Synthesis of the Polysubstituted Pyrroles via Tandem Electrophilic Cyclization – Cyclopropane Ring Opening of 1-(1-Alkynyl)Cyclopropyl Imines

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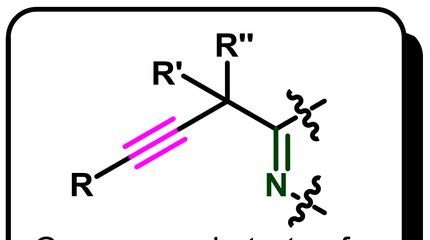
Introduction

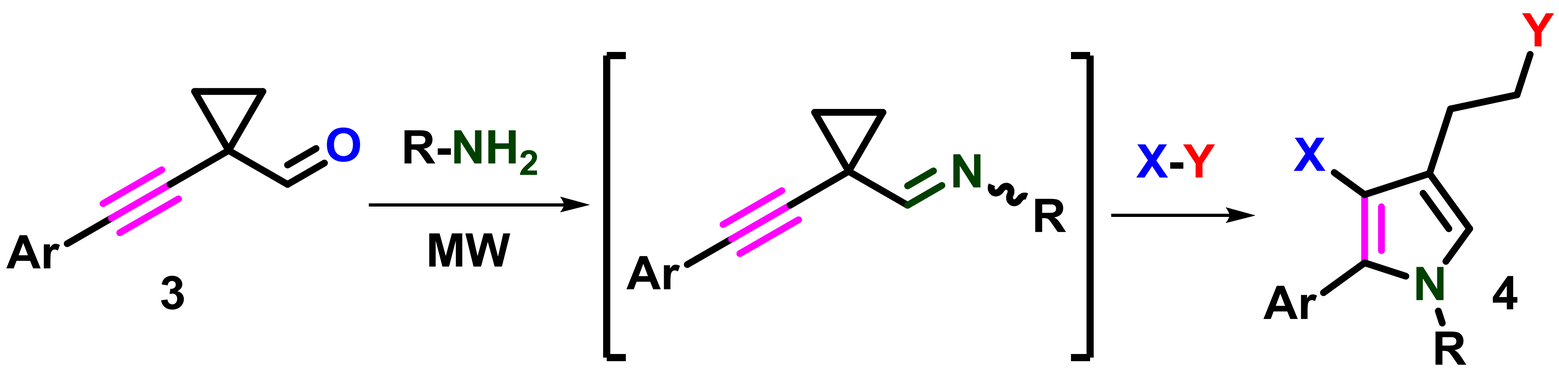
Polysubstituted pyrroles are widely investigated class of organic compounds. Moreover, pyrrole ring containing systems are valuable do to their versatile biological properties.[1] 5-*Endo*-dig cyclizations of alkynes, bearing imino groups in close proximity can be applied for the preparation of pyrroles. While on one hand, transition metal salts mediated intramolecular cyclizations are common approaches,[2] but on the other hand, there are only few publications about catalyst-free intramolecular cyclizations of these compounds in the literature.[3].



Common substrates for **5-*endo*-dig** cyclizations

The aim of the work

Herein we describe very smooth and efficient tandem intramolecular cyclizations – cyclopropane ring opening of *in situ* generated 1-(1-alkynyl)cyclopropyl imines with iodine, iodine monochloride, phenyl hypochlorselenoite, hypoiodyl azide, acetyl hypoiodite or alcohols.



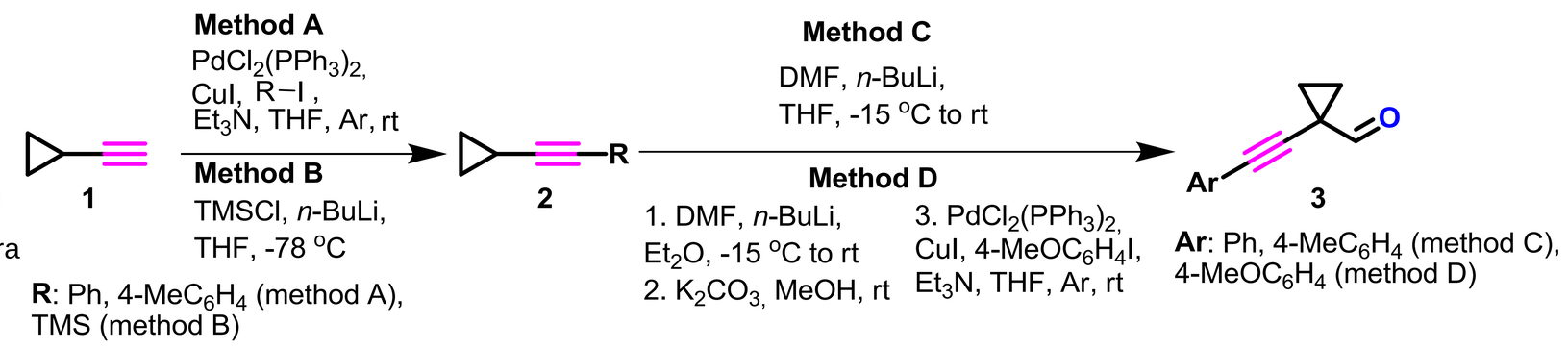
X-Y:

I-I, I-Cl, I-N_3, PhSe-Cl, H-Cl, I-OAc, H-OC_3H_7, H-OMe

Ar: Ph, 4-MeC_6H_4, 4-MeOC_6H_4. **R**: *t*-Bu, *c*Hex, *n*-Bu, *i*-Pr, Bn, Ph.

Results and Discussions

The starting 1-(alkynyl)cyclopropanecarbaldehydes **3** were prepared from cyclopropylalkynes **2** using formylation reaction with DMF and *n*-BuLi (method C) or using formylation, desilylation and then Sonogashira coupling reaction (method D). Whereas cyclopropylalkynes **2** were synthezised from ethynylcyclopropane (**1**) and aryliodides using standart Sonogashira coupling reaction (method A) or silylation with *n*-BuLi (method B).



R: Ph, 4-MeC_6H_4 (method A), TMS (method B)

Ar: Ph, 4-MeC_6H_4 (method C), 4-MeOC_6H_4 (method D)

Cyclization reactions of the *in situ* generated 1-(1-alkynyl)cyclopropyl imines

Entry	Starting aldehyde 3	Amine R-NH_2	X-Y	Reaction conditions	Product 4, yield	Entry	Starting aldehyde 3	Amine R-NH_2	X-Y	Reaction conditions	Product 4, yield
1	**3a:** Ar = 4-MeOC_6H_4-	R = *t*Bu	I-I	Method A	**4b,** 81 %	10	**3c**	R = *i*Pr	ICl	Method B	**4k,** 45 %
2	**3a**	R = Bn	I-I	Method A	**4c,** 78 %	11	**3b**	R = *t*Bu	PhSeCl	Method B	**4l,** 43 %
3	**3b:** Ar = Ph	R = *t*Bu	I-I	Method A	**4d,** 57 %	12	**3c**	R = *t*Bu	PhSeCl	Method B	**4m,** 65 %
4	**3b**	R = Bu	I-I	Method A	**4e,** 16 %	13	**3b**	R = *c*Hex	IN_3	Method B	**4n,** 35 %
5	**3c:** Ar = 4-MeC_6H_4-	R = *t*Bu	I-I	Method A	**4f,** 19 %	14	**3c**	R = *t*Bu	IN_3	Method B	**4o,** 76 %
6	**3c**	R = Bn	I-I	Method A	**4g,** 40 %	15	**3b**	R = *t*Bu	IOAc	Method C	**4p,** 21 % **and** **5,** 19 %
7	**3c**	R = *c*Hex	I-I	Method A	**4h,** 54 %	16	**3a**	R = Bn	$HOCH_3$	Method D	**4r,** 49 %
8	**3b**	R = *t*Bu	ICl	Method B	**4i,** 52 %	17	**3c**	R = *t*Bu	HOC_3H_7	Method D	**4s,** 33 %
9	**3c**	R = *c*Hex	ICl	Method B	**4j,** 95 %	18	**3c**	R = *c*Hex	$HOCH_3$	Method D	**4t,** 70 %

Method A: Amine (2 eq), MeCN, 120 °C, 150 W, 20 min, then I_2 (1 eq), rt. **Method B:** Amine (2 eq), MeCN, 120 °C, 150 W, 20 min, then ICl (1 eq), PhSeCl (1 eq) or IN_3 (2 eq), rt. **Method C:** Amine (2 eq), MeCN, 120 °C, 150 W, 20 min, then IOAc (1 eq) in $CHCl_3$, rt. **Method D:** Amine (2 eq), MeOH, NaOMe (1 eq) or *n*-PrOH, 3Å MS, MW.

Conclusions

Overall, we have developed catalyst-free, synthetic method for the preparation of polysubstituted pyrroles using tandem intramolecular cyclization – cyclopropane ring opening of the *in situ* generated 1-(1-alkynyl)cyclopropyl imines.

References

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