Pergamon

Tetrahedron Letters 43 (2002) 189–192

TETRAHEDRON LETTERS

The synthesis of 2-substituted azoles through a one-pot three-component reaction

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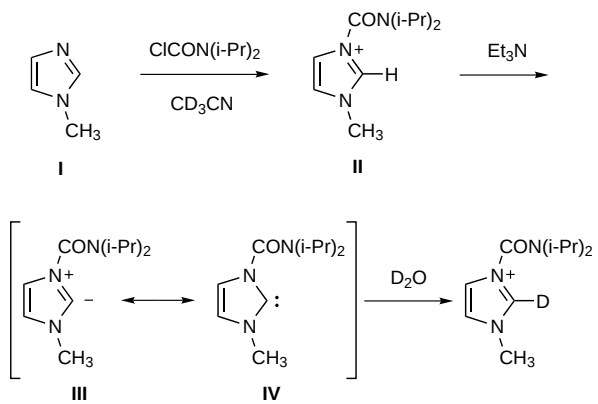
Received 15 August 2001; accepted 2 November 2001

Abstract—We have discovered a new reaction whereby 2-substituted azoles are formed in the reaction of an azolium ylide with reactive carbonyl compounds. These products contain a leaving group in the α-position, which on solvolysis in the presence of nucleophiles yield azoles with a variety of α-substituents. We have developed new aspects of this chemistry and expanded the scope to include imidazoles, thiazoles, benzimidazoles and triazoles, such that in two reaction steps a wide diversity of substitution patterns are obtained.

A number of biologically active molecules contain functionalized azole heterocycles.[1] Structurally diverse libraries of substituted azoles are therefore likely to give lead compounds after high-throughput screening against biological drug targets.[2] As part of our research effort, we seek to discover new synthetic methods that generate structurally diverse drug-like compounds. Recently, we reported our discovery where an imidazolium ylide was used in a novel way to synthesize 2-substituted imidazoles under mild conditions.[3] The reaction of 1-benzylimidazole was quite general with a variety of reactive carbonyl compounds, such as aldehydes, trifluoromethylketones, α-keto esters, and isocyanates. We subsequently found that when our previously described reaction conditions were applied to less reactive azoles, like thiazole, that poor yields of the desired product were obtained (10–30%). Herein, we report our recent results in developing new aspects of this reaction. We have improved the reaction conditions to obtain good yields with less reactive and previously problematic azoles. We also wish to report our findings on using a variety of nucleophiles to expand the scope of the solvolysis chemistry to 2-substituted imidazoles and 2-substituted thiazoles.

The rate of C-2 proton exchange in imidazole and thiazole is known to be enhanced by *N*-protonation or *N*-alkylation.[4] Our ^{1}H NMR spectroscopy study on the isotopic H/D exchange at C-2 of imidazolium species[5] (**II**) showed that (1) conversion (>95%) of imidazole **I** to **II** required about 48 h in the reaction of 1-methylimidazole with diisopropylcarbamyl chloride in CD_3CN; (2) complete H/D exchange (>95%) of the C-2 proton of 1-methylimidazolium **II** occurred in <10 min in presence of Et_3N; however, in the absence of base the exchange required about 24 h, and (3) no H/D exchange of the C-2 proton of 1-methylimidazole was observed after 72 h, even in presence of Et_3N.[6] These results support our contention that an azolium ylide **III** is an important intermediate in this reaction (Scheme 1). In the presence of a reactive electrophile, the azolium ylide can be trapped to form a 2-substituted azole derivative.



Scheme 1.

The reactive intermediate **III** can also be described by a carbene resonance structure **IV**, where the singlet state

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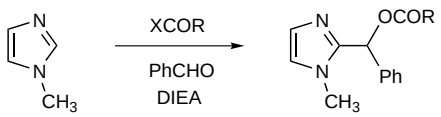
0040-4039/02/$ - see front matter
PII: S0040-4039(01)02110-4

carbene at C-2 is stabilized by push–pull stabilization. Stabilization of the singlet carbene has been proposed based on the π-electron donation of the two adjacent nitrogen lone pairs to the vacant p orbital at C-2 of the carbene, and on the σ-electron withdrawal by the electronegative nitrogen from the carbene pair of electrons in the s orbital at C-2. Diaminocarbenes have been previously described, and their reactivity is best described by the ylide resonance structure **III**. Indeed, the reactivity described in this paper mimics the reactivity of anion chemistry and not the typical reactivity of carbenes.[7]

Both steric hindrance and the reactivity of the acylation species effect the outcome of this reaction. We initially expected that steric hindrance was the key factor to obtain a good yield in this reaction. Therefore, our first experiments focused on the use of diisopropylcarbamyl chloride and we obtained 2-substituted imidazoles in good yields (e.g. Table 1, entry 1). In exploring the effect of steric hindrance and reactivity, we found that less sterically hindered carbamyl chlorides gave even better yields (entries 2 and 3). In a ^{1}H NMR experiment, dimethylcarbamyl chloride was shown to completely form an imidazolium chloride in 6 h, much faster than diisopropylcarbamyl chloride (48 h). Since an improved yield of the 2-substituted imidazole in entry 3 was found, we suggest that the rate-limiting step in entry 1 is the formation of the imidazolium chloride. The reaction di-*t*-butyl dicarbonate (entry 4) did not required base. We presume that in the formation of the imidazolium salt, carbon dioxide and the base *t*-butoxide are liberated. Thus, the *t*-butoxide then deprotonates the C-2 position of the imidazolium to form the ylide/carbene leading to the formation of the 2-substituted imidazole in 77% yield. The less sterically encumbered diethyl dicarbonate gave very poor results (entry 5), as did isopropyl chloroformate (entry 6).

Table 1. Acylator modifications

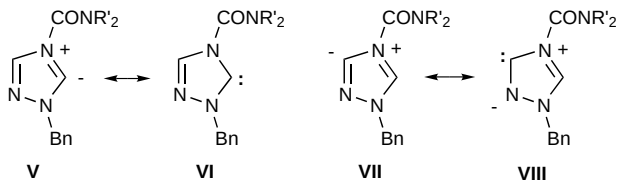


Entry	XCOR	Conditions (°C/h)	Product (R)	Yield (%)
1	$ClCON(i\text{-}Pr)_2$	60/24	$N(i\text{-}Pr)_2$	85
2	$ClCONEt_2$	60/20	NEt_2	92
3	$ClCONMe_2$	60/20	NMe_2	93
4	$O(COO\text{-}t\text{-}Bu)_2$	25/3	O-*t*-Bu	77[a]
5	$O(COOEt)_2$	25/20	OEt	4
6	$ClCOOCH(CH_3)_2$	25/20	$OCH(CH_3)_2$	20

[a] No base was used in the reaction of entry 4.

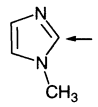
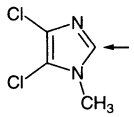
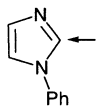
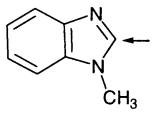
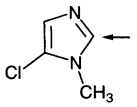
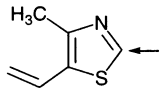
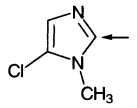
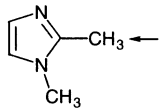
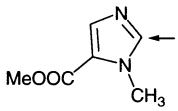
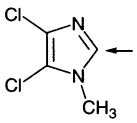
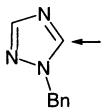
Nucleophilicity and basicity (pK_a) are known to correlate when the structure of the nucleophiles are very similar, and linear relationships have been reported between nucleophilic rates and pK_a values.[8] This relationship was also found in our studies. Our ^{1}H NMR experiments showed that the rate of formation of the azolium intermediate **II** depends on both the reactivity of the acylation species and the nucleophilicity of the azoles. For example, after 48 h, only 5% of thiazolium chloride but 95% of imidazolium chloride was detected by NMR in the reaction of diisopropylcarbamyl chloride with thiazole and 1-methylimidazole, respectively. Also, in the series of 1-methylimidazole (pK_a 7), thiazole (pK_a 2.5), and oxazole (pK_a 0.8),[9] the best product yields were found with 1-methylimidazole, and thiazole only gave good yields with more reactive acylation species. In reactions with oxazole, 2-substituted oxazole products were not detected, probably since *N*-acylation is very slow due to the low nucleophilicity of oxazole.

Furthermore, the use of an appropriate acylation species can be critical in affording good yields in these reactions. Earlier we discussed the improved yields that were obtained with imidazoles when the less sterically hindered and more reactive dimethylcarbamyl chloride were used in comparison to diisopropylcarbamyl chloride (Table 1, entries 1–3). This difference in reactivity was even more pronounced in the reaction of less reactive azoles. In reactions where we used our previously described conditions with diisopropylcarbamyl chloride and benzaldehyde on less reactive azoles, we consistently obtained poor to moderate yields (Table 2, entries 4, 7, and 9). When more reactive acyl chlorides were used, the yields were improved (Table 2, entries 5, 8 and 10).



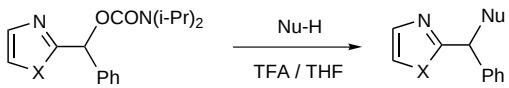
Interestingly, the reaction of 1,2-dimethylimidazole gave an α-C extended product in very good yield (entry 12). The reactive intermediate presumably is a 1,3 dipole like ylide (isoelectronic with an exocyclic bisenamine), which is sufficiently reactive to form the isolated product. Unexpectedly, only the 5-substituted isomer was isolated in the reaction of the unsymmetrical 1,2,4-triazole (Table 2, entry 14). The regioselectivity for exclusive reaction at the 5-position can be explained by the ylide/carbene resonance structures. Formation of an ylide/carbene **V**/**VI** at the 5-position is favored by the same electron effects described earlier for resonance structures **III** and **IV**. While formation of an ylide/carbene **VII**/**VIII** at the 3-position is not favored, even though the C-3 carbon is adjacent to two nitrogen atoms. An empty p orbital at C-3 can not be stabilized by π-electron donation, since the lone pairs on the adjacent nitrogens are not available for donation through the π-system. In order to assess the relative stabilities of the two possible ylidenes **V**/**VI** and **VII**/**VIII**, ab initio calculations[11] were carried out using density functional theory (DFT) at the B3-LYP/6-31G* level of theory.[12] These calculations showed a strong preference for **V**/**VI**, with **V**/**VI** being calculated to be 16.9 kcal/mol more stable than **VII**/**VIII**.

Table 2. Reaction of azoles with benzaldehyde and carbamyl chlorides $ClCONR'_2$[10]

entry	azole[a]	NR'2	yield (%)	Entry	Azole	NR'2	yield (%)
1		N(*i*-Pr)2	85	8		NMe2	55
2		N(*i*-Pr)2	86	9		N(*i*-Pr)2	40
3		N(*i*-Pr)2	88	10		NMe2	65
4		N(*i*-Pr)2	66	11		N(*i*-Pr)2	50
5		NMe2	85	12		N(*i*-Pr)2	78
6		NMe2	70	13		N(*i*-Pr)2	68
7		N(*i*-Pr)2	42	14		N(*i*-Pr)2	66[b]

[a] The reaction site is indicated with "→". [b] 25% of the starting material, 1-benzyl-1,2,4-triazole was isolated.

Table 3. Solvolysis reactions of carbamates[13]



Entry	Heterocycle (X)	Nucleophile (Nu–H)	Product (Nu)	Yield (%)
1	NMe	H_2O	OH	100
2	NMe	CH_3OH	OCH_3	85
3	NMe	CH_3CONH_2	$NHCOCH_3$	63
4	NMe	PhOH	OPh	85
5	NMe	$PhNH_2$	NHPh	80
6	NMe	Morpholine	Morpholin-1-yl	82
7	NMe	NaN_3	N_3	80[a]
8	S	H_2O	OH	80
9	S	$CH_3SO_2NH_2$	$NHSO_2CH_3$	65
10	S	Morpholine	Morpholin-1-yl	68

[a] The reaction was run with $BF_3{\cdot}Et_2O$ in DMF at 70°C overnight.

The diversity of the azoles in Table 2 that afford 2-substituted azole products in good yield is noteworthy, and highlights the broad scope of this chemistry. The products in Table 2 can be readily transformed by direct solvolysis chemistry into a range of functionalized azole derivatives, since the α-carbamyl group is a good leaving group. We previously described a limited number of nucleophile examples in the solvolysis reactions of 2-(α-diisopropylcarbamoylbenzyl)-1-benzylimidazole. In Table 3 are shown additional examples of this chemistry. Solvolysis reactions of both the 2-substituted-1-methylimidazole and the 2-substituted-thiazole gave good yields of the desired products.

The breadth and scope of the chemistry described herein demonstrates the broad application of this chemistry in the synthesis of azoles, including imidazoles, thiazoles, benzimidazoles, and triazoles, with a wide diversity of substitution patterns. The simplicity and efficiency of these reactions make this method particularly appealing for application to the solid-phase synthesis of compound libraries for high-throughput screening against therapeutic targets. In due course, the extension of this reaction to solid-phase synthesis will be reported.

Acknowledgements

We thank the Johnson & Johnson Corporate Office of Science and Technology for postdoctoral fellowship funding for Y.D. through the Excellence in Science Award Program. We also thank Diane Gauthier for assistance in the 2D NMR structure assignments of these compounds, and Dr. Charles Reynolds for the ab initio calculations.

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10. *Typical procedure*: To a solution of 1-methyl imidazole (164 mg, 2.0 mmol) in acetonitrile (5 mL) under nitrogen, was added subsequently diisopropylcarbamyl chloride (360 mg, 2.2 mmol), benzaldehyde (0.31 mL, 3.0 mmol) and diisopropylethylamine (1.0 mL, 6 mmol) at room temperature. The resulting mixture was stirred at reflux for about 24 h. The solvent was then removed. The residue was purified by flash chromatography on a silica gel with 50% ethyl acetate in hexanes to give entry 1 product in 85% yield.
11. Jaguar 4.1, Schrodinger, Inc., Portland, OR, 1991–2000.
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13. *Typical procedure for solvolysis*: To a solution of imidazole carbamate (315 mg, 1.0 mmol, Table 3, entry 1) in THF (5 mL), was added morpholine (0.9 mL, 10 mmol) and TFA (0.44 mL, 6 mmol) under nitrogen at room temperature. The resulting mixture was refluxed overnight. After cooling to room temperature, saturated $NaHCO_3$ aqueous solution (10 mL) was added into the reaction mixture, followed by extraction with CH_2Cl_2. The organic phases were combined, dried and concentrated in vacuo. The residue was purified by flash chromatography on a silica gel column with 2% MeOH in ethyl acetate to yield the desired product in 82% yield.