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Full Paper

Steric and Electronic Effects in the Synthesis and Regioselective Hydrolysis of Unsymmetrical Imides

Jing Shang,[A] *Aysa Pourvali,*[A] *James R. Cochrane,*[A] *and Craig A. Hutton*[A,B]

[A]School of Chemistry and Bio21 Molecular Science and Biotechnology Institute, The University of Melbourne, Melbourne, Vic. 3010, Australia.
[B]Corresponding author. Email: chutton@unimelb.edu.au

The Ag^{I}-promoted coupling reaction of thioamides and carboxylic acids is shown to be a useful method for the generation of unsymmetrical imides. The reaction proceeds efficiently with unhindered and electron-rich or neutral coupling partners, but not with hindered thioamides (such as thiopivalamides) or electron deficient thioamides (such as trifluorothioacetamides). Intriguingly, thioformamides are also ineffective coupling partners, despite having minimal steric or electronic influence. Hindered carboxylic acid coupling partners (such as pivalic acid) are tolerated, but electron deficient acids, such as trifluoroacetic acid, are ineffective coupling partners. Furthermore, an interplay of both steric and electronic effects is observed in the subsequent hydrolysis of unsymmetrical imides. Imides with a dimethoxybenzoyl group give high regioselectivity upon hydrolysis, favouring cleavage of the distal acyl group. Imides with a *p*-nitrobenzoyl or pivaloyl group give reversed selectivity, favouring cleavage of the proximal acyl group.

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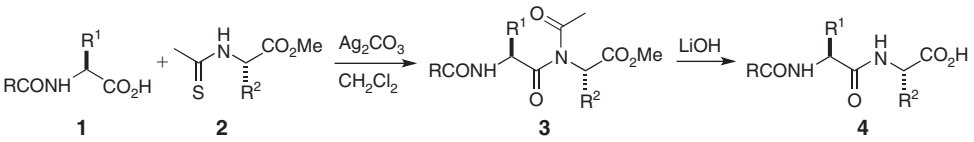
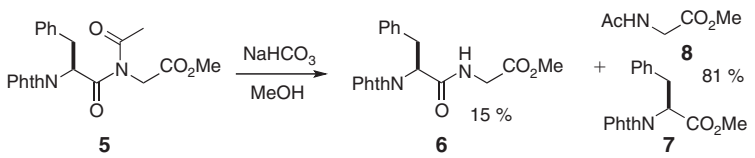
Introduction

Despite the voluminous work on the synthesis of amide bonds, the preparation of acyclic imides has received relatively little attention.[1] We have recently developed a method for the synthesis of peptide imides through the coupling of amino ester thioacetamides **2** to the C-terminal carboxylic acid of a peptide or protected amino acid **1** in a process promoted by silver(I).[2] In its simplest sense, this process enables the high yielding preparation of unsymmetrical imides, which are difficult to access through the acylation of imides due to the propensity for acyl scrambling.[3] In the context of peptide synthesis,[4,5] this new method allows the N-to-C direction synthesis of peptides and proceeds through a peptide imide intermediate **3** (Scheme 1). Selective imide hydrolysis with concomitant ester deprotection then generates the homologated peptide acid **4**, suitable for iterative extension of the peptide chain.[2]

To date this process has only been investigated with *N*-thioacetyl amino acids. In our previous studies selective cleavage of the peptide imide **3** was postulated to proceed due to steric factors, with hydrolysis or methanolysis of the imide occurring at the less hindered acetyl carbonyl group.[2] However, we have observed in occasional cases (e.g. see Scheme 2) that imide cleavage is not selective or displays the opposite selectivity, leading us to investigate the scope and limitations of both the thioamide coupling step and the imide hydrolysis step, with regard to steric and electronic effects of both coupling partners.

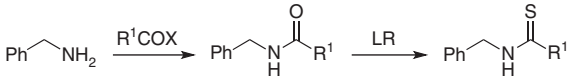


Scheme 1. Ag^{I}-promoted synthesis of peptide imides.



Scheme 2. Solvolysis of Phe–Gly dipeptide imide.

Table 1. Preparation of thioamides 11



9 **10** **11**

Entry	R^1COX	R^1	Yield **10** [%]	Yield **11** [%]
a	Ac_2O	Me	83	65
b	pivalic acid (+ HBTU[A])	^{t}Bu	74	47
c	$(F_3CCO)_2O$	CF_3	97	53
d	$(Cl_3CCO)_2O$	CCl_3	98	51
e	ethyl formate	H	89	66
f	benzoic acid (+ HBTU)	Ph	95	50
g	4-OMe-benzoyl chloride	PMP	89	83
h	2,4-$(OMe)_2$-benzoyl chloride	DMP	91	97
i	4-NO_2-benzoyl chloride	PNP	97	62
j	2,4-$(NO_2)_2$-benzoyl chloride	DNP	91	60

[A]HBTU = *O*-(benzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate.

Factors Affecting Ag^I-Promoted Thioamide Coupling

A range of *N*-benzylthioamides were chosen as model substrates and prepared in two steps from benzylamine. Benzylamine (**9**) was treated with a variety of acyl donors to generate the corresponding amides **10a**–**j**, which were then treated with Lawesson's reagent (LR) to generate the corresponding thioamides **11a**–**j** in 35–88 % yield over two steps (Table 1). The thioamides were chosen to provide substrates with a range of steric bulk (e.g. formyl, acetyl, pivaloyl) and electron donating/withdrawing capability (e.g. p-nitrophenyl (PNP) cf. p-methoxyphenyl (PMP); acetyl cf. trifluoroacetyl) (Table 1). Similarly, a range of carboxylic acids was chosen to investigate steric and electronic effects of these coupling partners (Table 2).

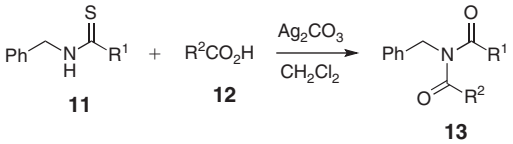
The imides **13** were generated by treatment of one equiv. of acid **12a**–**c** with two equiv. of thioamide **11a**–**j** and two equiv. Ag_2CO_3 at room temperature overnight (Table 2).

First, a comparison of the reactivity of the thioamides **11a**–**j** was undertaken, in reactions with silver carbonate and acetic acid (**12a**). Thioacetamide (**11a**) afforded the corresponding imide **13aa** in good yield (76 %, Table 2). However, hindered thiopivalamide (**11b**) gave only trace amounts of the corresponding imide **13ab**, and strongly electron deficient thioamides **11c** and **11d** yielded no imide product. Interestingly, use of thioformamide (**11e**) did not generate the corresponding imide product with only starting material and amide **10e** recovered. Aryl thioamides **11f**–**i** generally afforded the corresponding imides **13** in good yields, although the electron deficient thioamide **11j** gave only a moderate yield of imide **13aj** (Table 2).

Next, the effect of the acid partners was investigated. Pivalic acid (**12b**) was reasonably well tolerated, but generated the imides **13b**(**a**,**f**–**i**) in lower yield than the corresponding reactions with acetic acid (**12a**). The combination of sterically hindered pivalic acid (**12b**) and electron deficient dinitrobenzoyl thioamide **11j** gave no imide product. Trifluoroacetic acid (**12c**) did not undergo coupling with any of the thioamides.

These results indicate that steric hindrance from either coupling partner considerably reduces the yield of the imide adduct, as does the presence of strongly electron withdrawing substituents. Such findings are consistent with the proposed mechanism in which the carboxylate is acting as a nucleophile:[2,6,7] trifluoroacetate is presumably not nucleophilic enough for the reaction to proceed. Furthermore, the thioamide must first coordinate to the Ag^I ion, which is impeded by electron withdrawing substituents on the thioamide partner.

Table 2. Preparation and corresponding isolated yields (%) of imides 13 from coupling of thioamides 11 with carboxylic acids 12



11 **12** **13**

R^1 (**11a**–**i**)	R^2 (**12a**–**c**)		
	Me (**a**)	^{t}Bu (**b**)	CF_3 (**c**)
Me (**a**)	76	60	0
^{t}Bu (**b**)	trace	0	0
CF_3 (**c**)	0	0	0
CCl_3 (**d**)	0	0	0
H (**e**)	0	0	0
Ph (**f**)	88	68	0
PMP (**g**)	92	80	0
DMP (**h**)	89	83	0
PNP (**i**)	70	50	0
DNP (**j**)	41	0	0

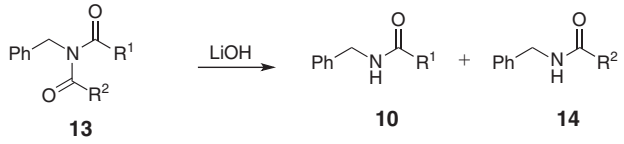
Factors Affecting Imide Hydrolysis

In the context of using this method for the preparation of amide bonds, regioselective hydrolysis of the imide adduct is essential.

To investigate the factors affecting the regioselectivity of imide cleavage, the imides were treated with LiOH to generate a mixture of amides **10** and **14** (Table 3).

Hydrolysis of the benzoyl/acetyl imide **12af** proceeded with low selectivity to give a 1.1 : 1 mixture of amides **10f** and **14a**. Hydrolysis of *p*-methoxybenzoyl/acetyl imide **12ag** displayed marginal selectivity, favouring cleavage of the acetyl group to give the benzamide **10g** with 2 : 1 selectivity. The electron-donating methoxy group presumably reduces the electrophilicity of the carbonyl group, such that hydroxide preferentially attacks the acetyl group. The dimethoxybenzoyl/acetyl imide **12ah** gave excellent regioselectivity (20 : 1), generating dimethoxybenzoyl amide **10h** as the major product. Presumably the *o*-methoxy group further disfavours attack at the benzoyl

Table 3. Regioselectivity in hydrolysis of imides 13[A]



R^2	R^1						
	Me (**a**)	^{t}Bu (**b**)	Ph (**f**)	PMP (**g**)	DMP (**h**)	PNP (**i**)	DNP (**j**)
Me (**a**)		1 : 7	1.1 : 1	2 : 1	20 : 1	1 : 3	6 : 5
^{t}Bu (**b**)	(7 : 1)		3 : 1	3 : 1	18 : 1	6 : 5	–

[A]Ratio of **10** : **14**, determined from isolated yield.

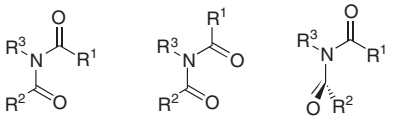


Fig. 1. Imide conformations.

group not only through increased electron donation but also due to a steric effect.

Hydrolysis of the *p*-nitrobenzoyl/acetyl imide **12ai** proceeded with moderate selectivity (1 : 3), with a reversal of selectivity compared with the electron rich systems, with predominant cleavage of the *p*-nitrobenzoyl group to give the acetamide **14a**. The electron-withdrawing nitro group presumably increases the electrophilicity of the benzoyl group, favouring attack by hydroxide at the benzoyl carbonyl group. However, hydrolysis of the dinitrobenzoyl/acetyl imide **12aj** proceeded with low selectivity (1.2 : 1). In this case, the electronic effects of the nitro groups are counterbalanced by the steric effect of the *o*-nitro substituent, such that low selectivity is observed.

In hydrolysis of the acetyl/pivaloyl imide **12ab**, unexpected regioselectivity was observed, with moderate selectivity (7 : 1) for cleavage of the more sterically hindered pivaloyl group to yield acetamide **14a**. Imides are known to adopt several conformations, with the predominant conformations being the planar *s-trans* and *s-cis* conformations **15a** and **15b** (Fig. 1).[8] In imides with bulky substituents (e.g. $R^2 = {}^t$Bu), the planar conformations are disfavoured through steric effects, such that the non-planar conformation **15c** is favoured. Conformational analysis of imides can be undertaken through IR spectroscopy: *s-trans* imides **15a** typically show a major IR absorbance at ~1695 cm^{-1}, with a shift to ~1680 cm^{-1} upon conversion into the non-planar conformation **15c**.[8] IR analysis of imides **13aa** and **13ab** shows a shift in the carbonyl absorbance from 1695 cm^{-1} in bisacetimide **13aa**, to 1676 cm^{-1} in acetyl/pivaloyl imide **13ab**, consistent with a switch to the non-planar conformation **15c**.[8] In the acetyl/pivaloyl imide **13ab** the pivaloyl group is therefore perpendicular to the plane of the N–C(CH_3)=O group and is not in conjugation, such that it is more ketone-like and therefore more electrophilic. This rationalisation has also been invoked for the cleavage of imide **13ab** with ammonia, which similarly occurs with predominant pivaloyl cleavage,[3] and of hydrolysis/acyl transfer reactions of related twisted amide- and imide-type systems.[9–11]

Similar effects were observed with pivalimides **13b(f–i)**, with moderate selectivity towards pivaloyl cleavage, despite it being the bulkier acyl group. IR analysis again shows a shift of carbonyl absorbance from ~1685 cm^{-1} in acetimides **13a*y***, to ~1675 cm^{-1} in pivalimides **13b*y***, consistent with a switch to the non-planar conformation **15c**.

Table 4. Regioselectivity in hydrolysis of imides 13*xy* upon treatment with MeOH/$NaHCO_3$[A]

R^2	R^1					
	Me (**a**)	^{t}Bu (**b**)	Ph (**f**)	PMP (**g**)	DMP (**h**)	PNP (**i**)
Me (**a**)		1 : 12	–	3 : 2	–	1 : 1
^{t}Bu (**b**)			2 : 1	5 : 2	–	5 : 6

[A]Ratio of **10** : **14**, determined from isolated yield.

Imide solvolysis reactions were also investigated under mild conditions using $NaHCO_3$ in methanol (Table 4),[4,5] and gave similar results to those observed for basic hydrolysis.

Conclusion

In summary, the Ag^I-promoted coupling reaction of thioamides and carboxylic acids to generate unsymmetrical imides is affected considerably by both steric and electronic factors. Hindered thioamides such as thiopivalamides do not generate the imide in good yield. Intriguingly, thioformamides are also ineffective coupling partners, despite having minimal steric influence. Hindered carboxylic acid coupling partners (such as pivalic acid) are tolerated, although they result in lower yields than acetic acid. Electron deficient acids, such as trifluoroacetic acid, are ineffective coupling partners, presumably due to the low nucleophilicity of the carboxylate.

Furthermore, an interplay of both steric and electronic effects is observed in the subsequent hydrolysis of unsymmetrical imides. Acetimides generally undergo cleavage of the less hindered acetyl group. However, with acetyl/pivaloyl imide **13ab** a change of conformation leads to a change in regioselectivity, with pivaloyl cleavage predominating. Electronic effects can be employed to manipulate regioselectivity of imide cleavage. Imides with an electron-rich dimethoxybenzoyl group give high regioselectivity upon hydrolysis, favouring cleavage at the distal acyl group. Contrastingly, imides with an electron poor *p*-nitrobenzoyl group give either reversed selectivity, favouring cleavage of the *p*-nitrobenzoyl group due to the increased electrophilicity at this site, or are non-selective.

Experimental

General Procedure A: Synthesis of Imides Using Silver Carbonate

To a solution of the thioamide **11** (2 equiv.) and carboxylic acid **12** (1 equiv) in dichloromethane (1.5 mL $mmol^{-1}$), silver carbonate (2 equiv.) was added at room temperature. The solution was stirred for 12 h at room temperature. The solvent was removed under reduced pressure and the black residue purified by flash chromatography to give the imide **13**.

N-*Acetyl*-N-*benzylacetamide* (***13aa***)[12]

Silver(I) acetate (330 mg, 2 mmol) was added to a solution of *N*-benzylthioacetamide **11a** (165 mg, 1 mmol) in CH_2Cl_2 (4 mL). The solution was stirred under nitrogen for 18 h. The solvent was evaporated and the residue was purified by chromatography on silica to give title compound **13aa** as a colourless oil (60 mg, 33 %). δ_H (600 MHz, $CDCl_3$) 7.33–7.23 (3H, m,

ArH), 7.13 (2H, m, ArH), 4.96 (2H, s, CH_2), 2.41 (6H, s, 2Me). δ_C (100 MHz, $CDCl_3$) 173.6, 136.6, 128.6, 127.3, 125.8, 47.4, 26.4. *m/z* (ESI) 192 ($[M + H]^+$, 100 %). HRMS *m/z* 192.1206; calcd for $C_{11}H_{13}NO_2$ 192.1019. ν_{max} ($CHCl_3$)/cm^{-1} 3032, 1695, 1606, 1497, 1370, 1267, 1208, 975, 872, 717, 694.

N-*Acetyl*-N-*benzylpivalamide* (***13ab***)[13]

N-Benzylthiopivalamide **11b** (80.0 mg, 0.4 mmol) and acetic acid (11 μL, 0.2 mmol) were treated according to general procedure A to give the imide **13ab** (37 mg, 82 %) as a colourless oil. δ_H (400 MHz, $CDCl_3$) 7.33–7.18 (5H, m, ArH), 4.83 (2H, s, CH_2), 2.22 (3H, s, Me), 1.25 (9H, s, *t*Bu). δ_C (100 MHz, $CDCl_3$) 187.5, 173.2, 137.2, 128.7, 127.4, 126.7, 49.1, 43.2, 28.1, 24.4; MS (ESI) *m/z*: 234 ($[M + H]^+$, 100 %). HRMS *m/z* 234.1417; calcd for $C_{14}H_{19}NO_2$ 234.1489. ν_{max} ($CHCl_3$)/cm^{-1} 3304, 2966, 2928, 1676, 1373, 1336, 1159, 975, 733, 699.

N-*Acetyl*-N-*benzylbenzamide* (***13af***)[14,15]

N-Benzylthiobenzamide (**11f**) (71 mg, 0.3 mmol) and acetic acid (**12a**) (8.2 μL, 0.15 mmol) were treated according to general procedure A to give the product **13af** (39 mg, 88 %) as a colourless oil. δ_H (400 MHz, $CDCl_3$) 7.56–7.22 (10H, m, ArH), 5.00 (2H, s, CH_2), 2.16 (3H, s, Me). δ_C (100 MHz, $CDCl_3$) 174.3, 173.2, 137.3, 135.8, 132.4, 128.8, 128.5, 128.4, 127.8, 127.4, 49.3, 26.4. *m/z* (ESI) 254 ($[M + H]^+$, 100 %). HRMS *m/z* 254.1201; calcd for $C_{16}H_{15}NO_2$ 254.1176. ν_{max} ($CHCl_3$)/cm^{-1} 3031, 2971, 1686, 1659, 1215, 727, 696.

N-*Benzyl*-N-*pivaloylbenzamide* (***13bf***)[16]

N-Benzylthiobenzamide (**11f**) (85 mg, 0.3 mmol) and pivalic acid (**12b**) (22.6 μL, 0.2 mmol) were treated according to general procedure A to give the product **13bf** (36.4 mg, 71.5 %) as a white solid. δ_H (400 MHz, $CDCl_3$) 7.69–7.20 (10H, m, ArH), 4.83 (2H, s, CH_2), 1.21 (9H, s, tBu). δ_C (100 MHz, $CDCl_3$) 187.4, 174.8, 137.2, 135.0, 132.5, 129.0, 128.7, 128.5, 127.7, 127.4, 51.3, 43.5, 28.5. *m/z* (ESI) 296 ($[M + H]^+$, 100 %). HRMS *m/z* 296.1653; calcd for $C_{19}H_{21}NO_2$ 296.1645. ν_{max} ($CHCl_3$)/cm^{-1} 3065, 3031, 2970, 2924, 1676, 1655, 1342, 1239, 1167, 1125, 965, 721, 696.

N-*Acetyl*-N-*benzyl-4-methoxybenzamide* (***13ag***)[15]

N-Benzyl-4-methoxythiobenzamide (**11g**) (70.2 mg, 0.3 mmol) and acetic acid (**12a**) (8.2 μL, 0.15 mmol) were treated according to general procedure A to give the product **13ag** (39.6 mg, 92 %) as a colourless oil. δ_H (400 MHz, $CDCl_3$) 7.58–6.90 (9H, m, ArH), 5.00 (2H, s, CH_2), 3.85 (3H, s, OMe), 2.11 (3H, s, Me). δ_C (100 MHz, $CDCl_3$) 173.9, 173.0, 163.3, 137.4, 131.1, 128.5, 127.9, 127.7, 127.4, 114.1, 55.5, 49.5, 26.1. *m/z* (ESI) 284 ($[M + H]^+$, 100 %). HRMS *m/z* 284.1287; calcd for $C_{17}H_{17}NO_3$ 284.1281. ν_{max} ($CHCl_3$)/cm^{-1} 3030, 2971, 2938, 1682, 1655, 1602, 1256, 1217, 1167, 1026, 844, 699.

N-*Benzyl*-N-*pivaloyl-4-methoxybenzamide* (***13bg***)[16]

N-Benzyl-4-methoxythiobenzamide (**11g**) (48.5 mg, 0.2 mmol) and pivalic acid (**12b**) (11.6 μL, 0.1 mmol) were treated according to general procedure A to give the product **13bg** (27.4 mg, 84 %) as a white solid. δ_H (400 MHz, $CDCl_3$) 7.70–6.90 (9H, m, ArH), 4.83 (2H, s, CH_2), 3.68 (3H, s, OMe), 1.21 (9H, s, *t*Bu). δ_C (100 MHz, $CDCl_3$) 186.7, 174.4, 163.3, 137.4, 131.5, 128.5, 127.6, 127.3, 127.0, 114.1, 55.5, 51.5, 43.3, 28.6. *m/z* (ESI) 326 ($[M + H]^+$, 100 %). HRMS *m/z* 326.1747; calcd for $C_{20}H_{23}NO_3$ 326.1751. ν_{max} ($CHCl_3$)/cm^{-1} 2968, 2927, 1673, 1602, 1245, 1164.

N-*Acetyl*-N-*benzyl-2,4-dimethoxybenzamide* (***13ah***)

N-Benzyl-2,4-dimethoxythiobenzamide (**11h**) (83.2 mg, 0.3 mmol) and acetic acid (**12a**) (8.2 μL, 0.15 mmol) were treated according to general procedure A to give the product **13ah** (40.8 mg, 89 %) as a white solid. δ_H (400 MHz, $CDCl_3$) 7.33–7.18 (8H, m, ArH), 4.92 (2H, s, CH_2), 3.83 (3H, s, p-OMe), 3.75 (3H, s, o-OMe), 2.24 (3H, s, Me). δ_C (100 MHz, $CDCl_3$) 173.4, 171.5, 163.6, 157.9, 137.8, 131.5, 128.3, 127.8, 127.1, 118.5, 105.1, 98.5, 55.6, 55.5, 48.6, 25.9. *m/z* (ESI) 314 ($[M + H]^+$, 100 %). HRMS *m/z* 314.1376; calcd for $C_{18}H_{19}NO_4$ 314.1387. ν_{max} ($CHCl_3$)/cm^{-1} 3007, 2970, 2941, 2841, 1698, 1648, 1606, 1210, 1164, 978.

N-*Benzyl*-N-*pivaloyl-2,4-dimethoxybenzamide* (***13bh***)

N-Benzyl-2,4-dimethoxythiobenzamide (**11h**) (85.2 mg, 0.3 mmol) and pivalic acid (**12b**) (17.2 μL, 0.15 mmol) were treated according to general procedure A to give the product **13bh** (41.5 mg, 83 %) as a white solid. δ_H (400 MHz, $CDCl_3$) 7.33–7.15 (6H, m, ArH), 6.48–6.44 (2H, m, ArH), 4.70 (2H, s, CH_2), 3.83 (3H, s, OMe), 3.79 (3H, s, OMe), 1.24 (9H, s, tBu). δ_C (400 MHz, $CDCl_3$) 187.4, 172.0, 163.5, 158.3, 137.7, 132.1, 128.2, 127.7, 127.1, 117.8, 104.9, 98.6, 55.5, 51.1, 43.4, 28.4. *m/z* (ESI) 356 ($[M + H]^+$, 100 %). HRMS *m/z* 356.1875; calcd for $C_{21}H_{25}NO_4$ 356.1856. ν_{max} ($CHCl_3$)/cm^{-1} 3402, 3063, 3029, 3005, 2925, 2852, 1642, 1603, 1528, 1496, 1295, 1208, 1166, 1025, 699.

N-*Acetyl*-N-*benzyl-4-nitrobenzamide* (***13ai***)

N-Benzyl-4-nitrothiobenzamide (**11i**) (101 mg, 0.35 mmol) and acetic acid (**12a**) (11.1 μL, 0.2 mmol) were treated according to general procedure A to give the product **13ai** (38 mg, 70 %) as a yellow solid. δ_H (400 MHz, $CDCl_3$) 8.26–7.16 (9H, m, ArH), 4.99 (2H, s, CH_2), 2.31 (3H, s, Me). δ_C (100 MHz, $CDCl_3$) 173.1, 172.2, 149.4, 141.7, 136.5, 128.9, 128.6, 127.8, 127.1, 123.8, 49.1, 26.0. ν_{max} ($CHCl_3$)/cm^{-1} 3108, 3066, 3030, 2971, 2865, 1686, 1664, 1604, 1522, 1345, 1211.

N-*Benzyl*-N-*pivaloyl-4-nitrobenzamide* (***13bi***)

N-Benzyl-4-nitrothiobenzamide (**11i**) (103 mg, 0.4 mmol) and pivalic acid (**12b**) (22.5 μL, 0.2 mmol) were treated according to general procedure A to give the product **13bi** (25.2 mg, 50 %) as a yellow solid. δ_H (400 MHz, $CDCl_3$) 8.20–7.08 (9H, m, ArH), 4.80 (2H, s, CH_2), 1.19 (9H, s, *t*Bu). δ_C (100 MHz, $CDCl_3$) 186.9, 172.5, 149.5, 140.9, 136.5, 129.2, 128.8, 127.7, 127.1, 123.9, 50.6, 43.3, 28.4. ν_{max} ($CHCl_3$)/cm^{-1} 3316, 3030, 2971, 2927, 1738, 1644, 1600, 1523, 1247.

N-*Acetyl*-N-*benzyl-2,4-dinitrobenzamide* (***13aj***)

N-Benzyl-2,4-dinitrothiobenzamide (**11j**) (63 mg, 0.2 mmol) and acetic acid (**12a**) (6.0 μL, 0.1 mmol) were treated according to general procedure A to give the product **13aj** (32 mg, 41 %) as a light yellow oil. δ_H (400 MHz, $CDCl_3$) 9.08–9.06 (1H, m, ArH), 8.51–8.48 (1H, m, ArH), 7.43–7.24 (6H, m, ArH), 5.14 (2H, s, CH_2), 2.26 (3H, s, Me).

General Procedure B

To a solution of imide **13** (0.3 mmol) in 1 : 1 dioxane/H_2O (6 mL) was added $LiOH{\cdot}H_2O$ (41 mg, 0.9 mmol) and the

solution was stirred for 16 h at room temperature. The mixture was partitioned between EtOAc (40 mL) and 1 M HCl (30 mL). The aqueous phase was extracted with EtOAc (2 × 40 mL). The combined organic fractions were washed with brine (50 mL) and dried ($MgSO_4$). The solvent was evaporated and the residue was analysed by ^1H NMR spectrometry to determine the ratio of the two amides **10** and **14**.

General Procedure C

To a solution of imide **13** (0.17 mmol) in methanol (3 mL) was added $NaHCO_3$ (28.0 mg, 0.34 mmol) and the solution was stirred for 16 h at room temperature. The mixture was partitioned between EtOAc (30 mL) and 1 M HCl (15 mL). The aqueous phase was extracted with EtOAc (2 × 30 mL). The combined organic fractions were washed with brine (50 mL) and dried ($MgSO_4$). The solvent was evaporated and the residue was analysed by ^1H NMR spectrometry to determine the ratio of the two amides **10** and **14**.

Supplementary Material

Experimental procedures for the synthesis of amides **10** and thioamides **11**, and ^1H, ^{13}C NMR and IR spectra for imides **13a(a,b,f–j)** and **13b(f–i)** are available on the Journal's website.

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