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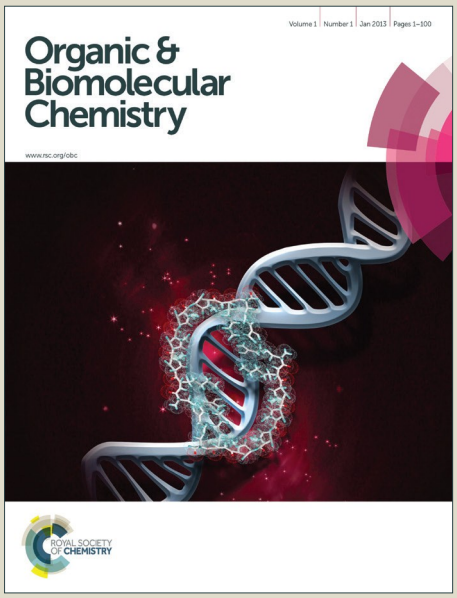

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Alkynylation of heterocyclic compounds using hypervalent iodine reagent

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M. Kamlar,[a] I. Císařová[b] and J. Veselý[a]

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Alkynylation of various nitrogen- and/or sulphur-containing heterocyclic comounds using hypervalent iodine TMS-EBX by utilization of tertiary amines under mild conditions is described. Developed metal-free methodology enables to obtain corresponding alkynylated heterocycles bearing quaternary carbon in high yields.

Heterocyclic compounds play an important role in biological processes. Heterocyclic moieties are often part of a biologically active natural and synthetic compounds.[1] Majority of synthetic drugs available on the market have a structural heterocyclic core[2] and therefore the new synthetic approaches leading to their preparation are of particular interests in organic synthesis.

Five-membered heterocyclic compounds such as pyrazolone, oxindole, azalactone or rhodanine derivatives are deeply studied due to their significant biological activity. For example pyrazolones belong to the group of compound which are well studied due to their broad application in drug chemistry[3], agrochemistry[4] or material science[5]. In the literature there are many examples of pyrazolone motif containing compounds possesing interesting biological properties such as metamizole which is used as pain reliever[6] and shows also antipyretic properties[7] or edavarone used in treatment of brain ischemia[8]. So far only few methodologies related to the synthesis of disubstituted pyrazolones are published.[9] Rhodanines, five-membered heterocyclic compounds containing thiazole nucleus, are known for antimicrobial[10], antifugal[11] or anti-inflammatory[12] properties. Another interesting group containing five-membered heterocyclic ring are oxinodoles, which can be used as tumor supressors.[13] Azlactones, the cyclic *N*-acyl-α-amino acids, which are also known to exhibit antifungal[14], antibacterial[15] and anti-inflammatory[16] activities. Some of them are used as synthones for preparation of immunomodulators[17] and biosensors[18].

Chemistry of heterocyclic compounds is diverse and varies based on the structural properties of a corresponding heterocycle. Alkynylation reaction of heterocycles containing acidic C-H bond using electrophilic acetylene is quite scarce, although there were developed several alkynylation methods for various nucleophiles containing tertiary acidic C-H bond either with hypervalent iodine reagents[19] or with another electrophilic acetylene source[20]. Specifically, in case of heterocycles there are only two references regarding the alkynylation of oxindoles[21] and azlactones[22]. Alkynylation of oxindoles was carried out using electron-deficient alkynes by catalysis of chiral scandium complexes and azlactones were alkynylated using hypervalent iodine reagents. Especially, in case of hypervalent iodine chemistry, which is nowdays well-estabilished field in organic synthesis[23], there were also a few reports related to the alkynylation of "non-acidic" heterocyclic compounds.[24] For example Waser and co-workers reported gold-catalyzed alkynylation of indoles[24a], pyrroles[23b] and thiophenes[24c] using 1-((triisopropylsilyl)ethynyl)-1,2-benziodaoxol-3(1*H*)-one (TIPS-EBX). Recently TIPS-EBX, as an efficient acetylene source, was also used for alkynylation of thiols.[25]

In accordance with our interest in hypervalent iodine chemistry[19b,26] and our previous experience with functionalization of pyrazolones[27] we wish to report efficient, metal free electrophilic alkynylation of heterocyclic compounds containing acidic C-H bond such as 4-substituted pyrazolones, oxindoles, rhodanines and azlactones using hypervalent iodine reagents. This methodology allows to obtain corresponding products under mild condition with high yields tolerating multitude of substrates.

Our preliminary studies have been carried out between benzylated pyrazolon **7a** as a model nucleophile and 1-((trimethylsilyl)ethynyl)-1,2-benziodoxol-3(1*H*)-one (TMS-EBX) **3a** as alkynylation agent in presence of tertiary amine Et_3N. Due to our previous experiences in alkynylation of fluorinated sulfones[19b] we chose toluene as a default solvent. Unfortunately, formation of a desired product **13a** wasn´t

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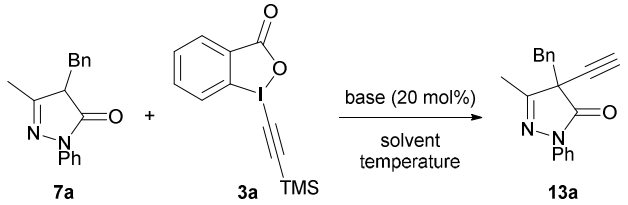
observed after 5 days of stirring even after heating up to 50 °C (table 1, entries 1-2). Switching to the polar solvents was essential for the formation of the corresponding alkynylated product **13a**. When DMF as the polar aprotic solvent was used, the reaction reached full conversion in 8 hours and desired product **13a** was isolated in good yield (77 %) (table 1, entry 3). The best results with respect to the yield and the reaction time were obtained in case of polar protic solvents such as ethanol and trifluoroethanol (table 1, entry 4-5). In both examples full conversion of the reaction was achieved up to 3 hours and the desired product was isolated in the yield exceeding 80 %. Besides, it was shown that other tertiary amines such as Dabco or *N*,*N*-diisopropylethylamine instead of Et_3N can be used at the cost of lowered yield (73-76 %) even with prolonged reaction time (table 1, entries 6-7). In summary, the best result (84 % of yield) was obtained using ethanol as a solvent in presence of Et_3N at room temperature. Under these conditions was full conversion reached after 3 hours.

Table 1 Solvent and temperature screening of alkynylation reaction[a]



7a 3a 13a

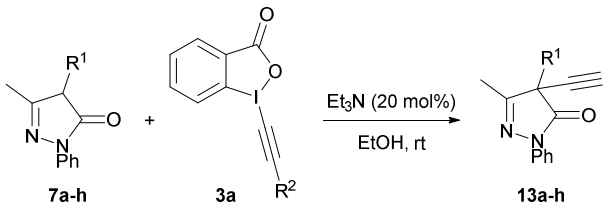
Entry	Base	Solvent	Temperature (°C)	Time (h)	Conversion (%)	Yield (%)
1	Et_3N	toluene	25	120	0	-
2	Et_3N	toluene	50	120	0	-
3	Et_3N	DMF	25	8	100	77
4	Et_3N	EtOH	25	3	100	84
5	Et_3N	CF_3CH_2OH	25	3	100	81
6	DIPEA	EtOH	25	5	100	76
7	Dabco	EtOH	25	10	100	73

[a] In a vial pyrazolone 7a (1.0 equiv.), base (20 %) and TMS-EBX (1.5 equiv.) were added in solvent (1 mL).

Next, we screened scope of the alkynylation reaction for diverse substituted pyrazolones and hypervalent iodine derivatives (table 2). First we turned our attention on hypervalent iodine reagent and apart from the model TMS-EBX (**3a**) we also examined 1-((triethylsilyl)ethynyl)-1,2-benziodoxol-3(1*H*)-one (TES-EBX) (**3b**) and 1-((triisopropylsilyl)ethynyl)-1,2-benziodoxol-3(1*H*)-one (TIPS-EBX) (**3c**). As we expected, TMS-EBX (**3a**) showed best activity and desired product was obtained in 84 % yield after three hours (table 2, entry 1). Lower activity toward alkynylation reaction was observed in case of sterically more hindered TES-EBX (**3b**) and TIPS-EBX (**3c**). Comparing to TMS-EBX, use of TES-EBX led to the formation of corresponding alkynylated pyrazolon **13a** in moderate yield of 52 % after 24 hours of stirring (table 2, entry 2). Employing the bulkiest TIPS-EBX (**3c**) didn´t lead to the formation of the corresponding product **13a** at all (table 2, entry 3) even under prolonged time. Instead, complete recovery of both starting materials, i.e. **7a** and **3c**, was observed. This observation was in accordance with our previous experiences, which revealed superior activity of **3a** over the other alkynylating agents.

Next was examined the scope of differently substituted pyrazolones. To our delight, reaction proceeded well in all cases. Formation of alkynylated product **13** was independent on substitution of starting pyrazolon derivatives and full conversion was reached in short reaction time. For example 3-methyl-4-(2-nitrobenzyl)-1-phenyl-1,4-dihydro-*3H*-pyrazol-5-one (**7e**) gave corresponding product **13e** in 82% yield and full conversion was reached after 3 hours (table 2, entry 7). The less sterically hindered 3,5-dimethyl-1-phenyl-1,4-dihydro-1*H*-pyrazol-5-one (**7g**) led to formation of alkynylated product **13g** in 95% yield (table 2, entry 9). Also the sterically hindered pyrazolon **7h** substituted with 1-naphthyl group gave the corresponding alkynylated product **13h** in 90% yield after 8 hours (table 2, entry 10).

Table 2 Scope of of alkynylation reaction[a]

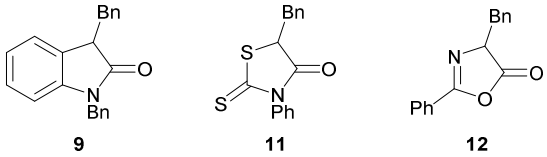


7a-h 3a 13a-h

Entry	R^1	R^2	Product	Time (h)	Conversion (%)	Yield (%)
1	$CH_2C_6H_4$	TMS	**13a**	3	100	84
2	$CH_2C_6H_4$	TES	**13a**	24	100	52
3	$CH_2C_6H_4$	TIPS	**13a**	48	0	-*
4	$CH_2(p\text{-}BrC_6H_4)$	TMS	**13b**	6	100	70
5	$CH_2(p\text{-}NO_2\ C_6H_4)$	TMS	**13c**	4	100	85
6	$CH_2(m\text{-}NO_2\ C_6H_4)$	TMS	**13d**	4	100	76
7	$CH_2(o\text{-}NO_2\ C_6H_4)$	TMS	**13e**	3	100	82
8	$CH_2(p\text{-}CN\ C_6H_4)$	TMS	**13f**	5	100	94
9	Me	TMS	**13g**	5	100	95
10	CH_2(1-naphthyl)	TMS	**13h**	8	100	90

[a] In a vial pyrazolone (1.0 equiv.), base (20 %) and TMS-EBX (1.5 equiv.) were added in solvent (1 mL).* recovery of starting pyrazolone **7a** and TIPS-EBX higher than 80 %.

To show the versatility of designed alkynylation procedure we decided to broaden the scope from pyrazolones to other heterocyclic compounds. With respect to the nucleophilicity, oxindole (**9**), rhodanine (**11**) and azlactone (**12**) derivatives were chosen as convenient candidates (figure 1).



9 11 12

Figure 1 Nucleophilic heterocyclic compounds used in alkynylation reaction.

At the beginning we took over the conditions used in alkynylation of pyrazolone derivatives. To our delight, in case of oxindole (**9**) and rhodanine (**11**) derivatives we observed formation of alkynylated products **14** and **15**, nevertheless, the yield was in both cases unsatisfactory (table 3, entries 1-2). Unfortunately, these conditions showed to be totally inefficient for azlactone derivative **12**, which decomposed without a trace of alkynylated product **16** (table 3, entry 3). Switching to polar aprotic solvent such as DMF showed to be suitable solvent in alkynylation of all three heterocycles. In the presence of DMF as a solvent and Et_3N reaction proceeded well and reached full conversion within an hour. Isolated yields of 1,3-dibenzyl-3-ethynylindolin-2-one (**14**) and 5-benzyl-5-ethynyl-3-phenyl-2-thioxothiazolidin-4-one (**15**) exceeded 80 % (table 3, entries 10-11). In case of alkynylated azlactone **16** was isolated yield lower and reached 63 % (table 3, entry 12). Replacement of DMF for $CHCl_3$ in case of azlactone derivative **12** led to dramatic improvement of the yield up to 85 % (table 3, entry 9). It is also apparent that substrates **9**, **11** and **12** in contrast to pyrazolone derivatives tolerate nonpolar solvents such as toluene, though the isolated yield of corresponding products are moderate (table 3, entries 9-12). As well as in case of pyrazolones, Dabco was found to

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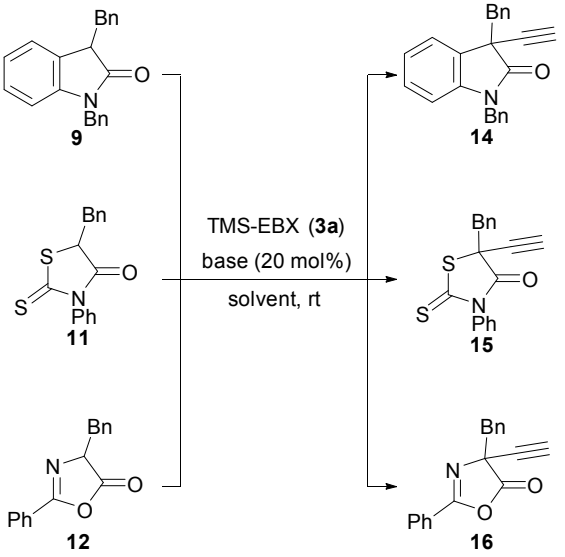
be a suitable base in acetylene transfer reaction of oxindol, rhodanine and azlactone derivatives (table 3, entries 13-15).

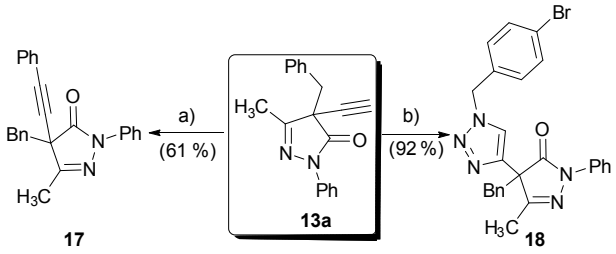
Table 3 Alkynylation of oxindol, rhodanine and azlactone derivatives[a]



Entry	Substrate	Base	Solvent	Time (h)	Yield (%)
1	9	Et_3N	EtOH	96	30
2	11	Et_3N	EtOH	48	47
3	12	Et_3N	EtOH	48	-[b]
4	9	Et_3N	Toluene	96	38
5	11	Et_3N	Toluene	15	69
6	12	Et_3N	Toluene	15	59
7	9	Et_3N	$CHCl_3$	96	41
8	11	Et_3N	$CHCl_3$	1	85
9	12	Et_3N	$CHCl_3$	1	85
10	9	Et_3N	DMF	1	85
11	11	Et_3N	DMF	1	94
12	12	Et_3N	DMF	1	63
13	9	Dabco	DMF	3	81
14	11	Dabco	DMF	2	75
15	12	Dabco	$CHCl_3$	2	78

[a] In a vial substrate 9, 11, 12 (1.0 equiv.), catalyst (20 %) and TMS-EBX (1.5 equiv.) were added in solvent (1 mL)[b] degradation of a starting azlactone

The utility of acetylene functionalized heterocycles has been demonstrated by Sonogashira coupling of **13a** with iodobenzene affording compound **17** in good yield 61 %. Alkynylated pyrazolone **7a** was also subjected to "click" reaction with 1-(azidomethyl)-4-bromobenzene leading to corresponding triazole derivative **18** in high yield (92 %). Structure of corresponding triazole derivative **18** was confirmed according X-ray diffraction analysis (figure 2).



a) C_6H_5I, $Pd(PPh_3)_2Cl_2$, CuI, Et_3N, DMF;
b) 1-(azidomethyl)-4-bromobenzene, sodium ascorbate, $CuSO_4 \cdot 7H_2O$, *t*-BuOH/H_2O.

Scheme 1 Transformation of **13a** to compounds **17** and **18** via Sonogashira and Huisgen reaction.

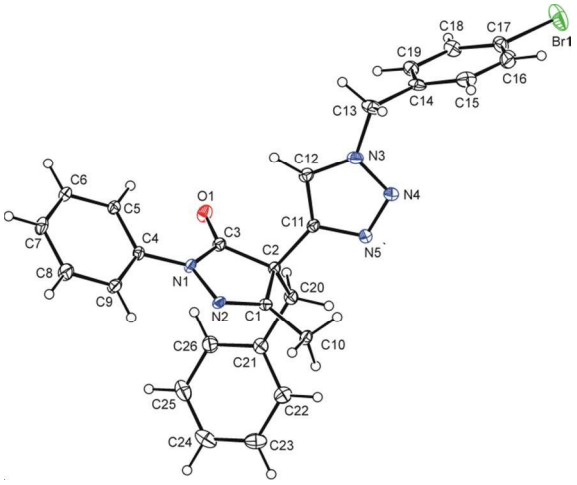


Figure 2 View on the one of two symmetrically independent molecules **18** with atom numbering scheme.

We have also made an investigation regarding to asymmetric version of designed alkynylation reaction employing various chiral tertiary amines as catalysts. In that context several of cinchona alkaloids were tested in order to induce enantioselectivity in our alkynylated products (table 4). In our preliminary reaction we tested quinine as a catalyst of reaction between pyrazolone **7a** and TMS-EBX (**3a**). We observed formation of corresponding alkynylated product **13a** in good yield in ethanol but with unsatisfactory enantiomeric excess. (table 4, entry 2). We have also examined other cinchona based alkaloids but with similar results in terms of enantioselectivity (entries 3-6). When toluene was used to slow down the reaction, no formation of **13a** was observed (entry 1). On the other hand, the reaction utilized with bifunctional Takemoto catalyst (**VI**) in toluene afforded the corresponding product **13a** in low yield (38%) with unsatisfactory enantioselectivity (14%, entry 7).

Table 4 Attempts in enantioselective alkynylation of pyrazolone 7a [a]

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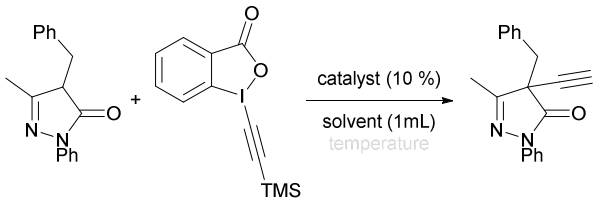
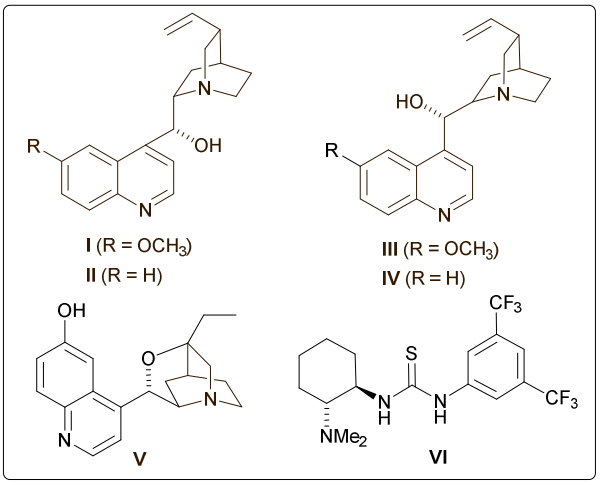


7a 3a 13a



Entry	Catalyst	Solvent	Temperature (°C)	Time (h)	Yield (%)	Ee (%)
1	I	Ethanol	25	15	72	8
2	I	Toluene	25	120	n.d.	-
3	II	Ethanol	25	15	69	0
4	III	Ethanol	25	15	77	0
5	IV	Ethanol	25	15	76	4
6	V	Ethanol	25	120	32	0
7	VI	Toluene	25	10	71	-14
8	VI	Toluene	-10	96	38	-11

[a] In a vial pyrazolone 7a (1.0 equiv.), catalyst (10 %) and TMS-EBX (1.5 equiv.) were added in solvent (1 mL). [b] Determined by HPLC (Chiral AD 90:10 Hept:iPrOH, 1mL).

In order to understand the mechanism of above mentioned alkynylation, NMR experiments were performed. When TMS-EBX (**3a**) was subjected to trimethylamine in CD_2Cl_2 without appropriate nucleophile, no formation of ethynyl-1,2-benziodoxol-3(1*H*)-one (EBX) at -40 °C and lower temperatures took place. Slow formation of EBX in equilibrium with products of decomposition was observed at – 40 °C. Full conversion of TMS-EBX (**3a**) to EBX and products of decomposition was observed at -30 °C. Our observed instability of EBX is in accordance with data reported by Waser *et al*. [19a] Moreover, above mentioned results lead us to suggest that reaction proceeds via EBX intermediate, which reacts with nucleophile by β-addition-elimination mechanism.[28]

Conclusions

In conclusion, we report metal-free organocatalytic alkynylation of heterocyclic compounds containing acidic C-H bond employing hypervalent iodine reagents. Our methodology gives access to alkynylated heterocyclic compounds containing quaternary centres. Alkynylated pyrazolone, oxindole, rhodanine or azlactone derivatives were obtained in good to excellent yields. Acetylene bearing pyrazolone derivative **13a** was used in Sonogashira coupling and "click" reaction leading to corresponding products **17** and **18** in good to high yield. Further studies and synthetic applications based on this methodology are currently ongoing in our group.

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Notes and references

[a] Department of Organic Chemistry, Faculty of Science, Charles University in Prague, Hlavova 2030, 128 43, Praha 2, Czech Republic, e-mail: jxvesely@natur.cuni.cz, fax: +42-221951226.

[b] Department of Inorganic Chemistry, Faculty of Science, Charles University in Prague, Hlavova 2030, 128 43, Praha 2, Czech Republic.

† Electronic Supplementary Information (ESI) available: ^{1}H and ^{13}C NMR spectra of **11**, **13a-h**, **14-18**. See DOI: 10.1039/c000000x/

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