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Full Papers

A Comparison of Catalysts to Promote Imidazolide Couplings Including the Identification of 2-Hydroxy-5-nitropyridine as a New, Safe, and Effective Catalyst

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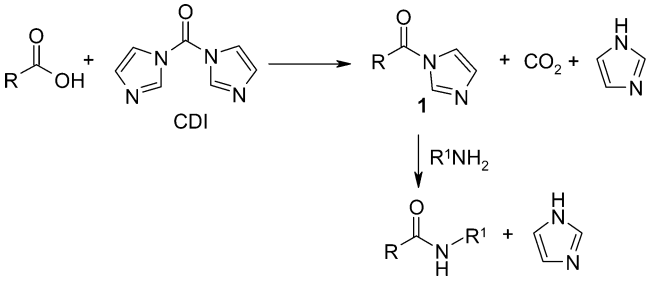
Abstract:

Five catalysts were compared with respect to their safety and catalytic effectiveness for promoting imidazolide couplings. Reaction rate enhancement, shock sensitivity, and differential scanning calorimetry (DSC) data were considered in this analysis. 6-Chloro-1-hydroxybenzotriazole, which has been described in the literature as a safe catalyst, was found to be shock sensitive. 2-Hydroxy-5-nitropyridine is a new catalyst for this type of reaction and was found to be safe, effective, readily available, and similar in price to that of the 1-hydroxybenzotriazole, a common catalyst for promoting acylation reactions.

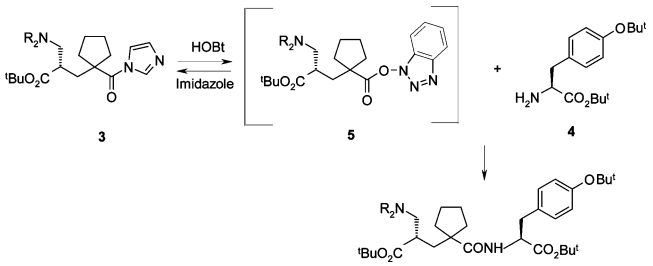
Introduction

The use of *N*,*N*[1]-carbonyldiimidazole (CDI) as a coupling agent for amide bond formation has recently been applied to the large-scale synthesis of a number of pharmaceutical products, for example, sildenafil,[1] darifenacin,[2] and sunitinib.[3] In addition a survey of 128 chemical processes recently developed by AstraZeneca, GlaxoSmithKline (GSK), and Pfizer revealed that CDI was the third most common reagent used for *N*-acylation reactions and was used in 9 out of 84 examples.[4] The advantages are that the byproducts, carbon dioxide and imidazole, are innocuous and that the evolution of carbon dioxide in forming the imidazolide **1** provides a driving force for the reaction[5,6] (Scheme 1). In addition the imidazole byproduct can be removed by an acidic wash[2] or remains in solution in the organic solvent.[1]

Scheme 1



Scheme 2



One factor influencing the increased use of CDI on a large scale is its relatively low price (around $8/mol for a large-scale purchase). Although CDI is more expensive than traditional amide-forming reagents, such as thionyl chloride and isobutyl chloroformate, in some cases the high yields and clean environmental conditions can justify its use.

A disadvantage of CDI is that the resulting imidazolide **1** is less reactive than the corresponding acid chloride, and hence amide couplings with either hindered carboxylic acids or weakly nucleophilic amines can be unacceptably slow. One way around this issue is to use a catalyst. The first reported example was the use of 1-hydroxybenzotriazole (HOBt, **2**) to catalyse the reaction of the hindered imidazolide **3** with the tyrosine derivative **4** via the active ester **5**[7] (Scheme 2). However, the additional use of HOBt does have some drawbacks. The material is known to explode when heated beyond its melting point (around 160 °C).[8] The

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(1) Dale, D. J.; Dunn, P. J.; Golightly, C.; Hughes, M. L.; Levett, P. C.; Pearce, A. K.; Searle, P. M.; Ward, G.; Wood, A. S. *Org. Process Res. Dev.* **2000**, *4*, 17−22.

(2) Dunn, P. J.; Newbury, T. N.; Matthews, J. M.; O'Connor, G. World Patent WO 03/080599.

(3) Vaidyanathan, R.; Kalthod, V. G.; Ngo, D. P.; Manley, J. M., Lapekas, S. P. *J. Org. Chem.* **2004**, *69*, 2565−2568.

(4) Carey, J. S.; Laffan, D.; Thomson, C.; Williams, M. T. *Org. Biomol. Chem.* Submitted for publication.

(5) Anderson, G. W.; Paul, R. *J. Am. Chem. Soc.* **1958**, *80*, 4423.

(6) Anderson, G. W.; Paul, R. *J. Am. Chem. Soc.* **1960**, *82*, 4596.

(7) Dunn, P. J.; Hughes, M. L.; Searle, P. M.; Wood A. S. *Org. Process Res. Dev.* **2003**, *7*, 226−236.

(8) Urben, P. G., Ed. *Bretherick's Handbook of Reactive Chemical Hazards*, 6th ed.; Butterworth-Heinemann: Oxford, Boston, 1999; p 746.

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10.1021/op0580062 CCC: $30.25

Scheme 3

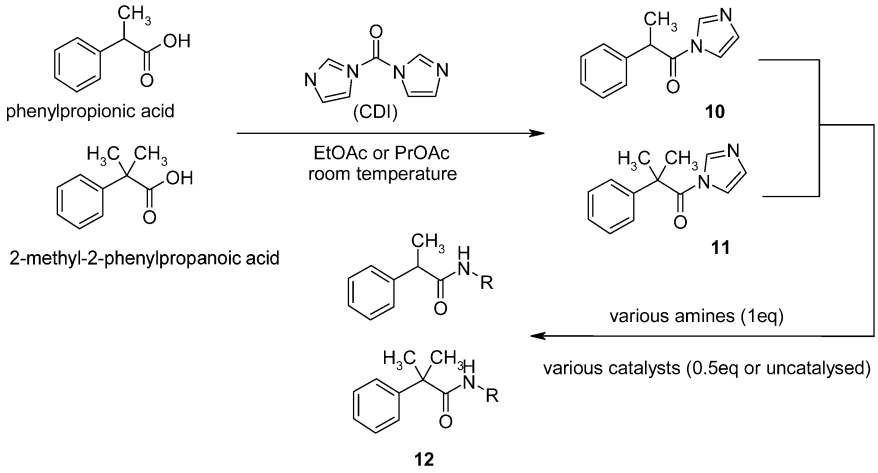
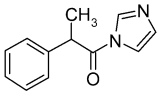
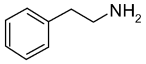
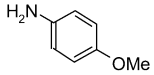
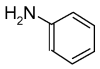
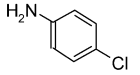
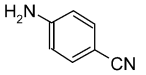
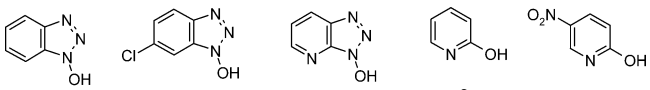


Table 1. **Comments on the speed of reaction between the imidazolide 10 and the various amines**

Imidazolide	Amine	Comments
 **10**		Reaction 97% complete without catalyst in boiling ethyl acetate in less than 5min.
		Reaction 86% complete without catalyst in boiling ethyl acetate after 10min.
		Reaction 86% complete without catalyst in boiling ethyl acetate after 3 hours.
		Reaction 80% complete with 0.5 equiv. of 1-hydroxybenzotriazole hydrate in boiling ethyl acetate after 13 hours.
		Reaction 32% complete with 0.5 equiv. of 1-hydroxybenzotriazole hydrate in boiling ethyl acetate after 13 hours

transportation of HOBt on a large scale is subject to restrictions in Europe because of this explosive potential. 6-Chloro-1-hydroxybenzotriazole (Cl-HOBt, **6**) is commercially available and has been reported[9] to be safer than HOBt. It also has a lower pK_a (4.15 vs 4.60)[10] which should make it a more effective catalyst, but no safety data were reported for this catalyst. 1-Hydroxy-7-azabenzotriazole (HOAt, **7**) is commercially available and has an even lower pK_a (3.47)[10] and hence should be a very effective catalyst in promoting imidazolide-coupling reactions. However HOAt is reported to have significant safety drawbacks and is shock sensitive.[11] Finally 2-hydroxypyridine (HOPy, **8**) was reported to be a reasonable catalyst to promote imidazolide couplings[12] although this work involved proprietary compounds, and only partial structures were reported. The objective of this paper is to run a side-by-side comparison of the safety and catalytic effectiveness of these four catalysts. In addition as the pK_a of the catalyst was thought to be related to its catalytic effectiveness, we also decided to study 2-hydroxy-5-nitropyridine (NO_2-HOPy, **9**) as a potential catalyst as this compound will be significantly more acidic than 2-hydroxypyridine.



Results and Discussion

The first part of the work (summarised in Scheme 3) was to define the scope of the reaction and select a reaction for the side-by-side comparison study, the results of which are summarised in Tables 1 and 2.

The imidazolide **10** undergoes rapid reaction with aliphatic amines, and amide formation proceeds at a reasonable rate with aromatic amines; hence, these reactions do not need catalysis. The reaction of **10** with weakly basic amines such as 4-aminobenzonitrile and 4-chloroaniline are sluggish and can be catalysed. However, as can be seen from Table 2, the more hindered imidazolide **11** undergoes a very sluggish

(9) Marder, O.; Albericio, F. *Chem. Oggi* **2003**, 35−40.
(10) Koppel, I.; Koppel, J.; Leito, I.; Viljar, P.; Grehn, L.; Ragnarsson, U. *J. Chem. Res. (S)* **1993**, 446−447.
(11) See MSDS, Applied Biosystems, July 2002.
(12) Bright, R.; Dale, D. J.; Dunn, P. J.; Hussain, F.; Kang, Y.; Mason, C.; Mitchell, J. C.; Snowdon, M. J. *Org. Process Res. Dev.* **2004**, *8*, 1054−1058.

Table 2. **Comments on the speed of the reaction imidazolide 11 and various amines**

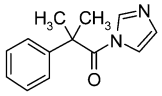
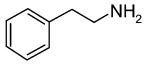
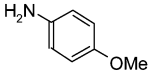
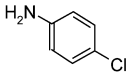
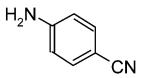
Imidazolide	Amine	Comments
 11		Reaction 96% complete without catalyst in boiling ethyl acetate in less than 5min
		Reaction 70% complete without catalyst in boiling ethyl acetate after 13 hours.
		Slow reaction, 24% complete in boiling ethyl acetate after 13 hours without any catalyst; conversion of amine to amide reached 82% with 0.5 equiv. of 1-hydroxybenzotriazole hydrate at 78°C after same period.
		There is only a trace of product observed without catalyst, and 50% complete in boiling ethyl acetate within 3 hours with 0.5 equiv. of 1-hydroxybenzotriazole hydrate.
		No product was observed without catalyst after 3 h, and the reaction was only 2% complete in boiling ethyl acetate with 0.5 equiv of 1-hydroxybenzotriazole hydrate after 3 hours.

Table 3. **Percentage conversion of aniline to 2-methyl-2-phenylpropananilide (12, R = Ph) with 0.5 equiv of various catalysts in boiling ethyl acetate (78 °C)**

	Percentage (%) of 2-methyl-2-phenylpropananilide (**12**) relative to aniline					
time (h)	uncatalyzed	HOPy (**8**)	NO_2-HOPy (**9**)	HOBt·H_2O (**2**)	Cl-HOBt (**6**)	HOAt (**7**)
0	0	0	0	2.1	6.2	4.8
0.25	N/A	N/A	N/A	N/A	N/A	67.1
0.5	N/A	1.6	6.2	49.4	62.2	77.9
1	3.5	3.8	11.1	63.9	74.8	83
2	4.2	7.4	21.9	72.7	83	87.6
4	9.7	15.1	34.3	79.1	85.9	88.4
8	18	28.6	50.1	81.5	88.5	89.5
13	26.6	41	63	82.7	90.4	N/A
17	33.2	49.5	68.1	N/A	N/A	N/A
24	44	52.8	73.6	93.2	90.9	N/A

reaction with aromatic amines, and these reactions benefit from the addition of a catalyst. Finally, the reaction of the imidazolide **11** with 4-aminobenzonitrile is unacceptably slow even in the presence of a catalyst. Hence, it appears that the reactions of very hindered imidazolides and weakly basic aromatic amines are probably outside of the scope of this methodology.

From the reactions shown in Tables 1 and 2 the reaction of imidazolide **11** with aniline was selected as the reaction for the side-by-side comparison of the five catalysts. These reactions were carried out in boiling ethyl acetate with some representative samples taken at different time points over 24 h. The results were examined with GC/MS and are shown in Table 3 and Figure 1. These results clearly show that the order of catalytic effectiveness is:

HOAt > Cl-HOBt > HOBt·H_2O > NO_2-HOPy > HOPy

Perhaps not surprisingly the relative effectiveness of the three fused triazole-based catalysts matches the pK_a of the hydroxy proton. For the two least effective catalysts **8** and **9** it was shown that increasing the amount of catalyst and switching to a higher-boiling solvent gave good reaction rates. These results are summarised in Table 4 and Figure 2.

Process Safety Work. The five catalysts were evaluated for shock sensitivity by drop hammer testing and for thermal instability by DSC analysis. The results are summarised in Table 5.

There were two reasons to think that the fused triazole-based catalysts might have some shock sensitivity. The first

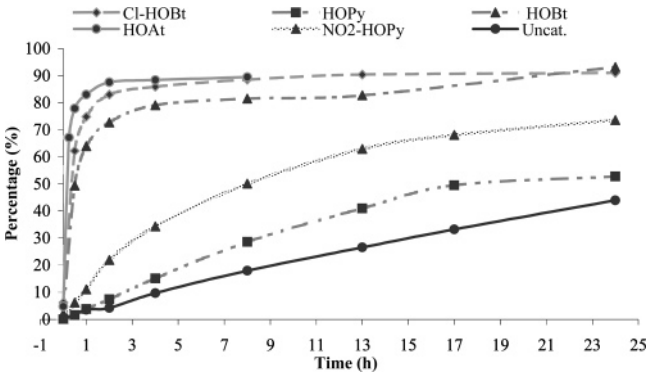


Figure 1. **Percentage conversion of aniline to 2-methyl-2-phenylpropananilide (12, R = Ph) with 0.5 equiv of various catalysts in boiling ethyl acetate (78 °C).**

Table 4. **Percentage conversion of aniline to 2-methyl-2-phenylpropananilide (12, R = Ph) with 2 equiv of catalyst in boiling *n*-propyl acetate (102 °C)**

	percentage (%) of 2-methyl-2-phenylpropananilide (**12**) relative to aniline		
time (h)	uncatalyzed	HOPy (**8**)	NO_2-HOPy (**9**)
0	0	0	0
0.5	N/A	11.5	50.5
1	6	23.4	65.3
2	13.6	41.2	77
4	23.5	60.5	86.3
8	39.8	74.4	91.5
13	55.6	82.2	93.5
17	61.7	85.5	100
24	70.1	86.3	100

Table 5. **The DSC and shock sensitivity results of the five catalysts**

		DSC results	
catalysts	shock sensitivity	onset temp (°C)	decomp. energy (J/g)
HOAt (**7**)	positive (5 J)	190	−2400
Cl-HOBt (**6**)	positive (30 J)	185	−2100
$HOBt.H_2O$ (**2**)	negative[a]	160	−1740
NO_2-HOPy (**9**)	negative	293	−1820
HOPy (**8**)	not tested	No exotherm up to 400 °C	æ

[a] No audible detonation, at either 50 or 100 J, but some decomposition is evident when subjected to a 100 J impact.

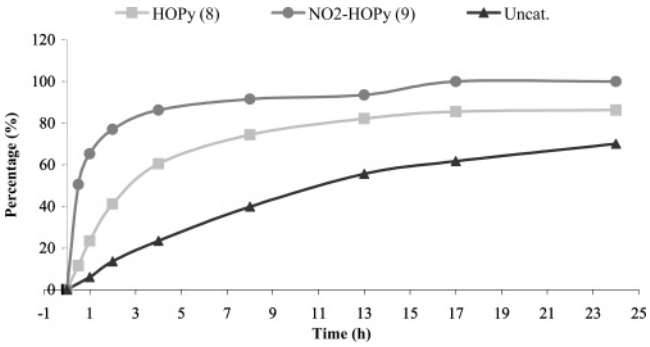


Figure 2. **Percentage conversion of aniline to 2-methyl-2-phenylpropananilide (12, R = Ph) with 2 equiv of catalyst in boiling *n*-propyl acetate (102 °C).**

was that HOAt had previously been reported to be shock sensitive.[11] The second is that shock sensitivity can be predicted with reasonable accuracy by plotting DSC results onto a Yoshida plot.[13] Figure 3 shows such a plot; compounds that lie above the line are expected to be shock sensitive, whereas compounds that lie below the line may not be. It should be stressed that this prediction should be backed up by actual testing. HOAt lies above the line and hence would be expected to be strongly shock sensitive. The compound had previously been reported to be shock sensitive, but no information was given on the degree of shock sensitivity.[11] This paper now reports that HOAt is shock sensitive when subjected to a 5-J impact. Of course shock

(13) Yoshida, T. *Kogyyo Kayaku* **1987**, *5*, 311−316 (in Japanese).

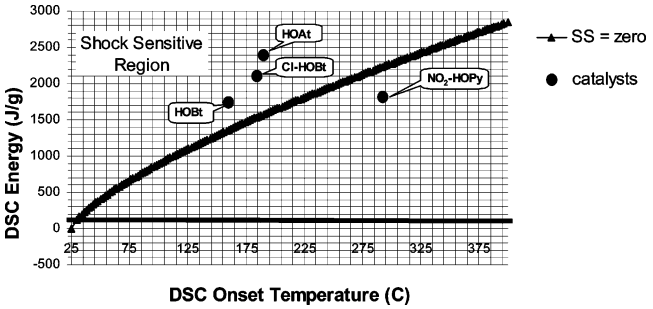


Figure 3. **Prediction of catalyst shock sensitivity by using the Yoshida DSC/Shock sensitivity correlation.**

sensitivity would also be observed with higher-energy impacts.

6-Chloro-1-hydroxybenzotriazole and $HOBt{\cdot}H_2O$ lie just above the line and hence would be predicted to be borderline cases. We found 6-chloro-1-hydroxybenzotriazole to be shock sensitive when subjected to a 30-H impact. In our hands 1-hydroxybenzotriazole hydrate was not shock sensitive when subjected to an impact of 50−100 J. However some other workers have reported that this material is shock sensitive;[14] thus, caution should be taken when handling this material.[15]

2-Hydroxy-5-nitropyridine lies below the line and hence would not be expected to be shock sensitive. This was confirmed by experiment. 2-Hydroxypyridine does not exhibit an exotherm at any temperature up to 400 °C and hence lies well below the line and is highly unlikely to be shock sensitive. This compound was not tested.

In conclusion, HOAt has the highest energy of decomposition on the DSC and has strong shock sensitivity. This was clearly the most hazardous of the five catalysts.

2-Hydroxypyridine is the safest catalyst, and this is followed by 2-hydroxy-5-nitropyridine which is not shock sensitive and has a relatively high onset of decomposition in the DSC (293 °C). $HOBt{\cdot}H_2O$ and 6-chloro-1-hydroxybenzotriazole have similar safety profiles; choosing between $HOBt{\cdot}H_2O$ or 6-chloro-1-hydroxybenzotriazole on a safety basis would depend on a full assessment of the individual reaction, although clearly the fact that 6-chloro-1-hydroxybenzotriazole is shock sensitive is a major consideration. In summary the safety order is:

$$\text{HOPy} > NO_2\text{-HOPy} > HOBt{\cdot}H_2O \approx \text{Cl-HOBt} > \text{HOAt}$$

Conclusions

Five catalysts have been assessed for their safety and their catalytic effectiveness in promoting imidazolide couplings. In terms of catalytic effectiveness the order was found to be:

$$\text{HOAt} > \text{Cl-HOBt} > HOBt{\cdot}H_2O > NO_2\text{-HOPy} > \text{HOPy}$$

(14) Wehrstedt, K.; Heitkamp D. *1-Hydroxybenzotriazole (HOBt) and Similar Compounds: Properties and Classification*; OECD-IGUS Energetic and Oxidising Substances (EOS) Working Group Meeting, Paris, France, March 2002. This information can be found on http://www.bam.de/english/index4.htm. In addition it is reported that anhydrous HOBt is more dangerous than the hydrate of HOBt.

In terms of their process safety the order was almost exactly the reverse:

$$HOPy > NO_2\text{-}HOPy > HOBt{\cdot}H_2O \approx Cl{-}HOBt > HOAt$$

In searching for a balance of process safety and effectiveness it seems that 2-hydroxy-5-nitropyridine (NO_2-HOPy, **9**) a new catalyst for promoting imidazolide couplings offers the best combination. 2-Hydroxy-5-nitropyridine is less effective than the fused triazole catalysts; however, it is safe and can be very effective (as seen in Figure 2); in addition it is readily available and comparatively inexpensive (price similar to that of 1-hydroxybenzotriazole hydrate). When the reaction is complete, it can easily be removed by washing with base. A full experimental procedure detailing its use is given in the Experimental Section.

Experimental Section

6-Chloro-1-hydroxybenzotriazole is available on a large scale and was obtained from GL Biochem Company, Shanghai, China. 1-Hydroxy-7-azabenzotriazole was purchased from Acros, and 1-hydroxybenzotriazole hydrate was purchased from Aldrich. All other chemicals were widely available.

Reactions were carried out with Mettler-Toledo's Multimax. ^{1}H spectra were recorded on a Varian (^{1}H 300 MHz) spectrometer, and melting points were measured with a Buchi Melting Point B-545 apparatus. Flash chromatography was carried out with Biotage Horizon Flash Collector. GC/MS data was obtained using a Hewlett-Packard, 6890 series GC system packed with capillary column (HP-5MS, 30.4 m × 250 μm × 0.25 μm), with helium as carrier gas (flow rate 23.2 mL/min), and a mass spectrometer as a detector. DSC were run on DSC 822^e, Mettler-Toledo, the scanning rate was 5 °C/min, with a temperature range up to 400 °C. Shock sensitivity tests were carried out with a BAM Fall Hammer.

1-(2-Phenylpropanoyl)-1*H*-imidazole 10. A suspension of *N*,*N*^{1}-carbonyldiimidazole (CDI) (48.4 g, 0.298 mol) in either ethyl acetate or *n*-propyl acetate (0.686 L) was treated with 2-phenylpropanoic acid (40 g, 0.266 mol) over at least a 10-min period. The initial suspension turned to a homogeneous solution as the acid was added. GC/MS confirmed complete consumption of the starting material. The resulting solution of the title compound was stored under nitrogen, and aliquots of this bulk solution were used in subsequent reactions.

1-(2-Methyl-2-phenylpropanoyl)-1*H*-imidazole 11. A suspension of *N*,*N*^{1}-carbonyldiimidazole (CDI) (46.7 g, 0.288 mol) in either ethyl acetate or *n*-propyl acetate (0.66 L) was treated with 2-methyl-2-phenylpropanoic acid (42.2 g, 0.257 mol) over at least a 10-min period. The initial suspension turned to a homogeneous solution as the acid was added. GC/MS confirmed complete consumption of the starting material. The resulting solution of the title compound was stored under nitrogen, and aliquots of this bulk solution were used in subsequent reactions.

General Procedure for Reactions Reported in Tables 1 and 2. The imidazolide solution (of either **10** or **11**) (50 mL, 0.39 M, 19.5 mmol) in ethyl acetate was heated to reflux (78 °C). The imidazolide solution was treated with an amine (19.5 mmol) (as specified in the table), followed by the addition of catalyst, HOBt·H_2O **2** (9.75 mmol) (if specified in the table). The reaction mixtures were stirred and heated at reflux for 13 h. Representative samples were taken during this period and analysed by GC/MS.

General Procedure for Reactions Reported in Table 3 (with 1-Hydroxybenzotriazole·hydrate, 6-Chloro-1-hydroxybenzotriazole, 5-Nitro-2-hydroxypyridine, and 2-Hydroxypyridine as Catalysts). A solution of 2-methyl-2-phenylpropanoyl-*1H*-imidazole **11** (50 mL, 0.39 M, 19.5 mmol) in ethyl acetate was heated to reflux. Aniline (1.82 g, 19.5 mmol) was added, followed immediately by the catalyst (9.75 mmol) as a single portion. The mixture was heated at reflux for 24 h during which time representative samples were taken and analysed by GC/MS.

2-Methyl-2-phenylpropananilide (12, R = Ph): Prepared Using 1-Hydroxy-7-azabenzotriazole as Catalyst. CAUTION: 1-Hydroxy-7-azabenzotriazole (HOAt) is strongly shock sensitive and a highly energetic molecule.[11] Hence, for this experiment the scale was reduced 5-fold and performed behind a blast screen.[16]

A solution of 2-methyl-2-phenylpropanoyl-*1H*-imidazole **11** (10 mL, 0.39M, 3.9 mmol) in ethyl acetate was heated to reflux. Aniline (364 mg, 3.9 mmol) was added, followed immediately by 1-hydroxy-7-azabenzotriazole (263 mg, 1.95 mmol) as a single portion. The mixture was heated at reflux for 8 h during which time samples were taken and analysed by GC/MS.

General Procedure for Reactions Reported in Table 4. A solution of 2-methyl-2-phenylpropanoyl-*1H*-imidazole **11** (50 mL, 0.39 M, 19.5 mmol) in *n*-propyl acetate was heated to reflux. Aniline (1.82 g, 19.5 mmol) was added, followed immediately by the catalyst (39 mmol) as a single portion. The mixture was heated at reflux for 24 h during which time samples were taken and analysed by GC/MS.

2-Methyl-2-phenylpropananalide (12, R = Ph): Prepared Using 2-Hydroxy-5-nitropyridine as Catalyst. A solution of 2-methyl-2-phenylpropanoyl-*1H*-imidazole **11** in *n*-propyl acetate (50 mL, 0.39 M, 19.5 mmol) was heated to reflux. Aniline (1.82 g, 19.5 mmol) was added, followed immediately by 2-hydroxy-5-nitropyridine **9** (5.4 g, 39 mmol), both reagents being added in one portion. The reaction was heated to reflux (102 °C) for 24 h. After cooling, the reaction mixture was washed with 1 M sodium hydroxide (2 × 30 mL) and brine, and the resulting solution was dried over sodium sulphate and evaporated to give the title compound as a solid (3.9 g, 84%). This material was chromatographed with high recovery to give the title compound as a pale-yellow solid, mp 99−99.5 °C (lit.[17] 100.5−101.5 °C), ^{1}H NMR ($CDCl_3$): 1.65 (6H, s, 2C*H*$_3$), 6.80 [1H, s (br), N*H* (disappears following D_2O shake)], 7.00−7.45 (10H, m, Ph*H*). The NMR data was in agreement

(15) Unfortunately a further reminder of the potential hazards of handling this material on a large scale was demonstrated by a recent explosion at Lacamas Laboratories, Portland, Oregon, U.S.A., which was caused by 1-hydroxybenzotriazole. The incident took place on May 9, 2005.

(16) Note that this material has recently become available as a 0.5−0.7 M solution in DMF from the Sigma-Aldrich company and other suppliers.

(17) Lyle, R. E.; Lyle, G. G. *J. Org. Chem.* **1953**, *18*, 1058−1064.

with that previously published.[18] GC/MS 239 (amide, retention time 11.15 min), 119 ($PhC(CH_3)_2$).

2-Methyl-2-phenylpropananalide (12, R = Ph): Prepared Using 1-Hydroxybenzotriazole Hydrate as Catalyst. A solution of 2-methyl-2-phenylpropanoyl-*1H*-imidazole **11** in ethyl acetate (50 mL, 0.39 M, 19.5 mmol) was heated to reflux. Aniline (1.82 g, 19.5 mmol) was added, followed immediately by 1-hydroxybenzotriazole hydrate **2** (1.46 g, 9.5 mmol) both reagents being added in one portion. The reaction was heated to reflux (78 °C) for 24 h. After cooling, the reaction mixture was washed with 1 M sodium hydroxide (2 × 30 mL) and brine, and the resulting solution was dried over sodium sulphate and evaporated to give the title compound as an oily solid (3.7 g, 80%). This material was purified by chromatography to give the title compound as a pale yellow solid, mp 99−100 °C (lit.[17] 100.5−101.5 °C), ^{1}H NMR ($CDCl_3$): 1.65 (6H, s, 2C*H*$_3$), 6.80 [1H, s (br), N*H* (disappears following D_2O shake)], 7.00−7.45 (10H, m, Ph*H*). The NMR data was in agreement with that previously published.[18] GC/MS 239 (amide, retention time 11.15 min), 119 ($PhC(CH_3)_2$).

Shock Sensitivity Testing. These tests were carried out according to the method of the UN Recommendation on the Transport of Dangerous Goods, the Official Journal of the European Community as well as to the directive 84/449/EEC and NF T 20-038 Test A.14 with the exception that the four materials were tested as supplied and were not dried, ground, or sieved before testing. A minimum of six tests were performed. One positive result or more in six tests indicated impact sensitivity.

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(18) Olsen, E. O. *Acta Chem. Scand.* **1975**, *B29*, 953−962.