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Converting oxazoles into imidazoles: new opportunities for diversity-oriented synthesis†

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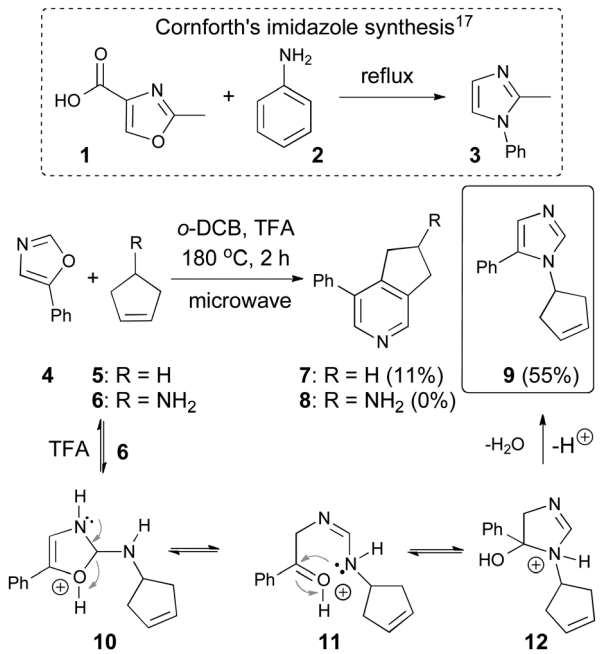
We report the optimization of a neglected reaction for the rapid and direct conversion of oxazoles into *N*-substituted imidazoles. The utility of this microwave-promoted reaction for diversity-oriented synthesis is demonstrated in the preparation of >40 *N*-substituted imidazoles, including α-imidazolyl esters.

Imidazoles are essential heterocycles in modern medicinal chemistry[1] and common in pharmaceuticals[2] and natural products.[3] As such, tremendous effort has been devoted to both imidazole synthesis[4] and functionalization,[5] from which many robust processes have emerged.[6] For example, the van Leusen imidazole synthesis[7] or multi-component reactions of 1,2-diketones with aldehydes and amines[8] are standard protocols. Despite these advances, several fundamental challenges to imidazole synthesis include the regioselective *N*-alkylation of asymmetric imidazoles,[9] production of *N*-tertiary alkyl imidazoles,[10] and the rapid synthesis of diverse libraries of *N*-substituted imidazoles.[11] Considering the ease with which oxazoles are prepared[12,13] and the well-established processes for their selective functionalization at C2[14] or C5,[15] they represent potentially useful synthetic isosters for imidazole. Thus, a direct conversion of oxazoles into imidazoles would provide unique opportunities for the regioselective synthesis of *N*-functionalized imidazoles, and new avenues for incorporating imidazoles into diversity-oriented drug discovery programs.

During our recent studies of Kondrat'eva reactions involving cycloalkenes (*e.g.*, **4** + **5** → **7**, Scheme 1),[16] we examined the microwave-assisted reaction of aminocyclopentene **6** with phenyloxazole **4**. Surprisingly,[16] the exclusive product of this reaction was not the expected cycloalka[*c*]pyridine **8**, but the structurally isomeric *N*-cyclopentenyl imidazole **9**. Formation of the imidazole **9** would involve attack at C2 of an oxazolium intermediate by the amine **6**, followed by ring opening/closing and extrusion of water. Despite obvious potential for exploiting this convenient reaction to overcome limitations in imidazole synthesis (see above), since the report of a single related example (see inset, Scheme 1) by Cornforth in 1947,[17,18] only a very limited number of additional examples have been disclosed.[19,20] In fact, this potentially important transformation is not considered among the fundamental reactions of oxazole or imidazole syntheses. Considering the value of imidazoles to the drug discovery process and the importance of identifying new methods to access *N*-functionalized imidazoles, we have investigated the oxazole to imidazole transformation, evaluated the scope of this reaction for the preparation of asymmetric *N*-alkyl imidazoles, and demonstrated the utility of this reaction for rapidly generating structurally diverse imidazoles.



Scheme 1 Cornforth's imidazole synthesis and related reaction of phenyl oxazole.

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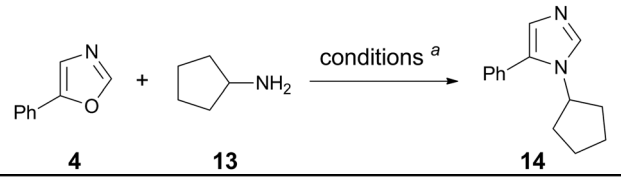
Table 1 Microwave-assisted oxazole to imidazole transformation



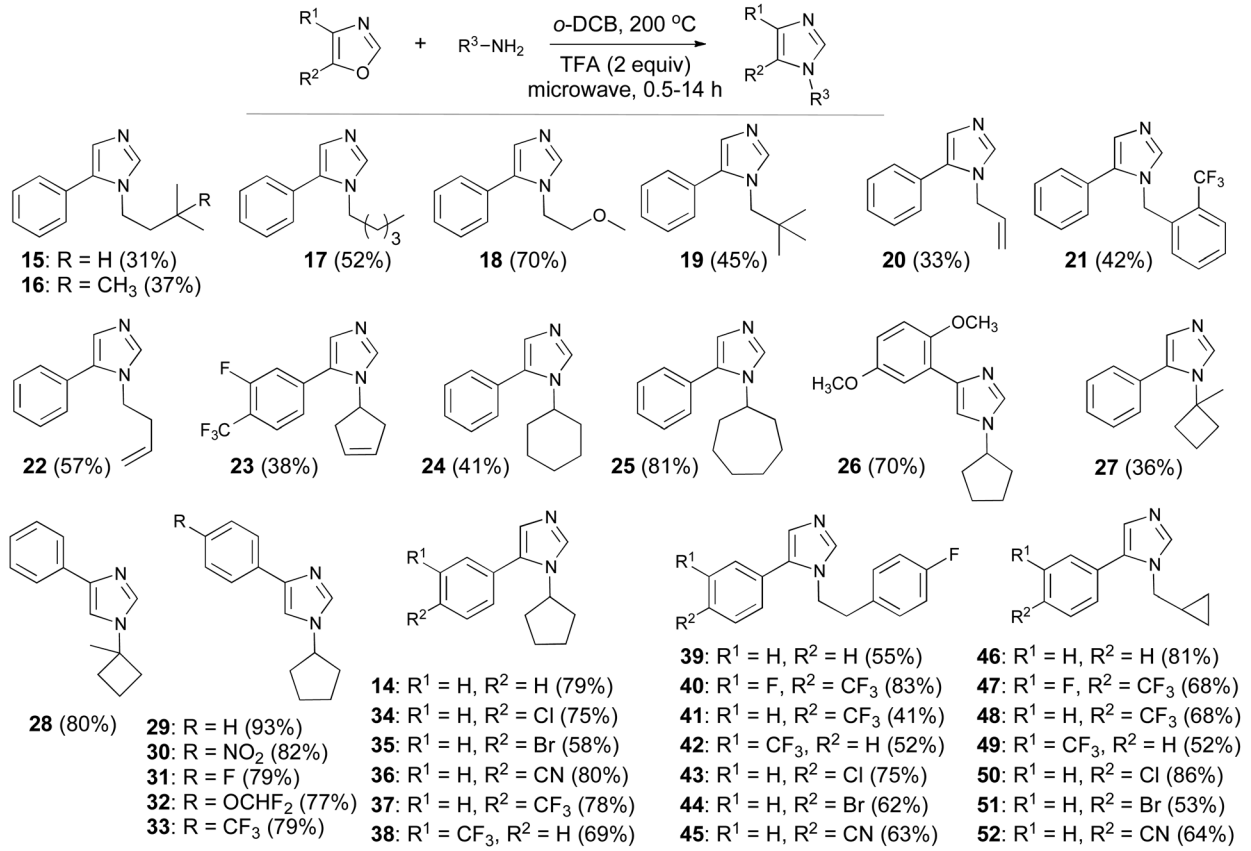
4 13 14

Entry	Ratio **4**:**13**	Additive (equiv.)	Temp. (°C)	Time (min)	**14**[b] (%)
1	1:3	TFA (3.0)	150	90	13
2	1:3	TFA (3.0)	180	30	33
3	1:3	TFA (3.0)	200	10	51
4	1:3	TFA (3.0)	220	10	67
5	1:3	TFA (3.0)	240	10	71
6	1:3	TFA (3.0)	260	10	48
7	1:1	TFA (1.0)	200	30	65[c]
8	1:1	TFA (2.0)	200	30	55[c]
9	1:1.5	TFA (1.5)	200	30	73[c]
10	1:2	TFA (2.0)	200	30	79[c]
11	1:1	$In(SO_3CF_3)_3$ (1.0)	200	30	59
12	1:1	$InCl_3$ (1.0)	200	30	7
13	1:1	$Mg(SO_3CF_3)_2$ (1.0)	200	30	42
14	1:1	$AgSO_3CF_3$ (1.0)	200	30	52

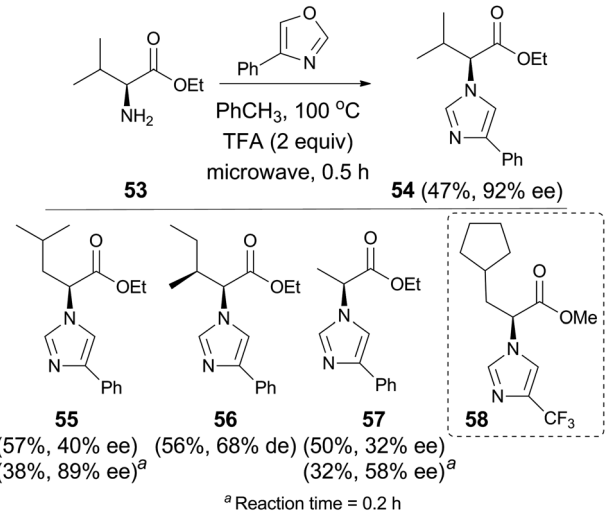
[a] Reactions carried out in a crimped (Teflon seal) vial and heated in an initiator+ microwave synthesizer (Biotage®) in *o*-DCB. [b] Percent yield based on HPLC-MS analysis with internal standard. [c] Isolated yield.

The microwave-assisted reaction of cyclopentylamine (**13**) with 5-phenyloxazole (**4**) is summarized in Table 1. While slow conversion to the imidazole **14** was observed at 150 and 180 °C (entries 1 and 2), at temperatures ranging from 200 to 240 °C, **14** was produced in good yield in only 10 min (entries 3–5). Further heating above 240 °C led to the production of a number of by-products and a reduced yield of **14** (entry 6). The use of fewer equivalents of TFA and cyclopentylamine was also examined (entries 7–10) and optimally, 2 equivalents of both the amine and TFA at 200 °C provided the imidazole **14** in reproducibly good yield (79%). A variety of Lewis acids were examined for their ability to promote the desired transformation, the most effective of which are summarized in entries 11–14. Several other solvents were also examined (*e.g.*, xylene, toluene, α,α,α-trifluorotoluene, *N*-methyl-2-pyrrolidine), however, the highest yield of **14** was obtained in *o*-dichlorobenzene (*o*-DCB).

Using the optimized reaction conditions (Table 1, entry 10), a collection of *N*-substituted imidazoles **15–52** were readily prepared from the combination of several commercially available 4- and 5-aryloxazoles and a variety of alkylamines. As depicted in Scheme 2, this microwave-assisted oxazole to imidazole transformation tolerates both functional and diversifiable groups (*e.g.*, alkene, F, Cl, Br, CN, CF_3) and provides direct access to *N*-secondary- and *N*-tertiary alkylimidazoles that would be difficult to prepare *via* direct alkylation (*e.g.*, **23–38**). Additionally, *N*-neopentyl (*e.g.*, **19**), *N*-homoallyl (*e.g.*, **22**), and *N*-homobenzyl imidazoles (*e.g.*, **39–45**) were all prepared regioselectively using these straightforward reaction conditions. The generally improved yields for the transformation of 4-aryloxazoles into imidazoles may be attributed to the intermediacy of an aldehyde as opposed to a ketone (*e.g.*, **11**, Scheme 1) in the



Scheme 2 Synthesis of 1-alkyl-4-aryl- and 1-alkyl-5-arylimidazoles from 4- and 5-aryloxazoles.



Scheme 3 Direct synthesis of α-imidazolyl esters from α-amino esters.

reactions of 5-aryloxazoles, and decreased steric congestion in the penultimate intermediate **12**.

In order to further demonstrate the utility of this process, we investigated the direct synthesis of 2-imidazolyl carboxylic esters. Notably, the imidazolyl ester **58** (Scheme 3) is a key intermediate in the synthesis of a hepatoselective glucokinase activator at Pfizer.[21,22] Employing our optimized conditions, reaction of valine ethyl ester (**53**) with 4-phenyloxazole provided the imidazolyl carboxylic ester **54** in good yield (49%). As analysis of the enantiomeric purity of **54** indicated partial racemization had occurred, the reaction was repeated at lower temperature (*e.g.*, 120 °C), which limited racemization (63% ee) with little effect on the yield. Optimally, shortening the reaction time to 0.5 h at 100 °C afforded the imidazolyl ester **54** in acceptable yield and enantiomeric purity (92% ee). Applying these modified conditions to the reaction of ethyl esters derived from leucine, iso-leucine, and alanine afforded the corresponding imidazolyl esters **55–57** in good yield and enantiomeric purity.

In summary, we have developed a microwave-assisted conversion of oxazoles into imidazoles and evaluated the scope of this fundamentally important transformation. Considering the ease with which oxazoles can be selectively functionalized at C2 or C5, these results highlight the utility of oxazole as a versatile scaffold for medicinal chemistry and diversity oriented synthesis. Furthermore, owing to the decreased basicity of oxazole ($pK_a \sim 1$) relative to imidazole ($pK_a \sim 7$) and ease of functionalization,[14,15] oxazole should be considered a protected imidazole. This stratagem should prove useful in synthetic sequences where interaction between the imidazole and a Brønsted or Lewis acid reagent would otherwise complicate the process, or where late stage diversification of imidazole is desirable.

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