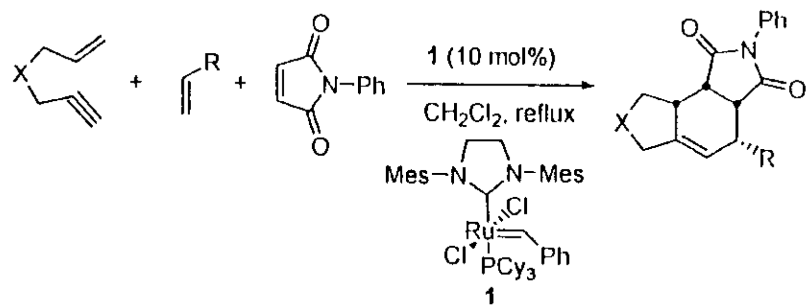
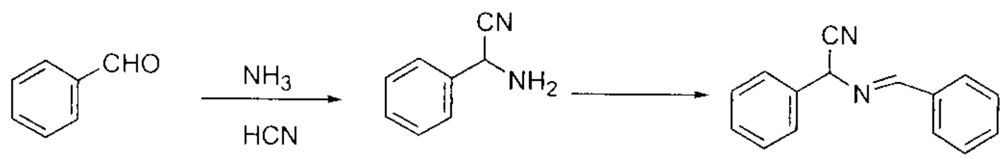
One-Pot Three-Component Tandem Metathesis/Diels-Alder Reaction

Lee, H.; Kim, H.; Tae, H.; Kim, B.; Lee, J. *Org. Lett.* **2003**, *5*, 3439.



Multi-Component Reactions (MCR)

-Chemical reactions that use three or more different starting materials and yields the final product in a one-pot procedure.
-Regarded as combinations or unions where the product of a two-component reaction reacts with a third component to give the next product and so on.....
-first MCR- Laurent and Gerhardt - 1838



-Today, about 300-400 different MCR's are known, 20-25% are based on isocyanides as one of the starting materials.

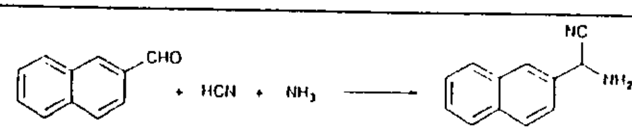
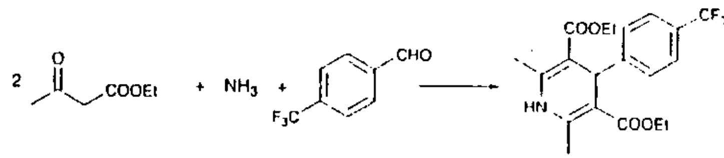
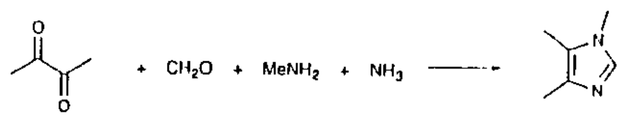
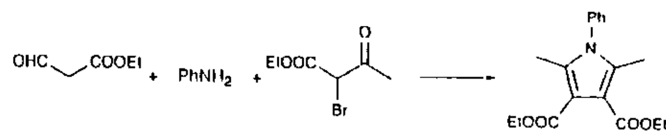
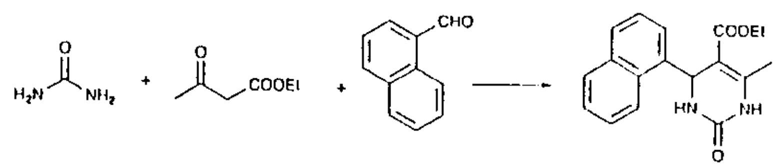
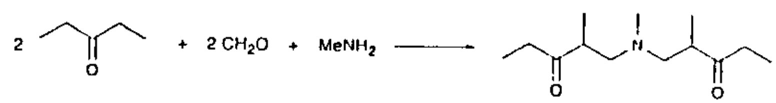
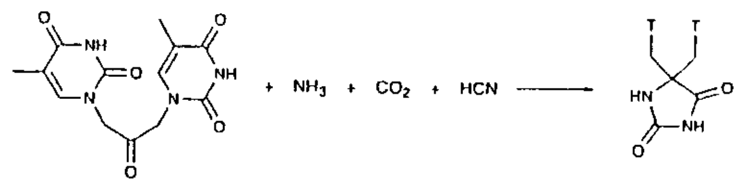
Advantages:
-Higly efficient, generate more than 2 chemical bonds per operation
-Structure can be easily varied by diversifying starting material
-Starting materials are commercially available or easily prepared
-quick acesss to heterocyclic compounds
-atom economy

-Careful consideration of reactivities of starting materials and respective products must be examined
-Optimal conditions for reactions represent a significant challenge since the involved two-component reactions usually require different conditions.

Domling, A; Ugi, I. *Angew. Chem. Int. Ed. Engl.* 1993, 32, 563.

Multi-Component Reactions

Table 1. Many of the historically significant MCRs are based on the reactivity of carbonyl or imine groups.

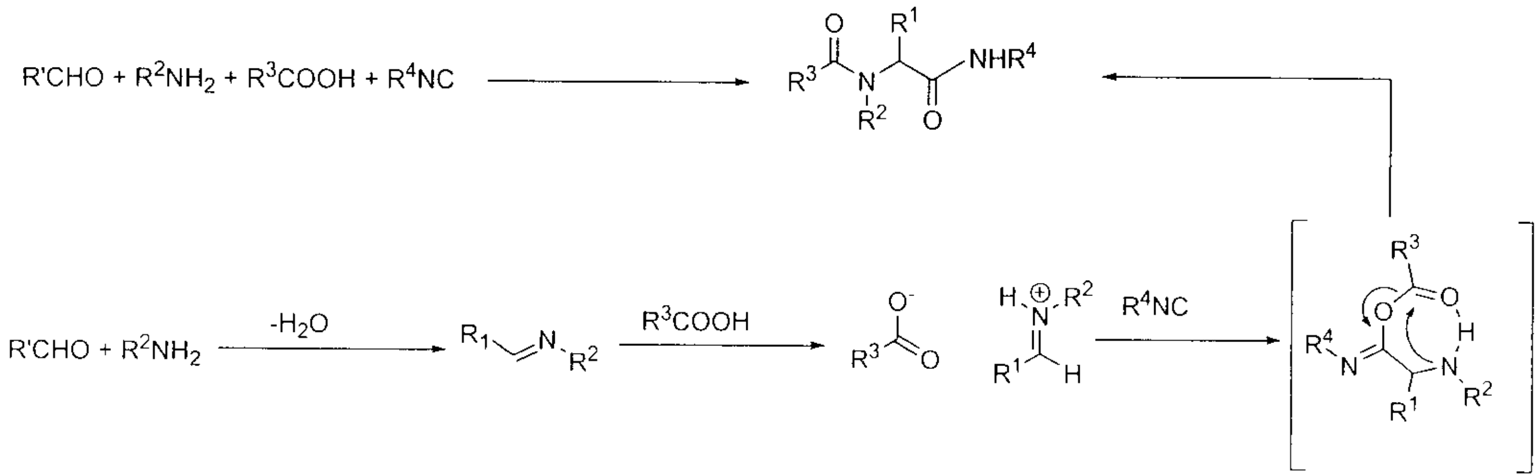
Name of the reaction	Year of discovery	Example[a]
Strecker synthesis[16]	(1838) 1850	
Hantzsch dihydropyridine synthesis[17]	1882	
Radziszewski imidazole synthesis[19]	1882	
Hantzsch pyrrole synthesis[23]	1890	
Biginelli reaction[25,26]	1891	
Mannich reaction[29]	1912	
Bucherer–Bergs hydantoin synthesis[30,26]	1941	

[a] T = thymine.

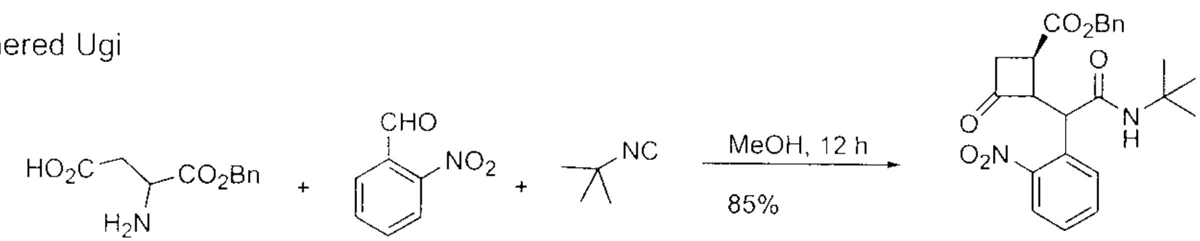
Ugi, I.; Domling, A. *Angew. Chem. Int. Ed.* 2000, *39*, 3168.

Ugi Reaction

-discovered in 1959, most utilized MCR



-tethered Ugi

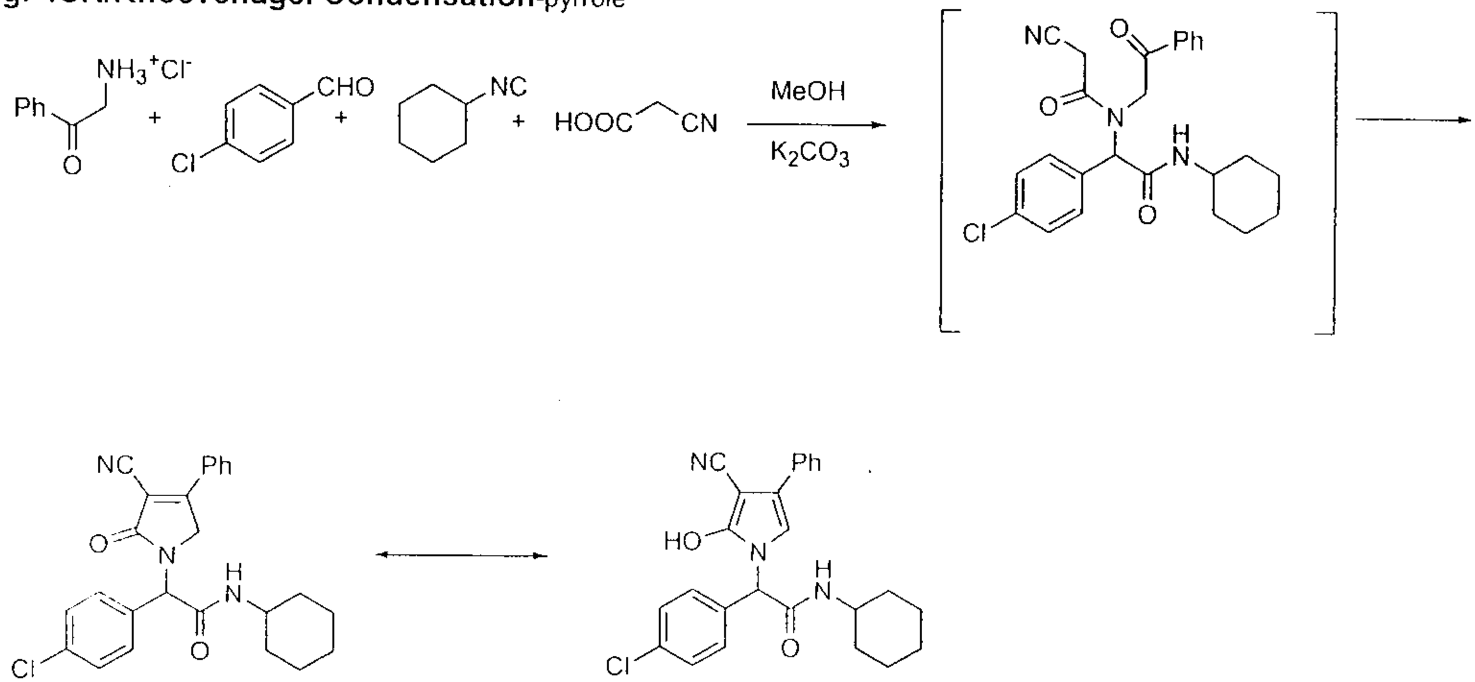


Weber, L. *Current Medicinal Chemistry* 2002, 9, 1241
Fukuyama, T. *et al. J. Am. Chem. Soc.* 2002, *124*, 6552

Combination of Ugi Reaction with Other Transformations:

-possible when starting materials bear other functional groups, that react after initial formation of Ugi adduct
-constraints--Ugi requires protic solvents- select a transformation compatible with protic solvents or develop novel conditions for Ugi

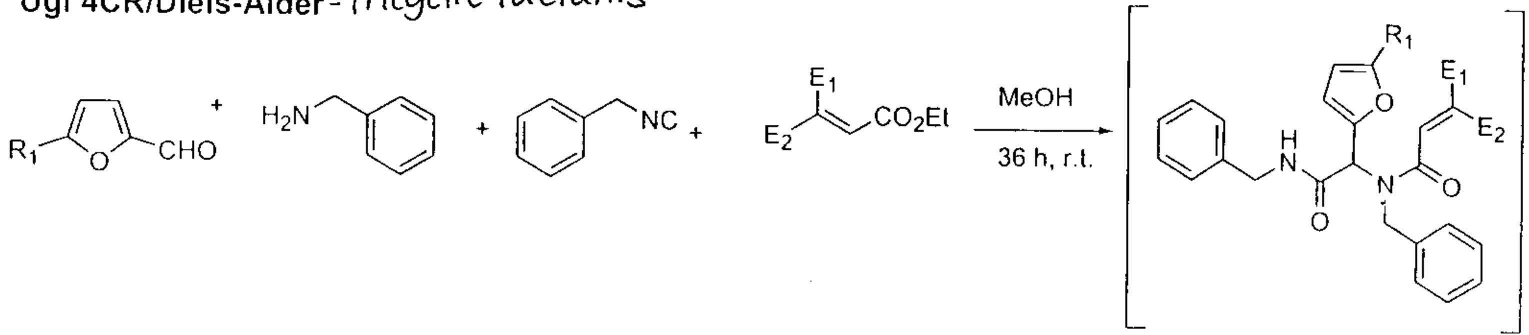
Ugi 4CR/Knoevenagel Condensation-pyrrole

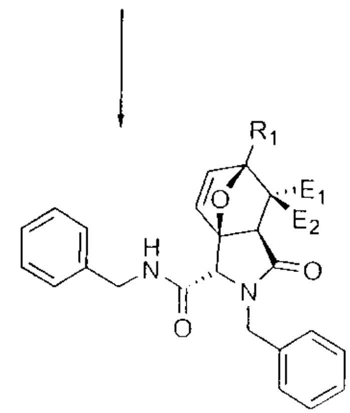


Zhu, J. Eur. J. Org. Chem. 2003, 1133-1144.

Combination of Ugi Reaction with Other Transformations:

Ugi 4CR/Diels-Alder-tricyclic lactams





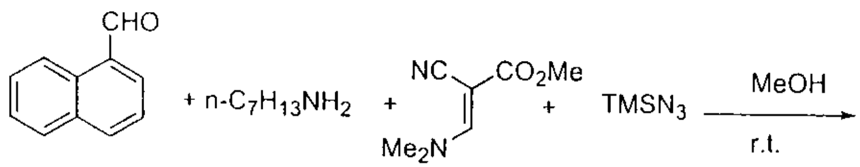
Entry	R_1	E_1	E_2	Yield %	Isomer Ratio
a	H	CO_2Et	H	89	92:8
b	H	H	CO_2Et	70	92:8
c	H	H	CONH-Bn	85	86:14
d	Me	CO_2Et	H	78	92:8
e	Me	H	CO_2Et	72	93:7
f	Me	H	CONH-Bn	81	83:17

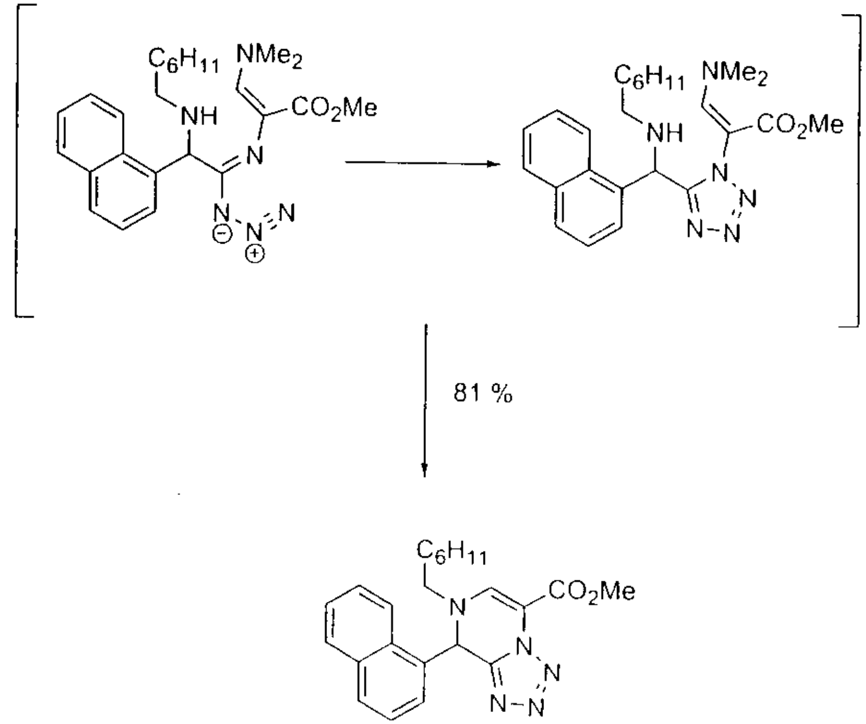
-can be used with polymer support

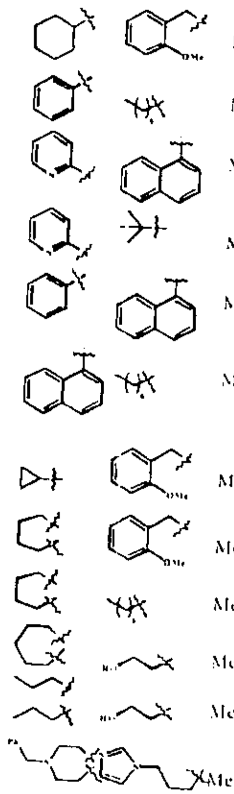
Paulvannan, K. *Tetrahedron Lett.* 1999, 1851-1854

<u>Combination of Ugi Reaction with Other Transformations:</u>

Ugi 4CR/Intramolecular 1,4-Addition and Elimination





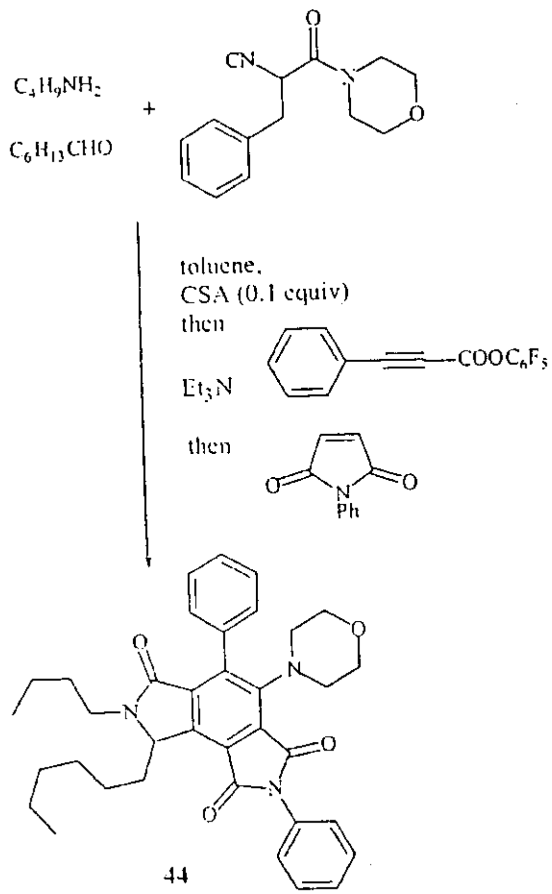


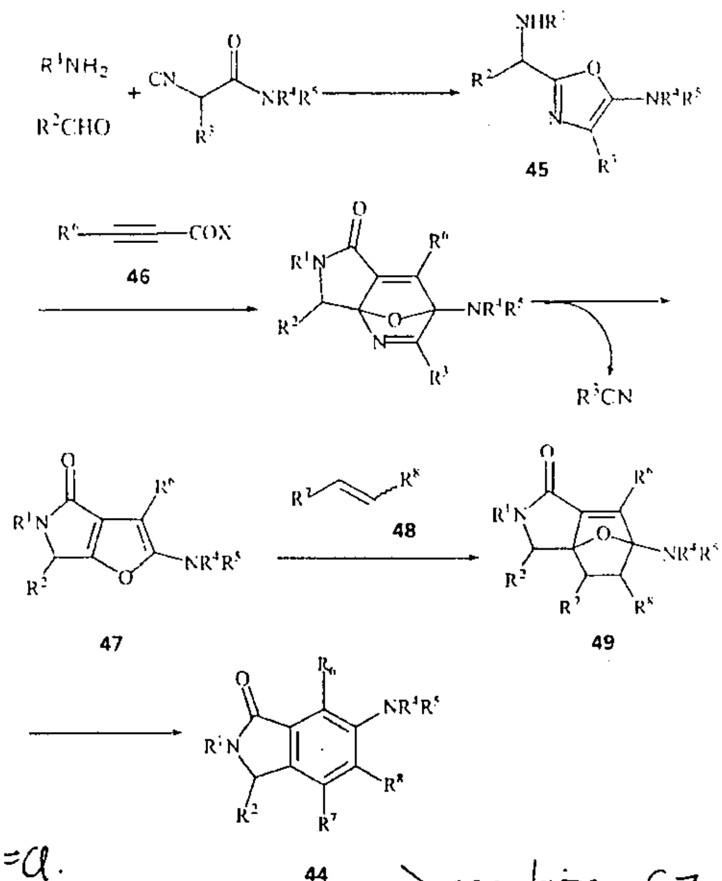
Entry	R1	R2	R3	Yield (A + B) Step 1 - %	Yield (C) Step 2 - %	Yield (C) Step 1+2 - %
1			Me	42	---	---
2			Me	68	100	---
3			Me	27 (cryst.)	100	---
4			Me	65	---	---
5			Me	46 (cryst.)	99	---
6			Me	---	---	81
7			Me	---	---	59
8			Me	---	---	46
9			Me	---	---	48
10			Me	---	---	46
11			Me	---	---	29
12			Me	---	---	72

Bienaymé, H. Bouzid, K. *Tetrahedron Lett.* 1998, 2735

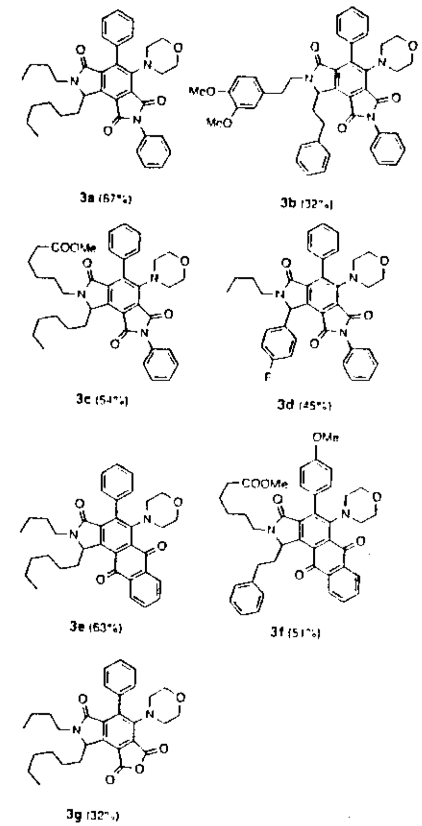
5-Component Reaction

-Hexasubstituted benzenes





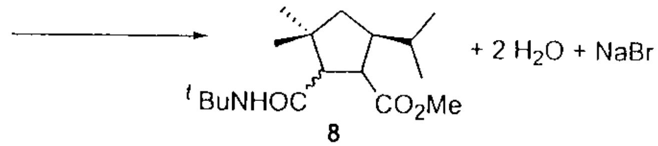
X=Cl.

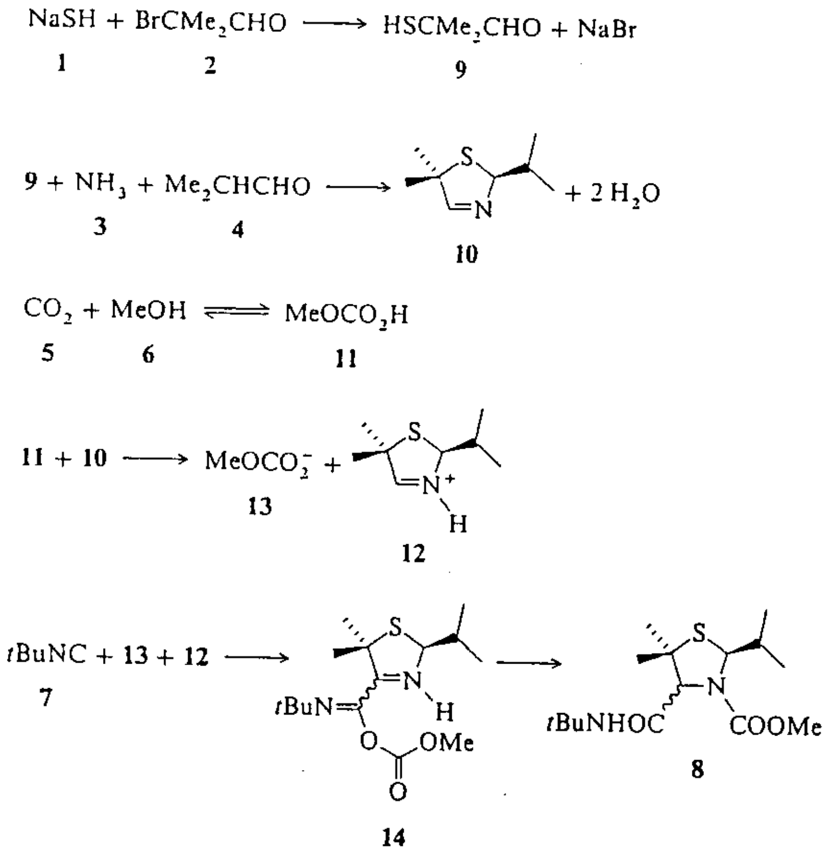


⇒ creation of 7-chemical bonds
5 points for diversity

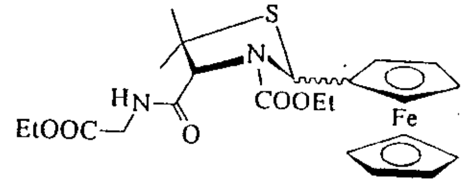
Zhu, J.; Jankar, P.; Bienayame, H.; Angew. Chem. Int Ed. 2002, 41, 4291.

Seven-Component Reaction

$NaSH + BrCMe_2CHO + NH_3 + Me_2CHCHO + CO_2 + MeOH + {}^tBuNC$ 



Scheme 2. Mechanism of the 7CC.



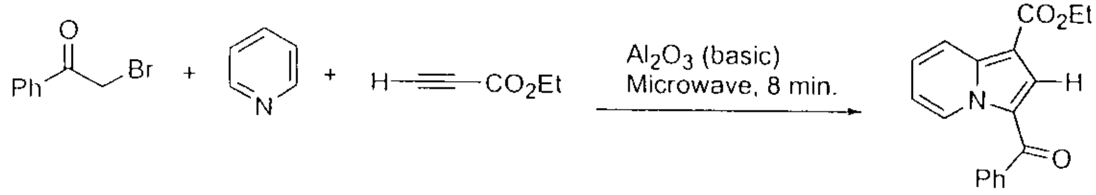
15

Table 1. Conditions and results of the syntheses of 8 and 15.

Product	Conversion [%] [a]	Yield [%] [b]	Diastereomeric ratio [c]	Solvent [d]	p [bar]
8	70	43	2:1	MeOH	16
15	58	18	14:9	EtOH	48

[a] Based on unchanged Asinger product (determined from the ^1H NMR spectrum of the reaction mixture). [b] Pure substance after flash chromatography. [c] Determined from the ^1H NMR spectrum of the reaction mixture. [d] Alcoholic component.

Microwave-Mediated MCR's: Indolizines



Scheme 3

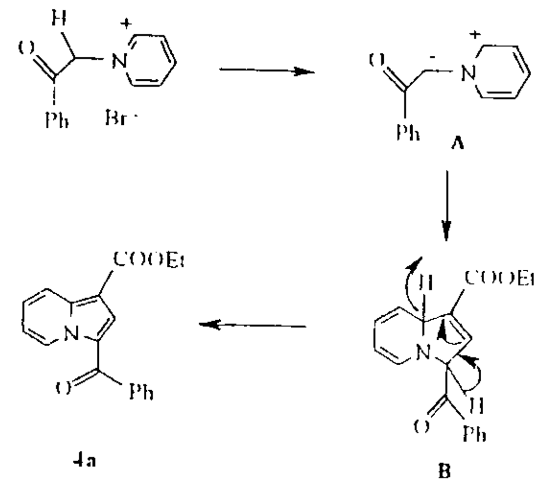


Table 1. Microwave-Promoted Three-Component Reaction[a] According to Scheme 1 Catalyzed by Alumina[b]

entry	catalyst	yield[c] of **4a** (%)
1	Al_2O_3	92
2	Nil	12
3	pyridine[d]	48
4	pyridine/Al_2O_3	78
5	toluene/Al_2O_3	68
6	THF/Al_2O_3	60
7	DMF/Al_2O_3	75
8	toluene/Et_3N/Al_2O_3	80
9	THF/Et_3N/Al_2O_3	76
10	DMF/Et_3N/Al_2O_3	82

[a] Reactions were carried using 1 mmol of phenacyl bromide, 1.2 equiv of pyridine, 1.2 equiv of ethyl propiolate, and 1 g of basic alumina. [b] Basic alumina was activated at 450 °C for 12 h. [c] Isolated yields. [d] An excess of pyridine was used without alumina.

Table 3. Three-Component Reaction of **1a**, **2**, and **3a** under Thermal Condition

entry	solvent	base	yield of **4a** (%)
1	toluene	Et_3N	60
2	THF	Et_3N	55
3	CH_3CN	Et_3N	50
4	pyridine	Et_3N	80
5	toluene	Al_2O_3	45
6	THF	Al_2O_3	42
7	CH_3CN	Al_2O_3	35
8	pyridine	Al_2O_3	88

Bora, U.; Saikia, A.; Boruah, R. Org. Lett 2003, 5, 435.

Microwave-Mediated MCR's: Indolizines

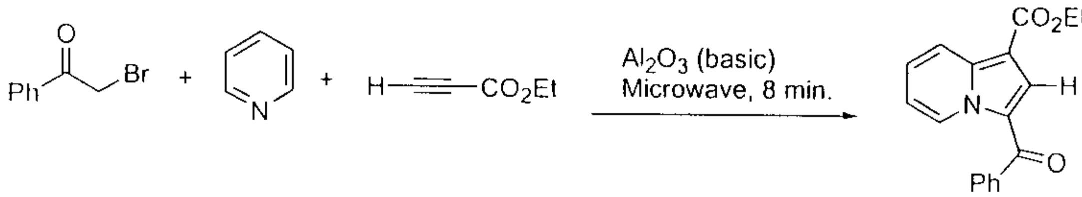
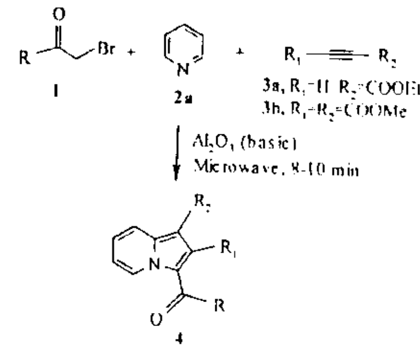
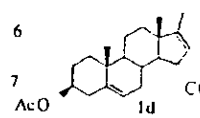
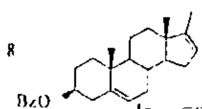


Table 2. Microwave-Mediated Three-Component Reaction of Acyl Halide **1**, Pyridine **2a**, and Acetylene **3** Catalyzed by Alumina



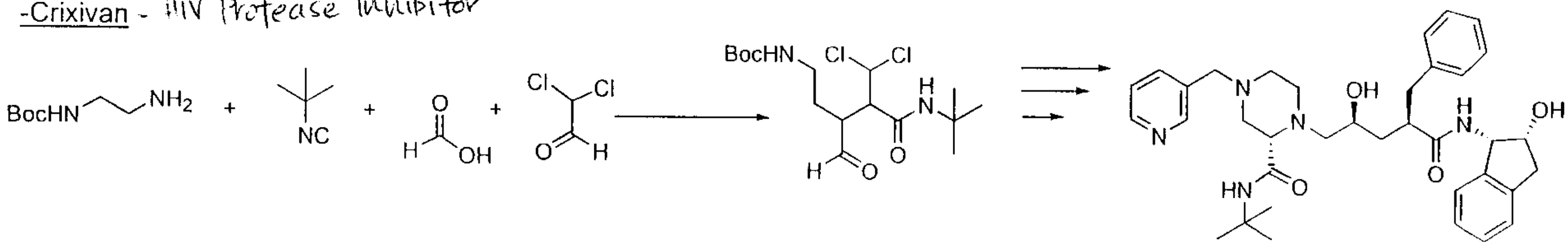
Entry	Product R		R_1	R_2		Yield (%) Solid	Solvent
1	Ph	1a	COOMe	COOMe	4b	94	71
2	*p*-Tolyl	1b	H	COOEt	4c	93	65
3	*p*-Tolyl	1b	COOMe	COOMe	4d	91	62
4	Styryl	1c	H	COOEt	4e	90	66
5	Styryl	1c	COOMe	COOMe	4f	87	60
6		1d	H	COOEt	4g	94	70
7		1d	COOMe	COOMe	4h	93	67
8		1e	H	COOEt	4i	92	64
9		1e	COOMe	COOMe	4j	90	62

Bora, U.; Saikia, A.; Boruah, R. *Org. Lett.* 2003, 5, 435.

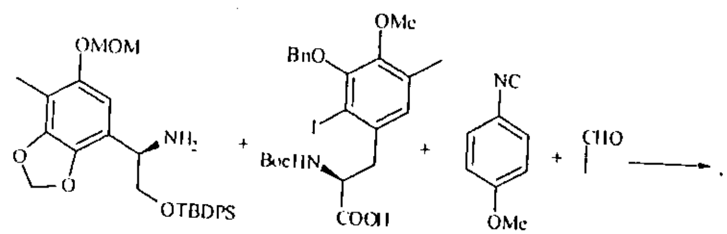
Multi-Component Reactions: Applications in Drug Discovery

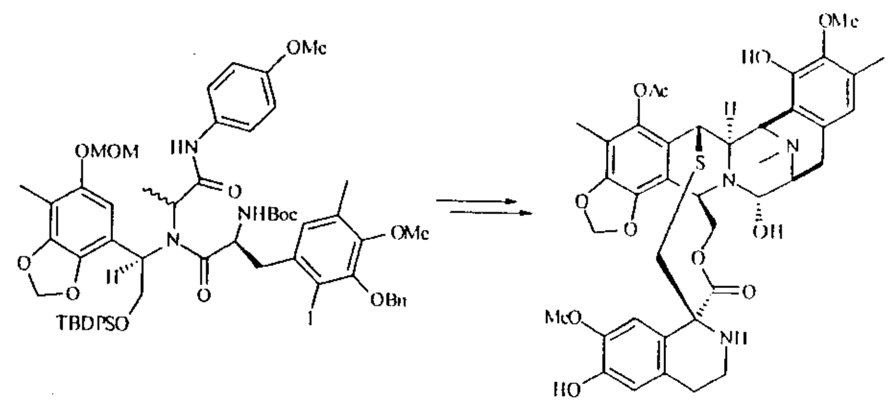
-useful for generating diverse libraries quickly

-Crixivan - HIV Protease Inhibitor



-Ecteinascidin 743 - anti-cancer

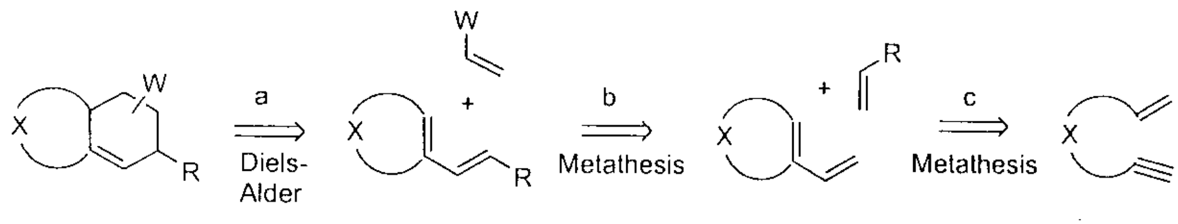




Weber, L. *Current Medicinal Chemistry* 2002, *9*, 1241.
Fukuyama, T. *et al. J. Am. Chem. Soc.* 2002, *124*, 6552

Scheme 19 Total synthesis of Ecteinascidin 743 with Ugi-4CR as key step.

Tandem Multi-Component Reaction



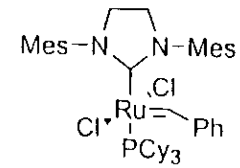
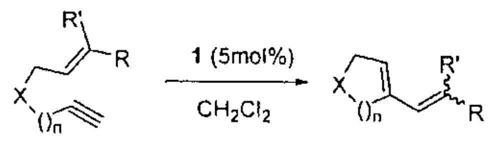


Table 1. Enyne Metathesis Reaction[11]

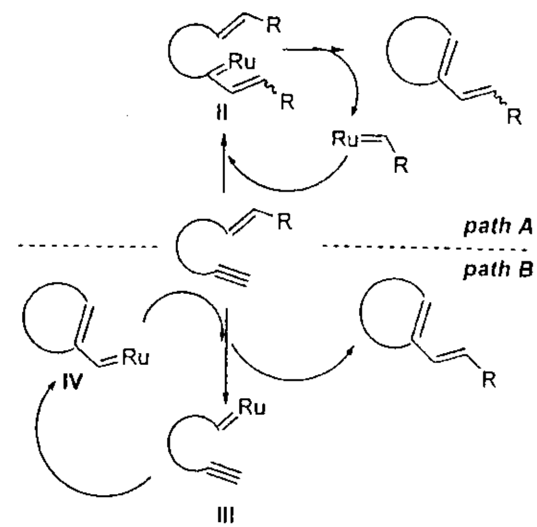


2 3

enyne	X	*n*	R	R'	product	yield[a] (*E/Z*)[b]
2a	NTs	1	CH_3	H	3a	85% (3/1)
2b	NTs	1	CH_2OH	H	3b	72% (3/1)
2c	NTs	1	CH_3	CH_3	3c	98%
2d	NTs	2	CH_3	H	3d	82% (6/1)
2e	NTs	2	CH_2OH	H	3e	86% (6/1)
2f	NTs	2	CH_3	CH_3	3f	92%
2g	CE_2[c]	1	CH_3	H	3g	83% (6/1)
2h	CE_2	1	CH_2OH	H	3h	88% (16/1)
2i	CE_2	1	CH_3	CH_3	3i	90%
2j	CE_2	2	CH_3	H	3j	82% (16/1)
2k	CE_2	2	CH_2OH	H	3k	96% (12/1)
2l	CE_2	2	CH_3	CH_3	3l	93%

[a] Isolated yield. [b] *E/Z* ratio was determined by ^{1}H NMR. [c] *E* = COOEt.

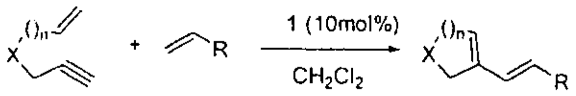
Scheme 3. Plausible Mechanistic Pathways



Lee, H.; Kim, H.; Tae, H.; Kim, B.; Lee, J. Org Lett 2003, 5, 3439

Tandem Enyne, Diene-ene Metathesis Reaction

Table 2. Tandem Enyne, Diene-ene Metathesis Reaction[15]



4 5

enyne	X	*n*	R	product	yield[a,b]
4a	NTs	1	Bu	**5a**	86%
4a	NTs	1	$(CH_2)_2$ac	**5b**	88%
4a	NTs	1	Ph	**5c**	86%
4a	NTs	1	Bn	**5d**	84%
4a	NTs	1	$(CH_2)_2$OBz	**5e**	73%
4a	NTs	1	$(CH_2)_2$Br	**5f**	78%
4a	NTs	1	CH_2TMS	**5g**	93%
4b	NTs	2	Bu	**5h**	85%
4b	NTs	2	$(CH_2)_2$ac	**5i**	74%
4b	NTs	2	Ph	**5j**	68%
4b	NTs	2	Bn	**5k**	86%
4b	NTs	2	$(CH_2)_2$OBz	**5l**	66%
4b	NTs	2	$(CH_2)_2$Br	**5m**	74%
4b	NTs	2	CH_2TMS	**5n**	81%
4c	C*E*$_2$	1	Bu	**5o**	85%
4c	C*E*$_2$	1	$(CH_2)_2$ac	**5p**	63%
4c	C*E*$_2$	1	Ph	**5q**	87%
4c	C*E*$_2$	1	Bn	**5r**	86%
4c	C*E*$_2$	1	$(CH_2)_2$OBz	**5s**	73%
4c	C*E*$_2$	1	$(CH_2)_2$Br	**5t**	82%
4c	C*E*$_2$	1	CH_2TMS	**5u**	65%

[a] Isolated yield. [b] *E*/*Z* ratio was determined to be >20:1 by ^{1}H NMR. [c] *E* = COOEt. [d] ac = CH_3CO

Three-Component Metathesis/Diels-Alder Reaction

Scheme 4. Multicomponent Tandem Reaction Sequence

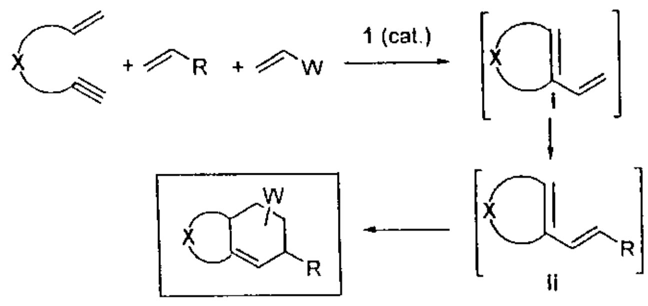
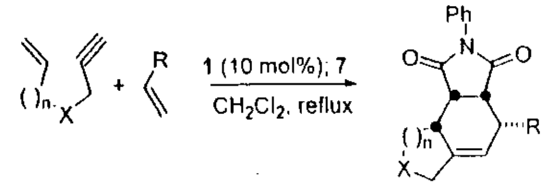


Table 3. Three-Component Metathesis/Diels−Alder Reaction[17]



4 6

enyne	X	*n*	R	product[a]	yield[b]
4a	NTs	1	Bu	**6a**	83%
4a	NTs	1	Bn	**6b**	75%
4a	NTs	1	$(CH_2)_2Br$	**6c**	71%
4a	NTs	2	Bu	**6d**	78%
4a	NTs	2	Bn	**6e**	78%
4a	NTs	2	$(CH_2)_2Br$	**6f**	71%
4a	CE_2	1	Bu	**6g**	74%
4b	CE_2	1	Bn	**6h**	74%
4b	CE_2	1	$(CH_2)_2Br$	**6i**	77%

[a] Relative stereochemistry of the product was confirmed through NOE experiment. [b] Isolated yield. [c] *E* = COOEt.

Org. Lett. 2003