ORGANIC LETTERS

2001
Vol. 3, No. 2
157−159

Novel Use of Imidazolium Ylides in an Efficient Synthesis of 2-Substituted Imidazoles

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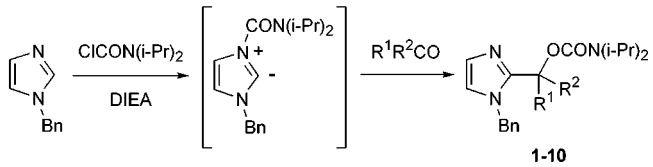
Received October 15, 2000

ABSTRACT

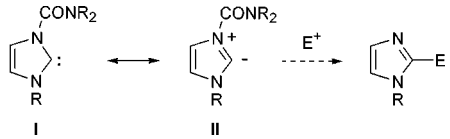


A new reaction of imidazoles was discovered involving the formation of an imidazolium ylide, which on trapping with various electrophiles afforded diverse 2-substituted imidazoles. The facile, convenient reaction conditions when compared to the existing procedures make this reaction the method of choice in the preparation of 2-substituted imidazoles. Moreover, the reaction differs from the reported methods since the products (viz., 1) contain an α-substituent that is transformed by solvolysis chemistry into further functionalized derivatives.

Imidazoles are important as heterocyclic components of many drugs and biologically active molecules.[1,2] Consequently, new, efficient methodology for the preparation of imidazole derivatives would provide a valuable tool to synthetic organic chemists. Relative to functionalizing imidazole at the 2-position, 2-lithioimidazoles are generated with strong bases (e.g., BuLi) at low temperatures and under anhydrous conditions and then captured by electrophiles.[1,3] Imidazoles can be directly acylated at the 2-position[4] or thermally condensed with aldehydes or isocyanates, although the yields in the aldehyde reaction can be highly variable and substrate-dependent.[5] 2-Substituted imidazoles are also prepared by reacting 2-trimethylsilyl-1-alkylimidazoles with aldehydes, typically in good yields.[6]

We sought to establish a new reaction of imidazoles involving formation of an imidazolium ylide species (viz., **II** in Scheme 1), which is isoelectronic to carbene species **I**,

Scheme 1



with subsequent trapping by electrophiles to afford diverse 2-substituted imidazoles. The related thiazolium ylides have long been known from the mechanism of thiamine,[7] and

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(4) Regel, E.; Buchel, K.-H. *Liebigs Ann. Chem.* **1977**, 145−158, 159−168.

(5) Roe, A. M. *J. Chem. Soc.* **1963**, 2195−2200. Papadopoulos, E. P. *J. Org. Chem.* **1977**, *42*, 3925−3929. Papadopoulos, E. P.; Schupbach, C. M. *J. Org. Chem.* **1979**, *44*, 99−104.

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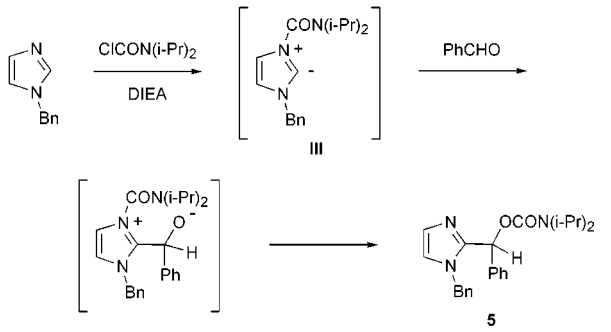
10.1021/ol006734y CCC: $20.00
Published on Web 12/29/2000

imidazolium ylides (or carbenes) have been postulated for some time.[8] In fact, the first stable, crystalline imidazolium carbene was isolated and characterized by X-ray crystallography in 1991.[9] Furthermore, Regel and Buchel proposed an imidazolium ylide as the reactive intermediate leading to 2-aroylimidazoles in the reaction of imidazole with benzoyl chlorides.[4] In a previous work, we found that imidazo[1,5-*a*]pyridine could be similarly acylated with benzoyl chlorides (at the 3-position) but that it did not react with sterically hindered 2,4,6-trimethylbenzoyl chloride.[10]

On the basis of this information, we decided to design a novel reaction for the synthesis of 2-substituted imidazoles. By way of example, a sterically hindered acyl chloride, such as diisopropylcarbamyl chloride, should react with 1-benzylimidazole at the 3-position to afford an intermediate imidazolium salt, which would be deprotonated in the presence of an amine base to form ylide **III**. Trapping with a suitable electrophile would then produce the target 2-substituted-1-benzylimidazole (Scheme 2). In fact, this

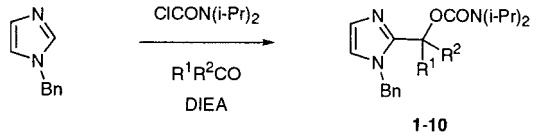
Scheme 2. Reaction Design via an Imidazolium Ylide **III**



reaction proceeded as designed to afford **5** in 78% yield! Herein, we describe our initial study of the scope and generality of this new reaction.

Omission of diisopropylethylamine from the reaction resulted in a low yield of **5** (Table 1, entry 8), indicating that the amine base is required, as expected from the aforementioned reaction plan in which ylide **III** is an intermediate. The reaction of 1-benzylimidazole with benzoyl chloride and benzaldehyde gave α-(1-benzylimidazol-2-yl)-benzyl benzoate **14** in only 2% yield, while 2-benzoyl-1-benzylimidazole was the major product isolated in 39% yield (Table 2, entry 5), indicating that a hindered acyl chloride is required. The examples presented in Table 1 show that an electrophile with significant reactivity is needed. Although

Table 1. Preparation of 2-Substituted Imidazoles[11]

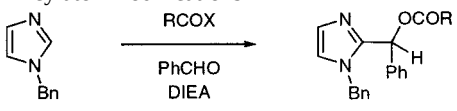


1-10

		conditions[a]			
entry	R^1R^2CO	temp	time	product	yield (%)
1	$(CH_3)_3CCHO$	reflux	24 h	**1**	66
2	$(CH_3)_2CHCHO$	rt	66 h	**2**	85
3	$PhCH_2CH_2CHO$	rt	29 h	**3**	75
4	$PhCH_2CHO$	reflux	20 h	**4**	32[b]
5	$PhCH_2CHO$	reflux	44 h	**4**	78[c]
6	PhCHO	reflux	24 h	**5**	78
7	PhCHO	rt	24 h	**5**	64
8	PhCHO	reflux	21 h	**5**	14[d]
9	4-(OMe)-PhCHO	rt	67 h	**6**	73
10	4-Cl−PhCHO	rt	30 h	**7**	77
11	$PhCOCF_3$	rt	3 d	**8**	89
12	CH=CHCHO	rt	68 h	**9**	67
13	$EtOOCCH(CH_3)$-COCOOEt	rt	68 h	**10**	73[e]
14	Ph-N=C=O	reflux	21 h		71[f]

[a] Reactions were run on a 2 mmol scale with 2.4 mmol of DIPC and 6.3 mmol of DIEA in 8 mL of acetonitrile. [b] Also obtained 55% of a 2:7 *trans* to *cis* mixture of $PhCH{=}CHOCON(i\text{-}Pr)_2$. [c] Three reagent charges. [d] No base was used. [e] Obtained a 3:1 mixture of diastereomers. [f] The product was 3-[(1-benzyl-imidazol-2-yl)carbonyl]-1,1-diisopropyl-3-phenyl-urea **11**.

Table 2. Acylator Modifications[11]



5, 12-14

		conditions[a]			
entry	RCOX	temp	time	product	yield (%)
1	$ClCON(i\text{-}Pr)_2$	reflux	24 h	**5**	78
2	$O(COO\text{-}t\text{-}Bu)_2$	reflux	21 h	**12**	52
3	$O(COOEt)_2$	reflux	21 h		*b*
4	$(CH_3)_3CCOCl$	reflux	21 h	**13**	32
5	PhCOCl	rt	4 d	**14**	2[c]

[a] Reactions were run on a 2 mmol scale with 2.4 mmol of RCOX and 6.3 mmol of DIEA in 8 mL of acetonitrile. [b] A mixture was obtained by TLC, and the product was not detected by MS. [c] The major product obtained in 39% yield was 2-benzoyl-1-benzyl-imidazole.

(7) Breslow, R. *J. Am. Chem. Soc.* **1958**, *80*, 3719−3726. Holzer, H. *Angew. Chem.* **1961**, *73*, 721−729.

(8) Wanzlick, H. W. *Angew. Chem.* **1962**, *74*, 129−134; *Angew. Chem., Int. Ed. Engl.* **1962**, *1*, 75−80 is a good leading reference.

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(11) All compounds gave satisfactory C, H, N analysis (±0.4%), and mass spectra and NMR spectra were consistent. Isolated yields are after flash chromatography on silica. **Typical Experimental Procedure:** To a suspension of 315 mg (2.0 mmol) of 1-benzylimidazole in 3 mL of acetonitrile at 0 °C and under nitrogen was added rapidly dropwise a solution of 396 mg (2.4 mmol) of diisopropylcarbamyl chloride in 5 mL of acetonitrile. To the slightly cloudy solution was added 0.31 mL (3.0 mmol) of benzaldehyde, followed by 1.1 mL (6.3 mmol) of diisopropylethylamine. The ice bath was removed, and after 10 min of stirring, the cloudy yellow solution was refluxed for 24 h, cooled to room temperature, and concentrated in vacuo. The residue was dissolved in ethyl acetate and washed successively with 2 N NaOH, water, and saturated brine. The organic layer was dried over magnesium sulfate, filtered, and concentrated to 1.01 g of a pale yellow oil. Flash chromatography on silica (50 mm × 18 cm column) eluted with ethyl acetate−hexanes (1:1) gave 611 mg (78%) of **5** as white crystals: mp 106−109 °C.; MS (ESP) *m*/*z* 392 [MH^+].

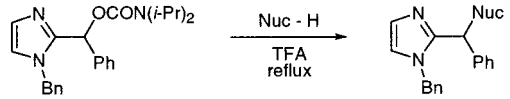
(12) Pratt, R. F.; Kraus, K. K. *Tetrahedron Lett.* **1981**, *22*, 2431−2434.

aldehydes, trifluoromethyketones, α-ketoesters, and isocyanates gave good yields of the desired products, the less reactive ketones, such as acetophenone and benzophenone, were not successful. Instead, the Bamberger degradation[12] product was obtained on aqueous workup.[13] Phenylacetaldehyde, which contains highly enolizable α-hydrogens, required special conditions to obtain a good yield of imidazole **4**. Under typical conditions (entry 4), phenylacetaldehyde competed for reaction with the ylide and diisopropylcarbamyl chloride, and desired product **4** was obtained in only 32% yield, along with the *O*-carbamoyl enol ether of phenylacetaldehyde. When the reaction was conducted with two additional charges of reagents at 6 and 24 h, and after a total reaction time of 44 h, a 78% yield of the imidazole **4** was obtained (entry 5).

A comparison of five acyl chlorides and anhydrides in the reaction of 1-benzylimidazole with benzaldehyde (Table 2) confirmed that a sterically hindered acyl chloride is required for good yields. As previously mentioned, benzoyl chloride afforded the 2-benzoyl imidazole in moderate yield and trace amounts of the desired product **14** (entry 5). Diethyl dicarbonate gave a complex mixture in this reaction (entry 3), while the more sterically encumbered di-*tert*-butyl dicarbonate gave the imidazole **12** in 52% yield (entry 2). Diisopropylcarbamyl chloride gave the best results.

Since the carbamoyl group of **5** is a good leaving group, we anticipated that various solvolysis reactions would provide imidazoles with a range of α-substituents. Imidazole **5** was converted to modified 2-substituted imidazoles as shown in Table 3. For example, treatment of **5** with methanesulfonamide and trifluoroacetic acid in THF at reflux gave the methanesulfonamido derivative **19** in 75% yield (entry 6). Similar results were obtained with acetamide, methanol, ethanol, and water (entries 1−5).

Table 3. Solvolysis Reactions of the Carbamate **5**[11]



5 **15-19**

entry	Nuc-H	rxn time[a]	product	yield (%)
1	H_2O	11 h	**15**	84
2	H_2O	21 h	**15**	quant[b]
3	CH_3OH	52 h	**16**	60[c]
4	CH_3CH_2OH	8 h	**17**	84[d]
5	CH_3CONH_2	18 h	**18**	63
6	$CH_3SO_2NH_2$	18 h	**19**	75

[a] Reactions were run on a 2 mmol scale with 20 equiv of the nucleophile in 10 mL of THF containing 0.5 mL of TFA at reflux. [b] A quantitative yield was obtained on a 15 mmol scale. [c] Isolated 11% of the alcohol **15**. [d] Isolated 12% of the alcohol **15**.

The new reaction described herein has tremendous potential in the synthesis of imidazoles bearing a wide diversity of substitution patterns. The facile, convenient reaction conditions when compared to the existing procedures make this reaction the method of choice in the preparation of substituted imidazoles. Furthermore, the reaction differs from the reported methods since the products contain an α-substituent that can be readily transformed by solvolysis chemistry into further functionalized derivatives. Studies on additional heterocycles and electrophiles, as well as asymmetric and solid-phase methods, are being pursued.

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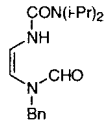
(13) The reaction of acetophenone under typical conditions gave on workup the Bamberger degradation product **20** in 52% yield with none of the desired product detected.



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