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Solid-Phase Preparation of Amides Using *N*-Acylbenzotriazoles

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Abstract—Wang resin linked amines were efficiently converted into amides using acylbenzotriazoles. Cleavage of resins gave the desired amides **7Aa–Gf** in 30–99% yields with good to excellent purities.

The amide bond is very important in organic chemistry. Amide groups contribute to the unique properties of peptides, proteins and numerous other natural and synthetic compounds. The preparation of amides and their physical and chemical properties are extensively documented.[1]

The formation of amides on solid support usually involves reactions of amines either (i) with acid halides[2] or anhydrides[3] in the presence of base, or (ii) with acids in the presence of coupling agents[4] such as 1-hydroxybenzotriazole (HOBt), 7-aza-1-hydroxybenzotriazole (HOAt), or their onium or phosphonium salts. The formation of amides, and analogues such as ureas, urethanes and thioureas, on solid support has been reviewed.[5]

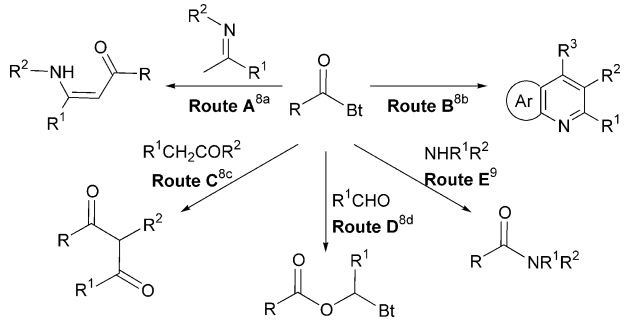
Applications of acylazolides, and *N*-acylimidazoles in particular were recently documented by Staab et al.[6] *N*-Acylimidazoles derived from sequential reactions of 1,1′-carbonyldiimidazole with carboxylic acids and amines were widely used in the reactions with ammonia and primary amines to give corresponding amides.[7] In the past few years *N*-acylbenzotriazoles found a wide scope of applications for the preparation of various classes of compounds[8] (Scheme 1) such as enaminones[8a] (Route A), quinazoline derivatives[8b] (Route B), 1,3-diketones[8c] (Route C), 1-(benzotriazol-1-yl)alkyl ethers[8d] (Route D), and amides[9a,b] (Route E).

N-Acylbenzotriazoles[9] are efficient acylating agents for the preparation of primary, secondary and tertiary amides in solution. Carboxylic acids or their salts are efficiently converted into acylbenzotriazoles using methansulfonylbenzotriazole.[9a] We now report conversions of amines into amides on solid support using *N*-acylbenzotriazoles.

We examined the conversion of Wang-resin-linked amines **5a–f** into amides using *N*-acylbenzotriazoles **3A–G**, due to the ease of cleavage from this support with trifluoroacetic acid (TFA) (Scheme 2). Resin-bound amines were obtained in a classic three-step procedure[10] involving the conversion of Wang-resin into the brominated resin, subsequent nucleophilic substitution with 4-hydroxybenzaldehyde in the presence of potassium *tert*-butoxide, and following a standard reductive amination protocol in the presence of an amine and sodium triacetoxyborohydride.

N-Acylbenzotriazoles **3A**, **B**, **D**, **F**, and **G** were obtained by a known procedure involving reactions of *N*-methansulfonylbenzotriazole with a carboxylic acid in the presence of base (TEA) (Table 1).[9a]

N-(4-Methylbenzoyl)-1*H*-benzotriazole **3C** and *N*-(4-bromo-benzoyl)benzotriazole **3E** were obtained by fusion of toluoyl or 4-bromobenzoyl chloride with benzotriazole at 100–120 °C.[9b]



Scheme 1.

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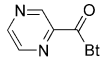
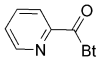
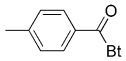
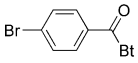
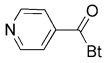
Resin-bound amines **5a–f** were reacted with the acylbenzotriazoles with electron withdrawing substituents **3A**, **B**, **E**, and **F** in THF under reflux for 24 h. After 24 h the desired products **7Aa–Bf** and **Ea–Ef** were obtained and mixed with unreacted starting amines. Increasing the reaction time up to 72 h gave the products **7Aa–Bf**, **Ea–Ed**, **Ef**, **Fa**, **Fd–Ff**, **Ga**, and **Gd–Gf** in 20–90% yield with good to excellent purities according to ^{1}H NMR data and HPLC or LC–MS analysis (Scheme 2, Table 2).

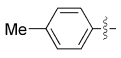
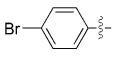
Table 1. Synthesis of acylbenzotriazoles **3A–G**

Entry	Product	Structure of acylating agent **3**	Yield
1	**3A**		69
2	**3B**		70
3	**3C**		80
4	**3D**		73
5	**3E**		93
6	**3F**		78
7	**3G**		95

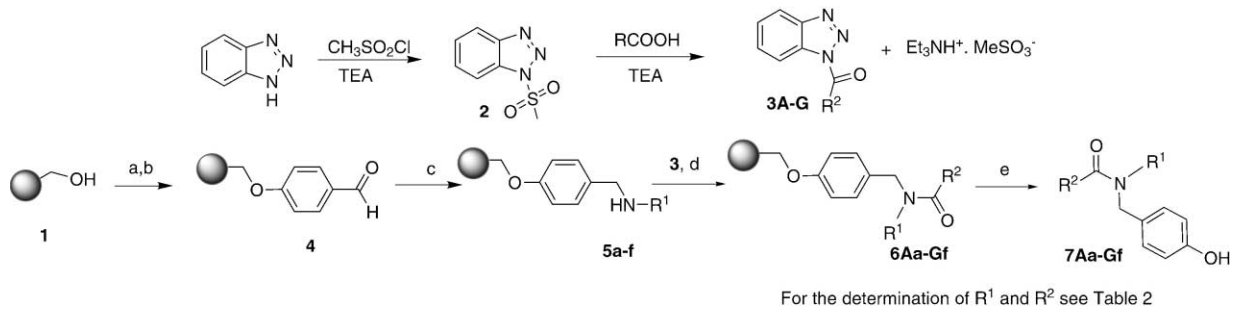
Reactions of *N*-(4-methylbenzoyl)-1*H*-benzotriazole **3C** gave positive results only for solid supported alkylamines. Reactions of **3C** with resin bound arylamines in refluxing THF failed, perhaps due to slight electron donating properties of methyl group in *para* position. The attempted use of harsher conditions to convert solid-supported amines **5** into corresponding amides gave complex mixtures after the cleavage of resins. The same result was obtained for the aminoalkyl substituted acylbenzotriazole **3D** and alkylsubstituted compound **3G**. Even weak electron-withdrawing groups as bromine in *para* position promote the acylation but the influence of substituents in resin-bound amines have to be recognized by additional experiment. Representative examples, (i.e., **7Ab**, **7Ac**, **7Bb**, and **7Bc**) were additionally purified by column chromatography and characterized by ^{1}H and ^{13}C NMR and by combustion analyses.[11]

In conclusion, we have developed an efficient protocol for the preparation of amides on solid support using *N*-acylbenzotriazoles as neutral acylating reagents. We disclose conditions for the successful acylation taking into account the nature of the substituents in the solid-supported amines as well as that of the acylation agents.

Table 2. Amount of cleaved materials[a] (%) and (content) of amides (%) in cleaved samples[b] **7Aa–Gf**

		a $PhCH_2CH_2$	b 4-CH_3O–C_6H_4	c 4-CH_3–C_6H_4	d $(CH_3)_2CH$–CH_2	e Cyclohexyl	f (Furan-2-yl)methyl
A		73 (95)	78 (95)	84 (95)	62 (98)	88 (64)	63 (75)
B		94 (96)	90 (95)	85 (95)	89 (98)	99 (95)	74 (95)
C		72 (90)	0[c]	0[c]	77 (85)	95 (30)	67 (70)
D		67 (85)	0[c]	0[c]	93 (90)	73 (42)	56 (42)
E		58 (80)	67 (84)	74 (95)	27 (85)	0[c]	88 (60)
F		94 (85)	77 (10)	66 (10)	97 (90)	98 (95)	66 (95)
G	C_5H_{11}-	75 (90)	71 (40)	0[c]	79 (95)	70 (80)	70 (76)

[a]Percentage amounts are based on original loading of resin and determined after washing of samples with 5% water solution of $NaHCO_3$.
[b]Content of desired amide in samples cleaved determined by HPLC or LC–MS analysis or calculated according to ^{1}H NMR are given in brackets; major admixtures are unreacted amines.
[c]No formation of amide.



Scheme 2. Preparation of amides **7Aa**–**Gf** using acylbenzotriazoles **3A**–**G**. Reaction conditions: (a) Ph_3PBr_2, CH_2Cl_2, rt, 4 h; (b) *t*-BuOK, HO–C_6H_4–CHO, DMA, 60 °C, 18 h; (c) R^1NH_2, $(AcO)_3BHNa$, $C_2H_4Cl_2$, rt, 36 h; (d) THF, reflux, 48 h; (e) TFA/DCM, 20%, 30 min.

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11. General procedure for the preparation of compounds **7**. Resin-bound amine **5** and a solution of the appropriate acylbenzotriazole (10 equiv, concd 0.25 mmol/mL) in THF were refluxed for 72 h. The resin was washed and dried. The washing procedure is as follows (~5 mL of a solvent was used for each 100 mg of a resin): THF*2, DCM*2, THF*2, MeOH*2, DCM*2, MeOH*2, DCM*2, MeOH*3. Cleavage of resin was performed with 20% solution of TFA in DCM for 30 min. The sample obtained after the cleavage of resin was evaporated to dryness, dissolved in DCM and washed with 5% water solution of $NaHCO_3$. The organic layer was separated, dried over $MgSO_4$ and concentrated. Compounds **7Ab**, **Ac**, **Bb**, and **Bc** were additionally purified on silica gel with ethyl acetate/hexanes as eluent. NMR spectra were recorded on Gemini-300 spectrometer in acetone-d_6 with tetramethylsilane as internal standard. ***N*-(4-Hydroxybenzyl)-*N*-(4-methoxyphenyl)-2-pyrazinecarbox amide (7Ab)**. White powder (74%), mp 149–151 °C; ^{1}H NMR δ 3.67 (s, 3H), 5.01 (s, 2H), 6.69 (d, J = 8.5 Hz, 2H), 6.77 (d, J = 8.4 Hz, 2H), 6.93 (d, J = 8.5 Hz, 2H), 7.16 (d, J = 8.3 Hz, 2H), 8.20–8.60 (m, 3H), 8.68 (br s, 1H); ^{13}C NMR δ 53.2, 55.6, 114.8, 116.1, 129.1, 130.7, 131.0, 135.5, 144.1, 145.1, 145.2, 151.9, 157.8, 159.4, 167.3. Anal. calcd for $C_{19}H_{17}N_3O_3$: C, 68.05; H, 5.11; N, 12.53. Found: C, 67.88; H, 5.13; N, 12.21. ***N*-(4-Hydroxybenzyl)-*N*-(4-methylphenyl)-2-pyrazinecarboxamide (7Ac)**. White powder (80%), mp 144–146 °C; ^{1}H NMR δ 2.16 (s, 3H), 5.04 (s, 2H), 6.76 (d, J = 8.3 Hz, 2H), 6.84–7.08 (m, 4H), 7.16 (d, J = 8.3 Hz, 2H), 8.2–8.58 (m, 3H), 8.70 (s, 1H); ^{13}C NMR δ 20.9, 53.1, 116.1, 129.0, 129.1, 130.3, 130.8, 137.6, 140.3, 144.1, 145.2, 145.3, 151.7, 157.7, 167.3. Anal. calcd for $C_{19}H_{17}N_3O_2$: C, 71.46; H, 5.37; N, 13.16. Found: C, 71.44; H, 5.35; N, 12.93. ***N*-(4-Hydroxybenzyl)-*N*-(4-methoxyphenyl)-2-pyridine carboxamide (7Bb)**. White powder (86%), mp 162–163 °C; ^{1}H NMR δ 3.64 (s, 3H), 4.99 (s, 2H), 6.64 (d, J = 8.1 Hz, 2H), 6.75 (d, J = 8.2 Hz, 2H), 6.88 (d, J = 7.8 Hz, 2H), 7.08–7.24 (m, 3H), 7.45 (d, J = 7.3 Hz, 1H), 7.60–7.74 (m, 1H), 8.28 (br s, 1H), 8.42 (s, 1H); ^{13}C NMR δ 53.1, 55.6, 114.5, 116.0, 124.0, 124.4, 129.4, 130.4, 130.8, 136.2, 137.0, 149.1, 156.4, 157.7, 159.0, 169.4. Anal. calcd for $C_{20}H_{18}N_2O_3$: C, 71.84; H, 5.43; N, 8.38. Found: C, 72.27; H, 5.61; N, 8.12. ***N*-(4-Hydroxybenzyl)-*N*-(4-methylphenyl)-2-pyridinecarboxamide (7Bc)**. White powder (81%), mp 170–172 °C; ^{1}H NMR δ 2.17 (s, 3H), 5.01 (s, 2H), 6.75 (d, J = 8.5 Hz, 2H), 6.80–7.00 (m, 4H), 7.10–7.30 (m, 3H), 7.48 (d, J = 7.3 Hz, 1H), 7.62–7.75 (m, 1H), 8.20–8.40 (m, 2H); ^{13}C NMR δ 20.9, 53.2, 116.0, 124.2, 124.5, 128.9, 129.6, 130.0, 130.7, 136.9, 137.1, 141.2, 149.1, 156.4, 157.7, 169.4. Anal. calcd for $C_{20}H_{18}N_2O_2$: C, 75.45; H, 5.70; N, 8.80. Found: C, 75.29; H, 5.46; N, 8.59.