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An Intramolecular Wittig Approach toward Heteroarenes: Synthesis of Pyrazoles, Isoxazoles, and Chromenone-oximes

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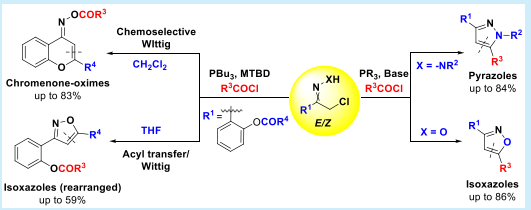
Supporting Information

ABSTRACT: α-Halohydrazones/ketoximes are transformed into trisubstituted pyrazoles/disubstituted isoxazoles by treatment with phosphine, acyl chloride, and a base. Mechanistic investigations revealed the in situ formation of azo/nitroso olefin intermediates which underwent a tandem phospha-Michael/*N*- or *O*-acylation/intramolecular Wittig reaction to afford the heteroarenes in moderate to good yields. Further, proper functionalization of α-haloketoximes and a change of conditions allowed the chemoselective synthesis of chromenone-oximes as well as rearranged isoxazoles, thereby realizing a diversity-oriented synthesis.



Pyrazoles and isoxazoles belong to a prominent class of nitrogen heterocycles exhibiting a wide range of potent biological properties.[1] In addition, they are also useful in the field of agriculture apart from being frequently found in many natural as well as synthetic products.[2] Recently, chromenone-oxime scaffolds have emerged as potent drugs for the treatment of Parkinson's disease.[3] Owing to their attractive medicinal properties (Figure 1), the development of new methods

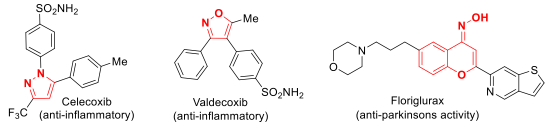
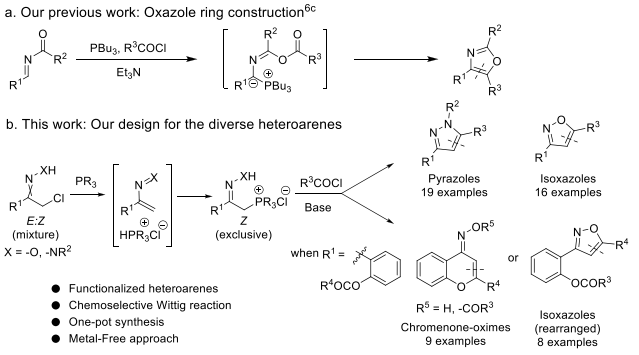


Figure 1. Some potent drugs containing pyrazole, isoxazole, and chromenone-oxime scaffolds.

toward their synthesis have attracted great interest.[4] Although some elegant methods are available for the synthesis of each of these heterocycles, the development of a single modular method that could generate all of these heterocycles is still desirable.

On the other hand, the Wittig reaction has recently witnessed its multifaceted applications toward the synthesis of diverse range of heterocycles.[5] Our group has long been devoted in the synthesis of various types of heteroarenes via a three-component tandem phospha-Michael addition/*O*-acylation/Wittig reaction from a variety of α,β-unsaturated carbonyl compounds.[6] In 2014, we reported an efficient synthesis of oxazoles from PBu_3, *N*-acylimines, and acyl chlorides via the Wittig reaction (Scheme 1a).[6c] To continue our effort toward the development of novel intramolecular Wittig strategies, we envisioned that the *E*/*Z* mixture of α-halohydrazones/ketoximes when treated with phosphine generate *Z*-phosphonium salts exclusively via transient conjugated azo-/nitroso-

Scheme 1. Our Earlier Synthesis of Oxazoles (a) and Our Design for Pyrazole, Isoxazole and Chromenone-oximes (b)



soalkenes,[7] and thus generated phosphonium salts could be transformed into bioactive pyrazoles/isoxazoles via a tandem acylation/Wittig reaction sequence (Scheme 1b). In this context, we report a metal-free approach for the synthesis of trisubstituted pyrazoles and disubstituted isoxazoles. In addition, we have also explored the possibility of chemoselective intramolecular Wittig reaction that could result rearranged isoxazoles and chromenone-oxime derivatives in a diversity-oriented manner.[8]

Initially, the α-halohydrazone mixture *E*/*Z*-**1a** was selected for our model reaction with PBu_3 and PhCOCl (**2a**) in the presence of Et_3N in CH_2Cl_2. The desired pyrazole **3aa** was obtained in 61% yield (entry 1, Table 1). Other phosphines such as PEt_2Ph and $PEtPh_2$ afforded **3aa** in 39% and 34% yields, respectively (entries 2 and 3). Delightfully, the reaction was efficiently facilitated by PPh_3, and **3aa** was obtained in 80%

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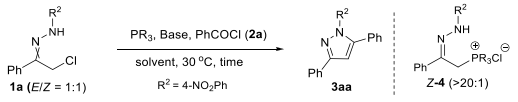
Table 1. Optimization of the Reaction Conditions for 3aa[a]



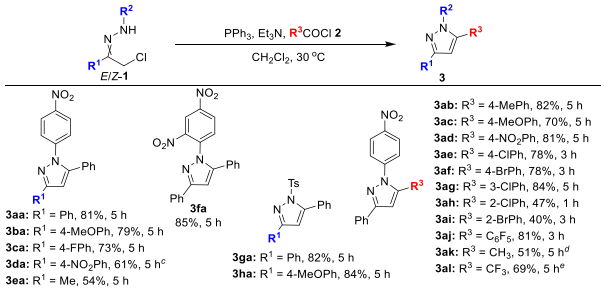
entry	PR_3	base	solvent[b] (%)	time (h)	3aa[b] (4)[b] (%)
1	PBu_3	Et_3N	CH_2Cl_2	1	61 (29)
2	PEt_2Ph	Et_3N	CH_2Cl_2	3	39 (32)
3	$PEtPh_2$	Et_3N	CH_2Cl_2	3	34 (32)
4	PPh_3	Et_3N	CH_2Cl_2	5	80 (0)
5	PPh_3	DIPEA	CH_2Cl_2	5	71 (0)
6	PPh_3	DBU	CH_2Cl_2	1	0 (15)
7	PPh_3	Et_3N	THF	3	26 (63)
8	PPh_3	Et_3N	CH_3CN	3	34 (35)
9[c]	PPh_3	Et_3N	CH_2Cl_2	5	81 (0)

[a]Reactions were performed with **1a** (0.3 mmol), PR_3 (1.1 equiv), base (3.0 equiv), and PhCOCl (**2a**) (1.2 equiv) in dry solvent (3 mL) under argon at 30 °C. [b]NMR yields. [c]Et_3N (2.5 equiv) was used.

yield (entry 4). To find the optimal conditions, several other bases and solvents were screened (entries 5−8). In most of the cases, the phosphonium salt **4** was observed in the reaction mixture. The stoichiometry of base and the effect of concentration was also examined. The optimal result was obtained by treating **1a** (1.0 equiv) and **2a** (1.2 equiv) in the presence of PPh_3 (1.1 equiv) and Et_3N (2.5 equiv) in anhydrous CH_2Cl_2 at 30 °C for 5 h (entry 9).

Having established the optimal conditions, the scope of the substrates (Scheme 2) was investigated. The protocol worked

Scheme 2. Substrate Scope of Trisubstituted Pyrazoles 3[a,b]

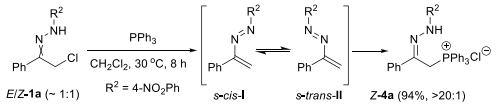


[a]Reactions were performed with **1a** (0.3 mmol), PPh_3 (1.1 equiv), Et_3N (2.5 equiv), and R^3COCl **2** (1.2 equiv) in dry CH_2Cl_2 (3 mL) under argon at 30 °C. [b]Isolated yield. [c]α-Bromohydrazone (**1d**) was used. [d]Acetic anhydride (**2k**) was used. [e]TFAA (**2l**) was used.

efficiently regardless of the electronic nature of substrates **1** and acyl chlorides **2**. Interestingly, the less reactive hydrazone **1e** (R^1 = CH_3) also participated smoothly to furnish **3ea** in 54% yield. Hydrazones bearing tosyl and 2,4-dinitrophenyl groups also generated products **3fa**−**3ha** in high yields. It is worth noting that although the electronic property of R^3 substitutions in **2** did not affect the yields of **3**, the steric hindrance of R^3 had a pronounced influence on the yield (**3ah** and **3ai**). Furthermore, it was encouraging to find that perfluorobenzoyl chloride (**2j**), acetic anhydride (**2k**), and TFAA (**2l**) were also able to provide the corresponding products in good yields.

To investigate the formation of exclusive *Z*-**4a** in our optimization studies, *E*/*Z*-**1a** was treated with PPh_3 in CH_2Cl_2 at 30 °C. After 8 h, the phosphonium salt *Z*-**4a** was obtained in 94% yield (Scheme 3). This could be explained by the in situ

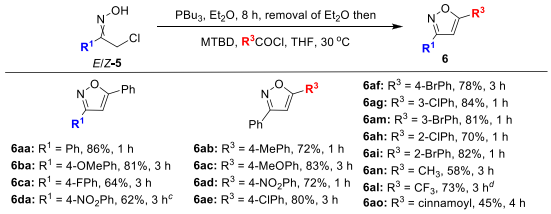
Scheme 3. Generation of *Z*-4a from (*E*/*Z*)-1a



formation of an equilibrating mixture of *s*-*cis*-**I** and *s*-*trans*-**II** species. Preferential addition of PPh_3 to *s*-*cis*-**I** furnishes exclusively *Z*-**4a** because of its extra stability resulting from the coordination between −NH and the phosphorus atom of PPh_3 (see the Supporting Information for crystal data).

Having observed a similar phenomenon with α-chloroketoxime **5a**, we turned our attention to generate isoxazole **6aa**. However, the standard conditions that worked for pyrazoles **3** resulted in a poor yield of **6aa**. After extensive optimization studies (see the Supporting Information), the optimal result was obtained when **5a** was treated with PBu_3 in dry Et_2O for 8 h, followed by evaporation of solvent, redissolving in THF, and then sequential addition of MTBD and PhCOCl (**2a**) in THF for 1 h at 30 °C in a one-pot synthesis (Scheme 4).

Scheme 4. Substrate Scope of Disubstituted Isoxazoles 6[a,b]



[a]Reactions were performed with **5** (0.2 mmol), PBu_3 (1.1 equiv), MTBD (4.0 equiv), and R^3COCl (1.2 equiv) in dry THF (2 mL) under argon at 30 °C. [b]Isolated yield. [c]α-Bromohydrazone (**5d**) was used. [d]TFAA (**2l**, 1.5 equiv) was used.

The substrate scope of isoxazoles was further investigated. A variety of α-haloketoximes **5** participated in the reaction with different acyl chlorides **2** to afford the expected products **6** in good yields. As in the case of hydrazones, the electronic nature of R^1 and R^2 substituents in **1** and **2**, respectively, has no considerable effect on the course of the reaction. Gratifyingly, aromatic acyl chlorides bearing *ortho*- and *meta*-substitutions were also converted to isoxazoles in good yields. Similarly, aliphatic acyl chlorides such as acetyl chloride (**2n**) and anhydride such as TFAA (**2l**) were also applicable. In addition, cinnamoyl chloride (**2o**) also furnished the isoxazole **6ao** although in moderate yield (45%).

After efficient synthesis of pyrazoles and isoxazoles, we also envisioned that the presence of appropriately positioned acyloxy functionality on ketoximes **8** could lead to bis-acylated species **9** and open the doors for the possibility of a chemoselective Wittig reaction that could subsequently lead to either of the biologically important isoxazoles **10** or chromenone-oxime scaffolds **11** (Scheme 5a). Accordingly, the phosphonium salt **8a** was treated with 4-ClPhCOCl (**2e**) in the presence of the MTBD in THF at 30 °C (Scheme 5b). Delightfully, isoxazole and chromenone-oxime were obtained in 53% and 13% yields, respectively. The X-ray analysis, however revealed the structure of isoxazole as **12ae** instead of **10ae**. After a series of control experiments, it was understood that the isoxazole **12ae** had resulted from **8a** via an unexpected intramolecular acyl-transfer from phenol to oxime/Wittig/*O*-

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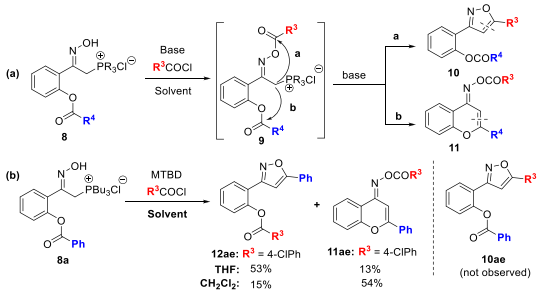
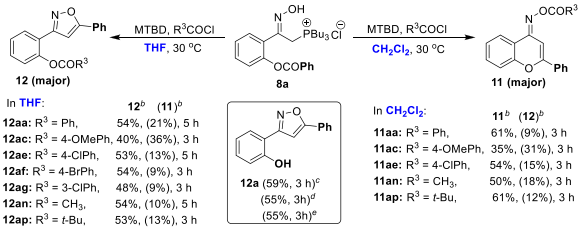
Scheme 5. Our Design of the Chemoselective Wittig Reaction (a) and Its Optimization (b)



acylation sequence and the chromenone-oxime **11ae** resulted via a *O*-acylation/chemoselective Wittig reaction. The formation of chromenone-oxime **11ae** in minor amounts hinted that chemoselective Wittig reaction could be achieved. After extensive studies, it was found that switching the solvent to CH_2Cl_2 could result in the predominant formation of **11ae** (Scheme 5b).

Further, different acyl chlorides were tested under the reaction conditions, and the desired isoxazoles **12aa**–**ap** could be obtained in 40–54% yields as major products. Notably, when TFAA was employed, the isoxazole **12a** (59%) obtained was devoid of trifluoroacetate ester. However, the acyl chloride **2c** bearing a *p*-MeOPh group resulted in poor selectivity (Scheme 6). The X-ray analysis of **12ac** as well as EIMS of all

Scheme 6. Synthesis of Isoxazoles and Chromenone-oximes[a,b]



[a]Reactions were performed with **8** (0.2 mmol), MTBD (2.5 equiv), and R^3COCl (1.2 equiv) in dry THF (2 mL)/ CH_2Cl_2 (2 mL) under argon at 30 °C. [b]Isolated yield. [c]TFAA (**2l**) was used. [d]Without R^3COCl in THF. [e]Without R^3COCl in CH_2Cl_2.

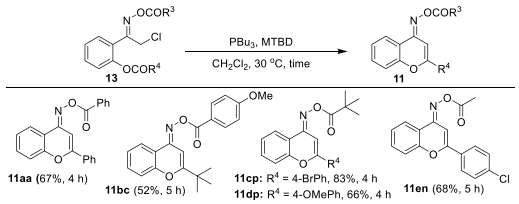
the products unambiguously demonstrated an initial acyl group (R^4CO) transfer from phenol to oxime followed by a Wittig reaction generating isoxazoles and a subsequent *O*-acylation (R^3CO) of phenols to finally afford rearranged isoxazole **12**.

Additionally, the reactions were also conducted in CH_2Cl_2 to test the chemoselective generation of chromenone-oximes **11**. Gratifyingly, in all cases, the desired chromenone-oximes **11aa**–**ap** were predominantly obtained in up to 61% yields. The selectivity was again disturbed when **2c** was employed. To understand the effect of solvent on the selective formation of **11** and **12**, we carried out an experiment with **8a** and MTBD in THF in the absence of R^3COCl. The rearranged isoxazole **12a** resulting from an acyl transfer/Wittig sequence was obtained in 55% yield in 3 h. Surprisingly, the same isoxazole **12a** was also obtained in similar yield (55%) when the reaction was conducted in CH_2Cl_2 (Scheme 6).

Although inconclusive, these results indicate that in the absence of a competing acyl chloride the intramolecular acyl transfer (R^4CO) occurs irrespective of the solvent employed. However, in the presence of a competing acyl chloride, intramolecular acyl transfer is faster than intermolecular acylation in THF, whereas CH_2Cl_2 as solvent facilitates intermolecular acylation over intramolecular acyl migration thus favoring **11**.

The formation of product **11** from **8** can be explained in two pathways, Wittig/*O*-acylation sequence, or an initial *O*-acylation followed by chemoselective Wittig reaction. To rule out the possibility of the former, bis-acylated oximes **13** were prepared and treated with PBu_3 in the presence of the MTBD in CH_2Cl_2 at 30 °C (Scheme 7). Gratifyingly, the chromenone-

Scheme 7. Chemoselective Synthesis of 11[a,b]

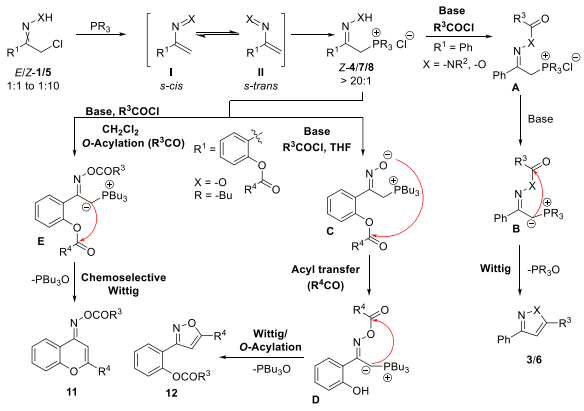


[a]Reactions were performed with **13** (0.2 mmol), MTBD (1.5 equiv), in dry CH_2Cl_2 (2 mL) under argon at 30 °C. [b]Isolated yield.

oxime derivatives **11** were obtained exclusively in yields of up to 83% within 4 h. This further demonstrates that chromenone-oximes **11** were indeed obtained from **8a** via a chemoselective intramolecular Wittig reaction of bis-acylated species and not from an initial Wittig reaction followed by *O*-acylation.

A tentative mechanism is outlined in Scheme 8. First, the reaction of phosphine (PPh_3 or PBu_3) with **1** or **5** generates

Scheme 8. Plausible Mechanism for Diverse Heteroarenes



the phosphonium salt *Z*-**4**/**7** via the in situ generated *s-cis*-**I** and *s-trans*-**II** isomers of azo-/nitroso-alkene intermediates. In presence of the base, the salt undergoes acylation with acyl chloride **2** to afford intermediate **A**. Deprotonation of **A** by another equivalent of base generates reactive phosphorus ylide **B**, which upon Wittig reaction affords pyrazoles **3** or isoxazoles **6**. The phosphonium salt **8** in the presence of MTBD in THF as solvent would form the intermediate **C**, which then undergoes intramolecular acyl group (R^4CO) transfer and generates **D**. Wittig reaction and a subsequent *O*-acylation with R^3COCl affords isoxazole **12**. On the other hand, the phosphonium salt **8** in CH_2Cl_2 as solvent undergoes acylation

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with R^3COCl to form the bis-acylated phosphonium salt **9**, which further provides the ylide **E** in the presence of the base. The ylide **E** then undergoes a chemoselective intramolecular Wittig reaction at the ester carbonyl (phenolic site) to afford the chromenone-oxime **11**.

In summary, an efficient strategy for the synthesis of substituted pyrazoles and isoxazoles is developed via a phosphine-mediated Wittig reaction of α-halohydrazones or ketoximes under mild and metal-free conditions. Further a chemoselective Wittig reaction was also realized by appropriate functionalization of ketoximes, which subsequently led to biologically relevant chromenenone-oxime scaffolds. Further investigations to construct diverse heteroarenes utilizing this protocol are underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b01395.

Optimization data, experimental procedures, characterization data and spectra of all compounds (PDF)

Accession Codes

CCDC 1588092−1588093, 1839883, 1845897, 1882452, 1893511−1893512, and 1904919 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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