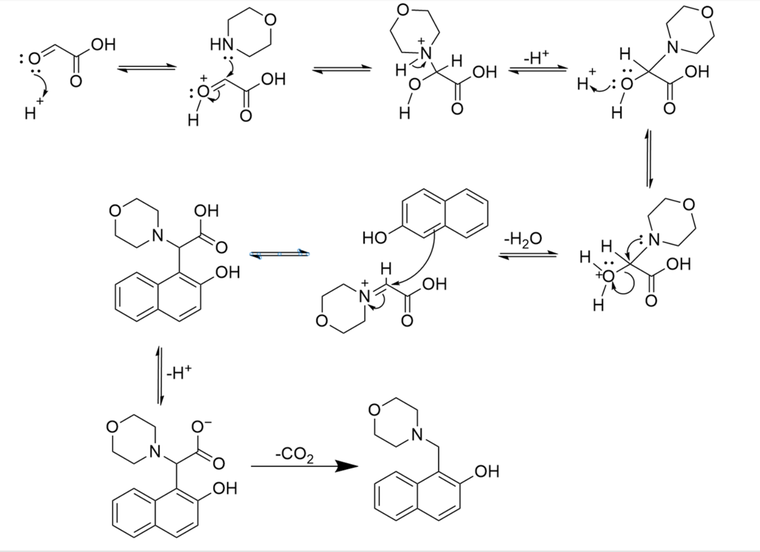
Note: DMF was used as the solvent

- The 2-napthol MCR had highest yield when DMF was used as the solvent.
- Various aliphatic amines were used to afford the 1 alkyl amine derivatives.
- Yields as high as 81% were obtained.
- Temperatures greater than 90 °C reduced transformation of the MCR.
- Polar protic solvents offered improved yield over aprotic solvents.

Table 3: Synthesis of various aminoalkyl naphthol derivatives

S.N	Products	Yield (%)
1		76
2		71
3		81
4		61
5		6
6		55

Proposed Reaction Mechanism



Conclusions and Future Perspectives

Various 2-naphthol analogs were synthesized via a catalyst-free one pot process. The reaction between naphthol, aliphatic amines, and glyoxylic acid was optimized by varying solvents and temperatures to afford yield as high as 81%. Future work will include optimization of the reaction conditions for aromatic amines. The derivatives will be evaluated for their anticancer and antimicrobial properties.

References

1. Drug Dev. Res., 2003, 60: 261-269.
2. ChemistrySelect, 2020, 5, 5515.
3. Med Chem Res, 2012, 21, 3321–3325.
4. Eur. J. Med. Chem, 1999, 34, 10, 877-882.
5. Med. Chem. 1987, 30, 4, 627–635.

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