Acylation

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Chemoselective N-Acylation of Indoles and Oxazolidinones with Carbonylazoles**

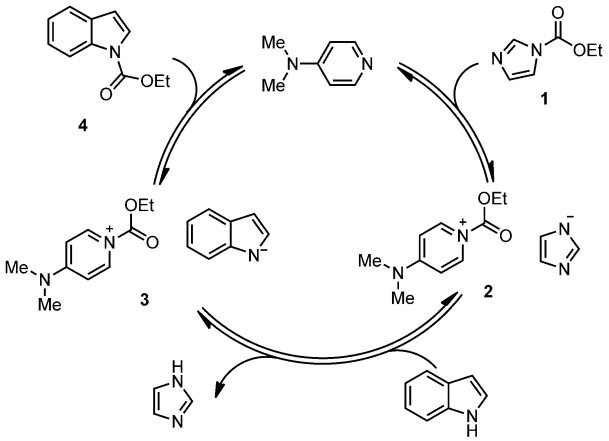
*Stephen T. Heller, Erica E. Schultz, and Richmond Sarpong**

The chemoselective acylation of molecules with multiple reactive sites is a long-standing problem in organic synthesis. A variety of reagents and reaction conditions have been developed to overcome this challenge. For example, influenced by the importance of carbohydrates, many methods to selectively functionalize sterically differentiated hydroxy groups have been developed.[1] More recently, progress in this area has exploited novel oligopeptides,[2] metal clusters,[3] fine-tuned organometallic complexes,[4] and organocatalysts[5] that achieve high levels of chemo- or regioselectivity. The emergence of methods to selectively O-acylate amino alcohols[6] led us to question whether novel selectivity for the functionalization of heteropolyfunctional molecules could be achieved.

Bearing in mind the dual challenges of chemoselectivity and operational simplicity, we sought to develop new methods for chemoselective acylation of heteropolyfunctional molecules at their inherently least nucleophilic site. Specifically, we wondered whether common non-nucleophilic (at nitrogen atom) azacycles, such as indoles, pyrroles, and oxazolidinones, could be N-acylated in the presence of stronger nucleophiles, such as amine or hydroxy groups. The ability to selectively N-functionalize heterocycles with multiple reactive sites would significantly simplify the preparation of pharmaceuticals, functional materials, and complex natural products by obviating protecting groups.[7]

Non-nucleophilic nitrogen atoms in heterocycles are typically acylated by quantitative deprotonation followed by treatment with reactive electrophiles, such as chloroformates or acid chlorides. However, the use of strong bases for the deprotonation step limits the functional-group tolerance of this approach. Alternatively, a wide variety of heterocyclic amines react with pyrocarbonates in the presence of 4-dimethylaminopyridine (DMAP) to afford carbamates. In all of these cases, the acylation reagent engages the most nucleophilic site first.[8]

We envisioned a conceptually novel approach that leveraged our previous studies using carbonylimidazole derivatives in esterification and amidation reactions.[9] By postulating that imidazole carbamates (e.g., **1**, Scheme 1) might react with a nucleophilic catalyst (e.g., DMAP) to give ion pair **2**, we anticipated that the imidazolide counteranion would be in the appropriate basicity range to deprotonate, for example, indole.[10] This would then lead to ion pair **3**, which could rapidly react to afford the desired product (**4**).



Scheme 1. Mechanistic hypothesis.

We anticipated that selective acylation could be achieved by matching the basicity of the counteranion in **2** (imidazolide) with the acidity of the group targeted for functionalization (e.g., the indole nitrogen atom in Scheme 1). Therefore, a scenario would develop in which an anionic nucleophile (i.e., the indole anion) competes for the acyl electrophile with neutral groups that are not acidic enough to be deprotonated. In most cases, this disparity should allow selective acylation of the more acidic group (i.e., the indole nitrogen atom), which is selectively deprotonated.

On the other hand, substrates with multiple acidic pronucleophiles might be selectively acylated by exploiting the reversibility of the acyl transfer reaction from imidazole carbamates (i.e., **1**) and the target functional group. Indeed, Birman has demonstrated that azolides are highly efficacious catalysts for acylation reactions with vinyl or aryl acetates as acyl donors, presumably through the generation of an acylazole intermediate.[11] On the basis of trends of pK_a values, it was expected that indole could be N-acylated in the presence of groups such as phenols, as the resulting indole carbamate would be much more stable under the reaction conditions than competing aryl carbonate by-products.

Our overall reasoning led us to investigate whether mildly reactive carbonylazole acyl transfer reagents could selectively engage indoles or other acidic non-nucleophilic amines in the presence of more nucleophilic groups. Our studies commenced with the attempted acylation of 5-fluoroindole (**5**)

[*] S. T. Heller, E. E. Schultz, Prof. R. Sarpong
Department of Chemistry, University of California, Berkeley
Berkeley, CA 94720 (USA)
E-mail: rsarpong@berkeley.edu

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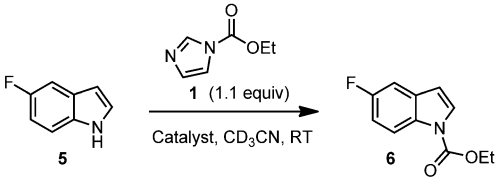
Table 1: Optimization of indole acylation.

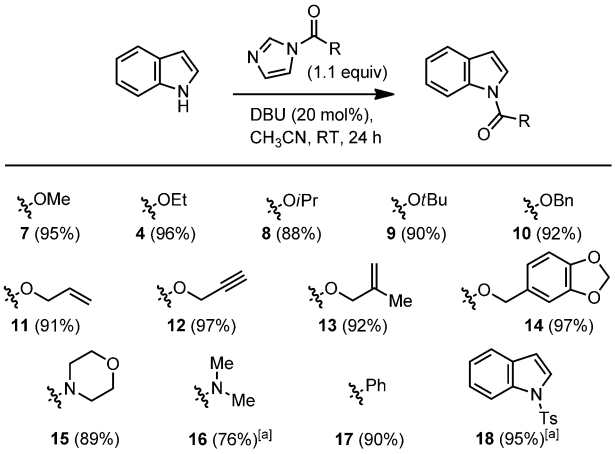


Entry	Catalyst	Mol%	Time [h]	Conversion [%][a]
1	Et_3N	100	24	n.r.
2	PBu_3	20	24	trace
3	MPO	20	24	trace
4	DMAP	20	24	10
5	DABCO	20	2.5	52
6	DBU	20	1	>95

[a] Conversion determined by integration of ^{19}F NMR resonances. DABCO = 1,4-diazabicyclo[2.2.2]octane, DBU = 1,8-diazabicyclo-[5.4.0]undec-7-ene, DMAP = 4-(dimethylamino)pyridine, MPO = 4-methoxypyridine *N*-oxide, n.r. = no reaction.

with **1** (Table 1). Classical nucleophilic catalysts, such as tributylphosphine and 4-methoxypyridine *N*-oxide (MPO), led only to trace amounts of products (Table 1, entries 2 and 3). However, consistent with our hypothesis, a small amount of **6** was obtained when DMAP was employed as a catalyst (entry 4). DABCO catalysis led to 52% conversion in less than three hours at 23 °C (entry 5). Moreover, employment of DBU, which has recently been recognized as an excellent nucleophilic catalyst,[12] led to rapid and efficient acylation of **5** (entry 6).

Several imidazole carbamates were then explored as acyl donors, and were found to cleanly afford the corresponding N-acylated indoles in excellent yield (Scheme 2). Primary, secondary, and even tertiary alkoxy-bearing imidazole carbamates were competent electrophiles (see **7**, **8** and **9**). However, for the formation of **9**, the reaction was discernably slower. Imidazole carbamates that are known to effect N-alkylation[13] afforded only the N-acylated products (i.e., **7** and **11**). In all cases, the only by-product was free imidazole, which was easily removed upon aqueous workup.



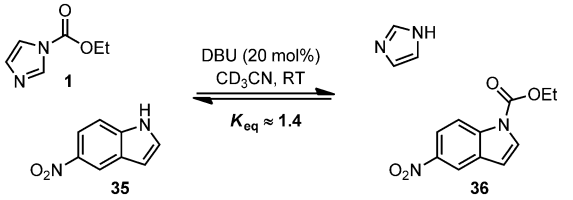
Scheme 2. Scope of the imidazole-based electrophile. [a] Reaction performed at 50 °C and with 50 mol% DBU. Yields in parentheses are for isolated compounds. Bn = benzyl, Ts = toluene-4-sulfonyl.

Carbamylimidazoles and acylimidazoles were also found to be competent reagents for the N-functionalization of indoles. However, the optimized reaction conditions varied significantly in these cases. For instance, while carbamylindole **16** can be prepared from the corresponding carbamylimidazole, a longer reaction time and a higher catalyst loading was required. Similarly, **18** may be prepared from indole and *N*-tosylimidazole, but in this case, heating to 50 °C was required.

With the effectiveness of the indole N-acylation established, we turned our attention to the selective acylation of molecules with multiple reactive sites. Gratifyingly, ethoxycarbonyl, Boc, benzoyl, and propionyl groups could be introduced at the indole nitrogen atom with excellent selectivity in the presence of other nucleophilic groups (Scheme 3). For example, the N-acylated product **19a** was obtained in greater than 20:1 selectivity. Similarly, acylation of the indole nitrogen atom could be efficiently accomplished (10:1 selectivity) in the presence of an amino group (see **20a/b**).[14,15] Moreover, acylation of the aniline group was not observed when 1-(*tert*-butoxycarbonyl)imidazole was employed as an acyl donor (see **21a**). Acidic functional groups, such as carboxylic acids, were tolerated in the N-acylation of the indole core (see **23**).

We then sought to further explore the scope of this mild acylation reaction by using a variety of functionalized indole substrates and ethyl imidazole carbamate (**1**) as the acylation reagent. Notably, groups, such as mono-protected amines (**26a/b**), alkyl halides (**26c**), acidic esters (**27**), and terminal alkynes (**25b**), were tolerated. The indole nitrogen atom of Boc-Trp-OMe (Trp = tryptophan) could be protected with a benzyloxycarbonyl (Cbz) group without loss of optical activity (see **24**).[16] C2- and C3-alkylated indoles reacted efficiently to afford the desired N-acylated indoles (see **30** and **29**, respectively). However, large groups at C2 (**31**) or C7 (see **32**) were found to impede acylation. Pyrrole could also be acylated with ethyl imidazole carbamate (**33**) and a stoichiometric quantity of DBU, but substituted pyrroles were poor substrates (**34**).[17]

In line with our hypothesis that selective acylation of indoles was thermodynamically controlled for substrates that contain highly acidic functional groups, we thought it might be possible to selectively acylate electronically unperturbed indole derivatives in the presence of relatively acidic heterocycles, such as 5-nitroindole [**35**, Eq. (1); $pK_a = 14.6$ in H_2O].[18] In this case, readily reversible acylation of the more acidic nitroindole species would be expected. Indeed, the reversible acylation of **35** in the presence of **1** was observed by ^1H NMR analysis.[19] Finally, competition between indole and **35** for acylation led to a 10:1 mixture of



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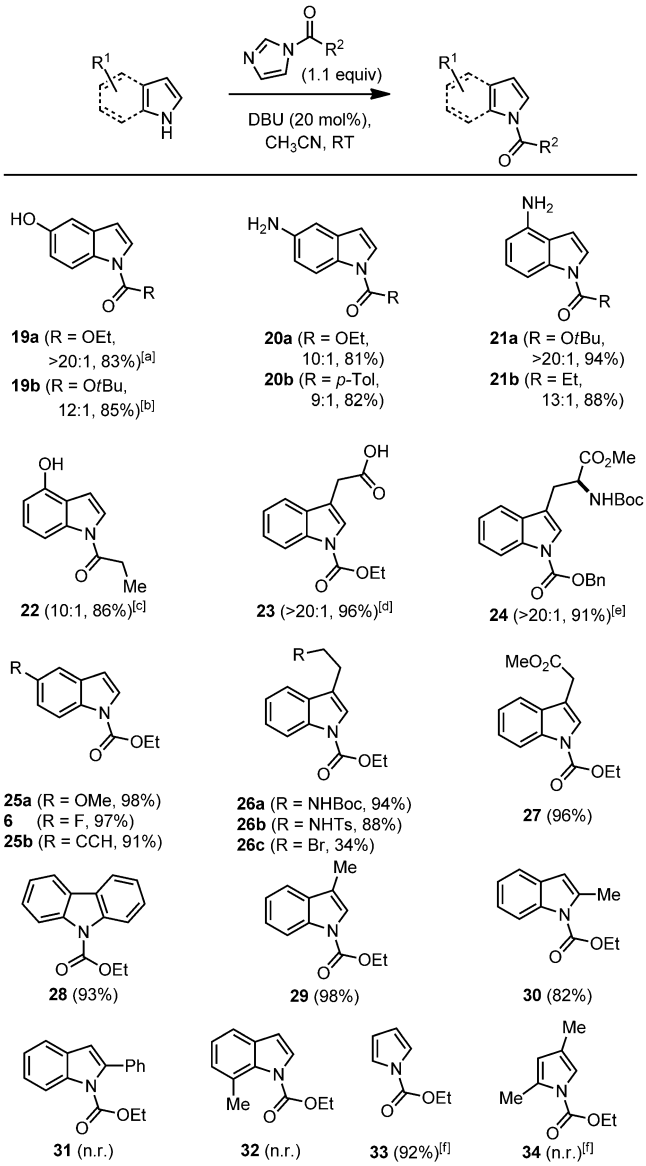
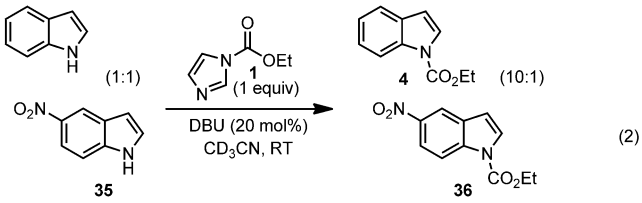


Scheme 3. Nucleophile scope of chemoselective acylation. [a] Reaction performed with 50 mol% DBU. [b] Reaction performed at 50°C with 50 mol% DBU. [c] **22** was obtained as a 11:1 inseparable mixture with the starting material. [d] 120 mol% DBU used. [e] No racemization was observed (see the Supporting Information). [f] 100 mol% DBU used. Ratios reflect acylation of indole nitrogen atom versus competing nucleophile. Yields in parentheses are of isolated products. Boc = *tert*-butoxylcarbonyl.

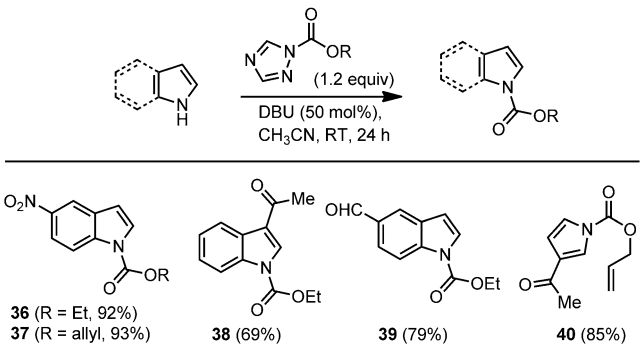
4 to **36** [Eq. (2)]. These observations strongly support a thermodynamically controlled acylation process.

The fact that 5-nitroindole has a pK_a value similar to that of imidazole (14.6 versus 14.5 in H_2O)[20] and that a nearly



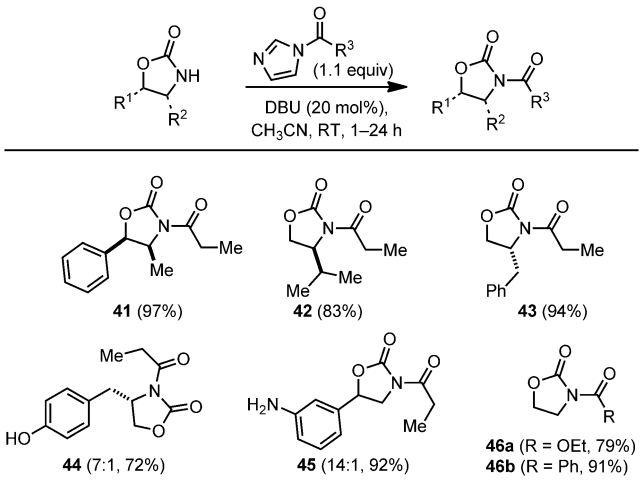
(2)

equimolar ratio of **36** and **1** remained in the DBU-mediated equilibration described in Equation (1) suggested that carbamate reactivity might be easily approximated by the pK_a value of the free heterocycle to which the carbonyl group is attached. On this basis, we investigated the acylation of nitroindole **35** with 1,2,4-triazole carbamates (Scheme 4; pK_a = 10.3 in H_2O for 1,2,4-triazole).[21] Nearly quantitative conversion of **35** to **36** or **37** was observed.[22] The use of carbonyltriazoles as acylation reagents for highly acidic azacycles appears to be general (see **38**–**40**). Importantly, ketone and aldehyde groups were generally well-tolerated in these reactions.[23,24]



Scheme 4. Acylation of acidic heteroaromatic compounds with carbonyltriazoles. Yields in parentheses are of isolated compounds.

Because the pK_a value of the pronucleophile appeared to correlate strongly with its selective acylation (i.e., indole NH), we reasoned that other nitrogen atoms with a similar pK_a value might be efficiently acylated. To that end, we investigated whether oxazolidinones (p$K_a \approx 20$ in DMSO)[25] could be acylated under our established conditions. Indeed, a variety of carbonylimidazoles have been found to acylate both the parent oxazolidinone (see **46**, Scheme 5), as well as several commonly used chiral auxiliaries (see **41**–**43**). Furthermore,

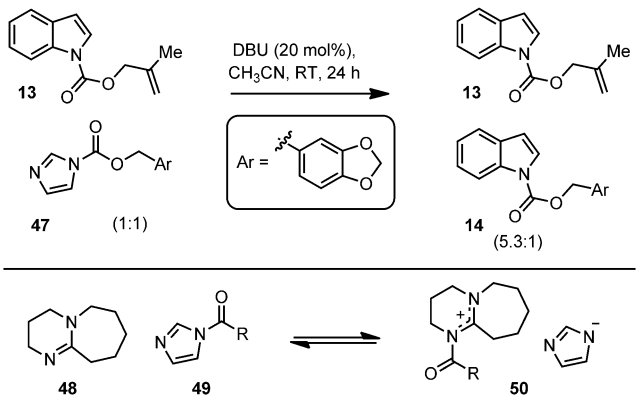


Scheme 5. N-acylation of oxazolidinones.

oxazolidinones can be acylated in the presence of phenol (**44**) and aniline (**45**) groups.

Acyloxazolidinones are typically prepared by quantitative deprotonation of the free oxazolidinone with strong base, thus contrasting sharply with the mild and rapid reaction at room temperature reported here.[26,27] Therefore, these mild acylation conditions should find widespread use in the exploitation of these important auxiliaries.[28]

Preliminary mechanistic investigations have been directed toward elucidating the role of DBU in these acylation reactions. Rather than simply acting as a base, we postulated that DBU might instead react as a nucleophilic catalyst (analogous to DMAP; Scheme 1) to produce imidazolide.[29] When **13** and **47** (Scheme 6, top) were treated with DBU, slow acyl group exchange was observed, thus suggesting that imidazolide was indeed generated directly from **47**. Even though this observation provided direct evidence that DBU could act as a nucleophilic catalyst toward carbonylimidazole derivatives, we could not rule out the possibility that DBU serves as a Brønsted base toward indole nitrogen groups bearing an acidic hydrogen.



Scheme 6. Acyl transfer by nucleophilic catalysis (top) and generation of equilibrium with imidazolide (bottom).

However, simple Brønsted catalysis is inconsistent with the observation that DABCO is a better catalyst compared to triethylamine or DMAP, even though it is less basic (Table 1).[30] Rather, this reactivity trend is strongly correlated with nucleophilicity.[31] It seems likely that DBU, albeit less nucleophilic, outperforms DABCO as an acylation catalyst because of its high carbon basicity.[32] That is, with DBU, a higher concentration of imidazolide could be accessed by shifting the equilibrium (Scheme 6, bottom) to favor the formation of **50**. Thus, a balance between nucleophilicity and carbon basicity is important in this strategy for catalysis of acylations with carbonylimidazoles.

This mechanistic hypothesis accounts for the observation that pronucleophiles with a pK_a value substantially higher than that of imidazole are not acylated under the conditions described here; in these cases deprotonation by imidazolide is inefficient. Therefore, we tentatively propose that pronucleophiles with pK_a values (in DMSO) greater than 23 will be relatively inert to the DBU-catalyzed acylation with carbonylimidazoles.[33] Conversely, functional groups or azacycles that are more acidic than imidazole will be rapidly acylated because they can be easily deprotonated by imidazolide. However, if the product of this acylation is less or similarly stable relative to the imidazole carbamate, the acylation may be readily reversible.[34] As a consequence, there is a functional lower limit to the pK_a value of the pronucleophile, which we tentatively assign to be approximately 19 (in DMSO).

In conclusion, we have demonstrated that DBU reacts with a series of carbonylazoles[35] to generate an ion pair with azolide as the counteranion. The basicity of the azolide allows the chemoselective N-acylation of pronucleophiles, such as indoles and oxazolidinones, in a certain pK_a range ($\approx$19–23 for carbonylimidazoles) in the presence of carboxylic acids, phenols, and anilines—a selectivity that has never before been observed in acylation reactions.

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Keywords: acylation · chemoselectivity · imidazole · indoles · oxazolidinones

[1] A large quantity of research has been conducted in this area. Some leading reviews include: a) M. Nahmany, A. Melman, *Org. Biomol. Chem.* **2004**, *2*, 1563; b) W. T. Greene, P. G. M. Wuts, *Protective Groups in Organic Synthesis*, *4th ed.*, Wiley, New York, **2006**; c) M. Miljković, *Carbohydrates*: *Synthesis Mechanisms*, *and Stereoelectronic Effects*, *1st ed.*, Springer, New York, **2010**.

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[8] See Ref. [1b]. Weak bases, such as triethylamine, have been used with an acyl halide and DMAP.

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[10] The pK_a values of imidazole and indole are 18.6 and 21.0 in DMSO, respectively. For imidazole, see: F. G. Bordwell, *Acc. Chem. Res.* **1988**, *21*, 456. For indole, see: F. G. Bordwell, G. E. Drucker, H. E. Fried, *J. Org. Chem.* **1981**, *46*, 632. Trends in pK_a values vary significantly depending on solvent. The publications listed herein also include a detailed account of trends of pK_a values in non-aqueous solvents.

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[12] a) M. Carafa, E. Mesto, E. Quaranta, *Eur. J. Org. Chem.* **2011**, 2458; b) C. Larrivée-Aboussafy, B. P. Jones, K. E. Price, M. A. Hardink, R. W. McLaughlin, B. M. Lillie, J. M. Hawkins, R. Vaidyanathan, *Org. Lett.* **2010**, *12*, 324; c) W. C. Shieh, S. Dell, O.

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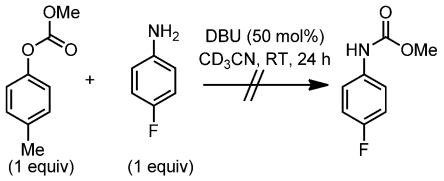
[14] Though it has been reported that DBU catalyzes the acylation of anilines by acylimidazoles at high temperature (Ref. [12b]), we did not observe any reaction between **1** and 4-fluoroaniline in the presence of DBU at room temperature after two days. Addition of indole to this mixture leads to rapid acylation of indole.
[15] Carbonates are not competent acyl donors in the absence of imidazole. For example, treatment of methyl phenyl carbonate with 4-fluoroaniline and DBU did not affect acyl transfer to the aniline amine group.



[16] If the reaction is allowed to run for long periods of time (i.e., 24 h), some loss of optical activity is noted. However, installation of the Cbz group requires only one hour.
[17] 2,4-Dimethylpyrrole was not acylated, even when exposed to **1** and DBU at 80 °C.
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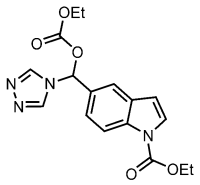
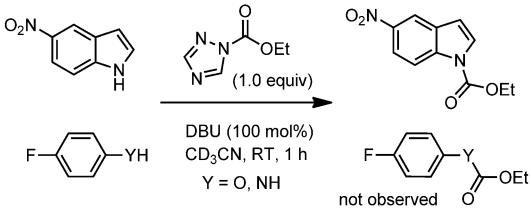
[22] Lower catalyst loadings resulted in incomplete reactions because of competitive protonation of DBU by free triazole.
[23] A small amount of a triazole adduct (see below) was observed when 5-indolecarboxaldehyde was used as a substrate.



[24] Competition experiments between 5-nitroindole and either 4-fluorophenol or 4-fluoroaniline demonstrated that even with the more reactive carbonyltriazole acylating reagents, the indole nitrogen atom was selectively functionalized over other nucleophilic groups [Eq. (3)].



(3)

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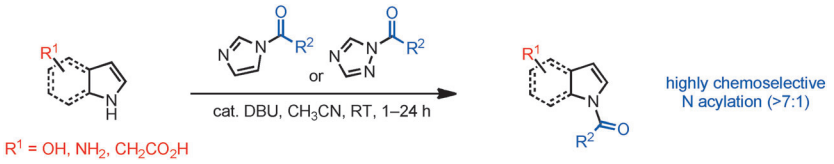
[30] Conjugate acid pK_a values in H_2O: $NEt_3 = 10.8$, DMAP = 9.2, and DABCO = 8.8 (J. March, *Advanced Organic Chemistry*, *4th ed.*, Wiley, New York, **1992**).
[31] M. Baidya, S. Kobayashi, F. Brotzel, U. Schmidhammer, E. Riedle, H. Mayr, *Angew. Chem.* **2007**, *119*, 6288; *Angew. Chem. Int. Ed.* **2007**, *46*, 6176.
[32] M. Baidya, H. Mayr, *Chem. Commun.* **2008**, 1792.
[33] Compounds that are sufficiently nucleophilic as neutral species may violate these guidelines. Therefore, we cannot recommend the use of this acylation system in the presence of unprotected aliphatic amines or alcohols at this time.
[34] The acetyl group of phenyl acetate was observed (by ^{1}H NMR spectroscopy) to transfer to the nitrogen atom of indole in the presence of DBU and imidazole.
[35] A range of these carbonylazoles are commercially available from Aldrich Chemicals (Product numbers: 424013, 752886, 748773, 748730, 748765, 748811, 748781, 748838).

Communications

Acylation

S. T. Heller, E. E. Schultz,
R. Sarpong* ——————— ■■■■–■■■■

Chemoselective N-Acylation of Indoles and Oxazolidinones with Carbonylazoles



Unique reactivity: In the presence of more reactive amine and alcohol functional groups and of carboxylic acids, the chemoselective N-acylation of indoles (see scheme) and oxazolidinones is achieved by taking advantage of the unique reactivity of carbonylazole acylating agents with catalytic amounts of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU).