Published in final edited form as:
J Am Chem Soc. 2008 April 23; 130(16): 5446–5448. doi:10.1021/ja800612r.

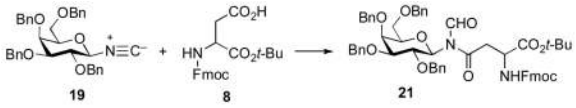
New Chemistry with Old Functional Groups: On the Reaction of Isonitriles with Carboxylic Acids - A Route to Various Amide Types

Xuechen Li† and **Samuel J. Danishefsky**†,‡,*

† *Laboratory for Bioorganic Chemistry, Sloan-Kettering Institute for Cancer Research, 1275 York Avenue, New York, New York 10065*

‡ *Department of Chemistry, Columbia University, Havemeyer Hall, 3000 Broadway, New York, New York 10027*

Abstract



Thermolysis of isonitriles with carboxylic acids provides, in one step, N-formyl imides (see, for example **8** + **19** → **21**). The resultant *N*-formyl group can be converted to N-H, NCH_2OH or NCH_3. This chemistry allows for a new route for synthesizing β-*N* (asparagine) linked glycosyl amino acids.

The dramatic progress achieved in reaching complex targets by chemical synthesis[1] has been largely fueled by major advances in methodology. For instance, huge breakthroughs in asymmetric catalysis,[2] group transfer reactions,[3] cross-coupling reactions[4] and chemistry flowing from olefin metathesis,[5] have had major impact on the practice of synthesis. The enabling major discoveries such as those cited above reflect the flowering of contemporary organometallic chemistry, wherein increasingly powerful mechanistic thinking and experimentation have paved the way for the emergence of new catalytic agents and newly designed supporting ligands, capable of providing high margins of stereocontrol (both relative and absolute).[6]

The study described in this Communication is of a very different genre, in that it combines two functional groups, known from virtually the dawn of organic chemistry, i.e. carboxylic acids (**1**) and isonitriles (**2**). Indeed, the new chemistry we describe herein *is currently not externally catalyzed.* Though the results related herein are of consequence to central contemporary problems in synthesis, they might well have been discovered a century ago.

Our thinking began by taking note of the Passerini reaction, shown in a mechanistic format in Scheme 1a.[7] We also took note of the Ugi-4 component coupling reaction, which had surely benefited from the logic of the Passerini chemistry (Scheme 1b).[8] With these applications of isonitriles in mind, we asked a simple question, i.e. do ordinary carboxylic acids (**1**) react with isonitriles **2**.[9] We began with a hypothesis that **1** and **2** might be combinable, for instance, by protonation followed by carboxylate nitrilium neutralization (see **1a** + **2a** →**3**, Scheme 1c). Alternatively, **3** could be envisioned as the direct insertion product of carbenoid-like **2** into the

E-mail: s-danishefsky@ski.mskcc.org.

OH bond of **1**. In either case, we anticipated that **3**, which is formally an O-acylated imidic acid,[10,11] could well give rise to high "value added" chemistry (*vide infra*).

Initial experiments were conducted with carboxylic acids and isonitriles wherein the R and R ′ entities did not, in themselves, embody any particularly advanced functionalities. However, it was anticipated that if the chemistry we had in mind were feasible, the components **1** and **2** being joined, might carry valuable functionality. This Communication reports on the combining of isonitriles and carboxylic acids and follow up chemistry of the resulting *N*-formyl imides (vide infra). Promising potential applications to the synthesis of interesting amide types are set forth.

In an orienting experiment, 1.2:1 molar equivalents of benzyl isonitrile (**4**) and benzoic acid (**5**) were dissolved in chloroform at room temperature.[12] Disappointingly at the time, no reaction could be detected either by spectroscopic or chromatographic criteria. However, when the solution was heated to 150 °C for 30 minutes in a microwave oven, an 83% yield of **7** was obtained (Scheme 2).[13] It seemed likely that the two components had reacted to afford a "high-energy" intermediate (perhaps mixed anhydride **6**) which, under thermolytic activation, had rearranged to the observed N-formyl amide **7** possibly through a 1,3 O→N-acyl transfer (see for instance **6a**).[14] For the completeness of the analysis, we note that, in principle, a novel but not inconceivable cycloaddition between **1a** (R= Ph) and **2a** (R′= $PhCH_2$) could lead directly to **6a**, the proposed intermediate in the postulated 1,3-acyl transfer.

In anticipation of possible applications of this chemistry to the construction of *N*-linked glycoproteins, a similar reaction was conducted with the differentiated aspartate (**8**)[15] and cyclohexylisonitrile (**9**), this time with microwave heating ~150 °C (Scheme 2, eq. 1). Indeed, asparagine derivative **11** was obtained in 82% yield. Additional insight into the aspartylation reaction was garnered. Compound **8** (1 eq) was treated with **9** (1 eq) in chloroform at room temperature for 24 hr. No new product was recognized. Then, 1 eq of *p*-methoxybenzylamine (**12**), again in chloroform, was introduced. After the resulting solution was stirred for an additional period of 24 hr at room temperature, a 10–15% yield of amide **14** was obtained (Scheme 2, eq. 2). No *N*-formylimide **11** was detected under the room temperature conditions. When the three components mixture (aspartate **8**, cyclohexylisonitrile (**9**), and benzylamine **12**) in chloroform was subjected to microwave heating at ca 130 °C from the outset, three products (**11**, **13**, and **14**) were obtained in the ratio shown (Scheme 2, eq. 3). These experiments suggest that acid **8** and isonitrile **9** react at room temperature in a *rather slow step*, producing *in situ* a competent acyl donor capable of aspartylating **12** (see formation of **14**). Under microwave/thermolysis, the acyl donor (conceivably **10**)[16] undergoes two competing reactions. It can aspartylate **12**, now under more stringent conditions, to provide **14** more rapidly. Alternatively, the intermediate can undergo a competitive 1,3-acyl rearrangement, giving rise to **11**. The latter can also function as an active formyl donor (with respect to formyl acceptor **12**) leading to **13**.

Our next goal was the preliminary evaluation of this chemistry for building asparagine-linked glycopeptides.[17] Accordingly, we prepared a β-anomeric glycosylisonitrile in the context of β-GlcNAc setting (see congener **15**, Scheme 3, eq. 1)[18]. The processing of **15** with aspartate **8** in the usual way provided, surprisingly at the time, *ester* **16** in a stereospecific fashion. We reasoned that activation of the isonitrile function, presumably by protonation, had set the stage for ejection of some form of "cyanide" presumably via participation of the N-acetyl group. The overall event generates a highly reactive β-GlcNAc donor. Following its reaction with carboxylic acid **8**, the β-configured ester **16**[19] is produced stereospecifically.

We next asked whether the removal of a strongly participating group at C_2 of the glycosyl isonitrile would allow for realization of the chemistry we were seeking. To study this

possibility, the isonitriles **19** and **20** were prepared from the corresponding, previously known glycosyl azides **17** and **18**. In the event, the individual anomeric isonitriles reacted with **8** under the usual circumstances to produce **21** and **22**, respectively (Scheme 3, eq. 2 and 3). These reactions appear to be anomerically specific, i.e. the respective α and β isonitriles produce, correspondingly, the α and β N-linked glycosyl amino acids.

Armed with these findings, we proceeded to prepare an anomeric isonitrile, containing a 2-α-azido function. The required substrate **24** was synthesized from the previously known bis azide **23**[20], taking advantage of the precedented feasibility of selectively reducing an anomeric azide to the corresponding amine, in the presence of the neighboring 2-α-azido function.[21] Compound **24** was subjected to the now usual conditions for combining with aspartate **8**. Happily, this reaction led to the 2-α-azido N-formyl asparagine system **25** (Scheme 3, eq. 4). Though much work remains before effective usage of this chemistry in the fashioning of real N-linked glycopeptides can be realized. However, the ability to reach a compound of the type **25** by this novel and straightforward way is already quite encouraging.

From the outset, it was anticipated that it would be possible to achieve selective deformylation of the *N*-formyl amides. These structures, which arise from the presumed addition-rearrangement sequence when starting with **1** and **2**, correspond to nucleophile cleavable mixed imides whose maximum vulnerability is at the formyl group. Indeed, this supposition proved to be the case (see conversion of **7**→**26** and **21**→**27** through the action of sodium methoxide, Scheme 4, eq. 1 and 2).

We then explored sequences which start with chemospecific reduction of the *N*-formyl function of the mixed imide to its "methylol" derivative.[22] Thus, for instance, reduction of compound **7** with sodium borohydride provides, after routine work-up and chromatographic purification, an 80% yield of the dihydro derivative, **28** (Scheme 4, eq. 3). Similarly, **11** provides a high yield of **29** (Scheme 4, eq. 4). Ordinarily, we do not fully purify the intermediate hydroxymethyl product. Rather, it can serve, even in crude form, as a valuable intermediate for reaching other amide-modifying structures. Thus, further reduction of the "methylol" intermediates with triethylsilane in the presence of trifluoroacetic acid affords the corresponding *N*-methyl compounds (see tertiary amides **31**, **32** and **33** derived from **28**, **29** and **30**, respectively).[23]

Thus, the isonitrile-initiated chemistry described goes beyond the synthesis of secondary amides. It also provides access to tertiary amides bearing *N*-methyl groups (see **31–33**). The incremental difficulties in acylating a secondary amine, containing even a supposedly small N-methyl group relative to that which pertains to primary amines is well-appreciated by practitioners of peptide chemistry.[24] Another promising result in this regard is seen in the two-step conversion **7**→**34** via Lewis acid-induced nucleophilic reaction of methylol intermediate **28** with allyl trimethylsilane (Scheme 4, eq. 6).[25] Classical acylation of secondary amines bearing two relatively large groups can be particularly demanding.

Still another avenue of progress provided by the N-formyl mixed imides arising from our isonitrile chemistry is suggested in the context of a pleasingly simple two-step synthesis of dihydropyridone **37**.[26] Combining of isonitrile **9** with the commercially available keto-acid **35** in the usual way, afforded **36**. The latter was converted to **37** in 55% yield over the two steps (Scheme 4, eq. 7).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

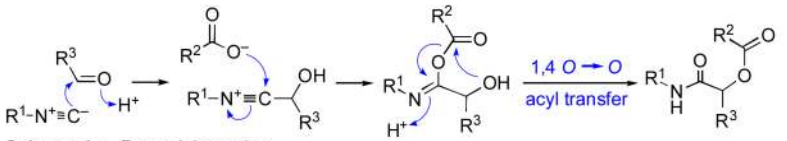
Acknowledgements

Support for this research was provided by the National Institutes of Health (CA28824).

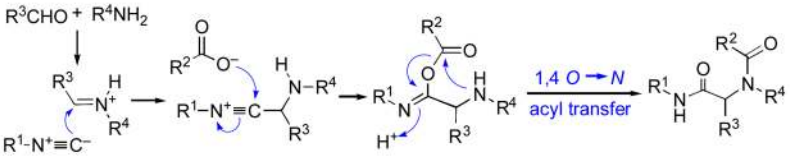
References

1. Nicolaou, KC.; Sorensen, EJ. Classics in Total Synthesis. Wiley-VCH; 1996. Nicolaou, KC.; Snyder, SA. Classics in Total Synthesis II. Wiley-VCH; 2003. c) Wilson RM, Danishefsky SJ. J Org Chem 2006;71:8329. [PubMed: 17064003] d) Wilson RM, Danishefsky SJ. Chem Soc Rev 2007;36:1207. [PubMed: 17619682]
2. Jacobsen, EN.; Pfaltz, A.; Yamamoto, H. Comprehensive Asymmetric Catalysis. Springer; 1999. b) Yoon TP, Jacobsen EN. Science 2003;299:1691. [PubMed: 12637734] c) Heitbaum M, Glorius F, Escher I. Angew Chem Int Ed 2006;45:4732.
3. a) Webster OW, Hertler WR, Sogah DY, Farnham WB, RajanBabu TV. J Am Chem Soc 1983;105:5706. b) Webster OW. Adv Polym Sci 2004;167:1.
4. de Meijere, A.; Diederich, F. Metal-Catalyzed Cross-Coupling Reactions. Wiley-VCH; 2004.
5. a) Chauvin Y. Angew Chem Int Ed 2006;45:3740. b) Schrock RR. Angew Chem Int Ed 2006 45;23:3748. c) Grubbs RH. Angew Chem Int Ed 2006 45;23:3760.
6. Taylor MS, Jacobson EN. Angew Chem Int Ed 2006;45:1520.
7. a) Passerini M. Gazz Chim Ital 1921;51:181. b) Banfi L, Riva R. Org React 2005;65:1.
8. a) Ugi I, Meyr R, Fetzer U, Steinbrückner C. Angew Chem 1959;71:386. b) Dömling A, Ugi I. Angew Chem Int Ed 2000;39:3168.
9. In this reference we collect several citations in the literature concerning the purported formation of O-acylated imidic acids via isonitrile. At the present writing, no compound corresponding to 3, arising from the reaction of isonitriles and acids, has been documented. a) Gloede J, Gross H. Zeitschrift fuer Chemie 1968;8:6–219. b) Gloede J. J f prakt Chemie 1982 324;4:667. c) Sung K, Chen CC. Tetrahedron Lett 2001;42:4845. d) Shaabani A, Soleimani E, Rezayan AH. Tetrahedron Lett 2007;48:6137. We have recently revisited the science reported in reference 9d. Our findings, which differ from those reported in 9d, will be disclosed in due course. Suffice it to say for the moment that the results described herein were not anticipated in the actual case covered by that reference.
10. We note that compound 3 can be also be looked upon as a hypothetical mixed anhydride comprising a carboxylic acid and an imidic acid.
11. Darbeau, White and co-workers have claimed syn, anti isomers corresponding to 3. These were generated from nitriles rather than isonitriles. Darbeau RW, White EH, Nunez N, Coit B, Daigle M. J Org Chem 2000;65:1115. [PubMed: 10814062]
12. We envisioned that we could favor chances for focusing on the reaction of isonitriles and carboxylic acids by conducting the reaction in a non-nucleophilic, aprotic solvent.
13. When the reactions are conducted in near stoichiometric equivalences, several minor products are noted. These are the starting isonitrile and carboxylic acid, and the formamide corresponding to the hydrated isonitrile.
14. We emphasize that not having established the presence of 6, the pathway from 4 + 5 → 7 must be regarded as conjectural. For instance, the possibility that 7 arises from a benzoic anhydride which is formed from the reaction of benzoate on 6 has not been ruled out.
15. Commercially available from NovaBiochem
16. At this writing, it has not been shown that the acyl donor leading to 14 and the precursor leading to 13 are one in the same species.
17. Reviews: a) Taylor CM. Tetrahedron 1998;54:11317. b) Arsequell G, Valencia G. Tetrahedron: Asymmetry 1999;10:3045. c) Kajihara Y, Yamamoto N, Miyazaki T, Sato H. Curr Med Chem 2005;12:527. [PubMed: 15777211] d) Buskas T, Ingale S, Boons GT. Glycobiology 2006;16:113R.
18. Ichikawa Y, Ohara F, Kotsuki H, Nakano K. Org Lett 2006;8:5009. [PubMed: 17048830]
19. a) Simerská P, Pisvejcová A, Kuzma M, Sedmera P, Kren V, Nicotra S, Riva S. J Mol Catal B: Enzymatic 2004;29:219. b) Bulusu MARC, Waldstätten P, Hildebrandt J, Schütze E, Shulz G. J Med Chem 1992;35:3463. [PubMed: 1404227]
20. Snider BB, Lin H. Synth Commun 1998;28:1913.

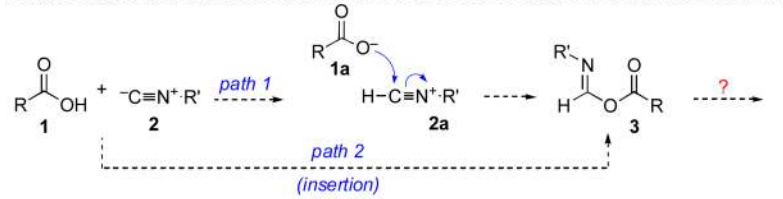
21. Sridhar PR, Prabhu KR, Chandrasekaran S. J Org Chem 2003;68:5261. [PubMed: 12816487]
22. a) Iley J, Moreira R, Calheiros T, Mendes E. Pharm Res 1997;14:1634. [PubMed: 9434286] b) Majumdar S, Sloan KB. Bioorg Med Chem Lett 2006;16:3590. [PubMed: 16616488] c) Peltier HM, McMahon JP, Patterson AW, Ellman JA. J Am Chem Soc 2006;128:16018. [PubMed: 17165738]
23. Dorow RL, Gingrich DE. Tetrahedron Lett 1999;40:467.
24. a) Kessler H. Angew Chem Int Ed 1970;9:219. b) Tantry SJ, Venkataramanarao R, Chennakrishnareddy G, Sureshbabu VV. J Org Chem 2007;72:9360. [PubMed: 17963403]
25. Wang DH, Hao XS, Wu DF, Yu JQ. Org Lett 2006;8:3387. [PubMed: 16836412]
26. a) Cook GR, Beholz LG, Stille JR. J Org Chem 1994;59:3575. b) Heureux N, Wouters J, Marko IE. Org Lett 2005;7:5245. [PubMed: 16268549] In the case at hand, 37 might arise directly from an aldol-like condensation of 36 or from condensation of the secondary amide with a β-ketoaldehyde generated from a formyl transfer.



Scheme 1a: *Passerini reaction.*

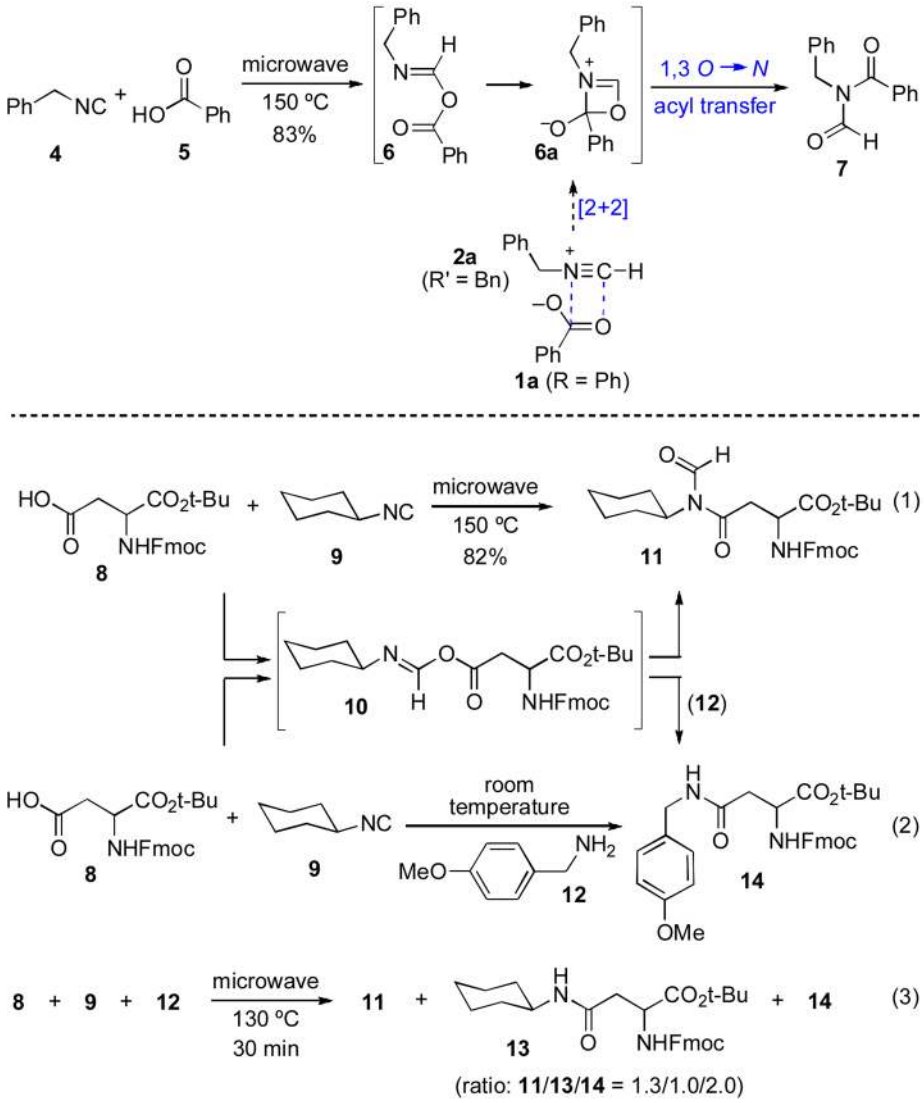


Scheme 1b: *Ugi four-component coupling reaction.*

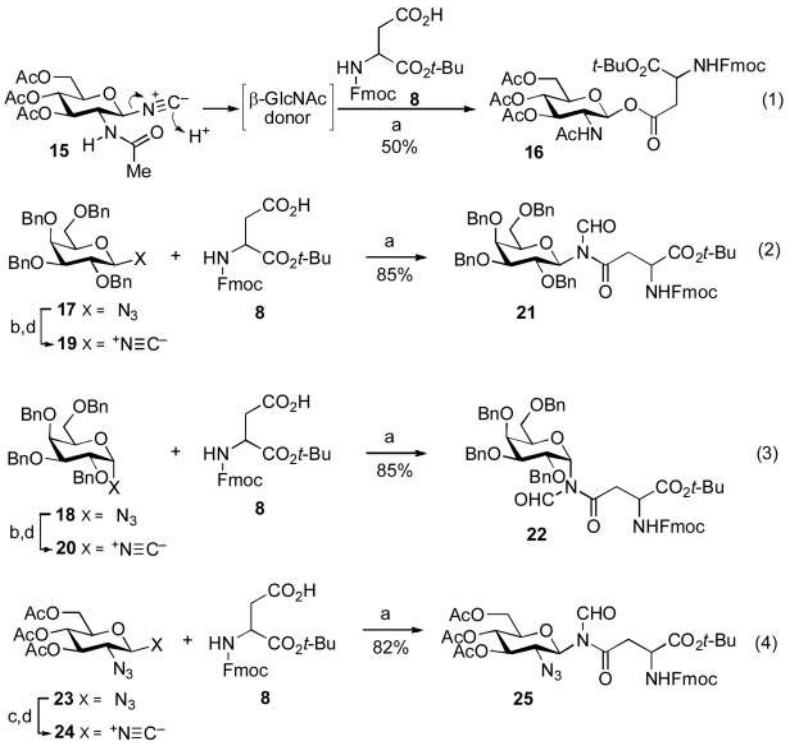


Scheme 1c: *Proposed transformation.*

Scheme 1.

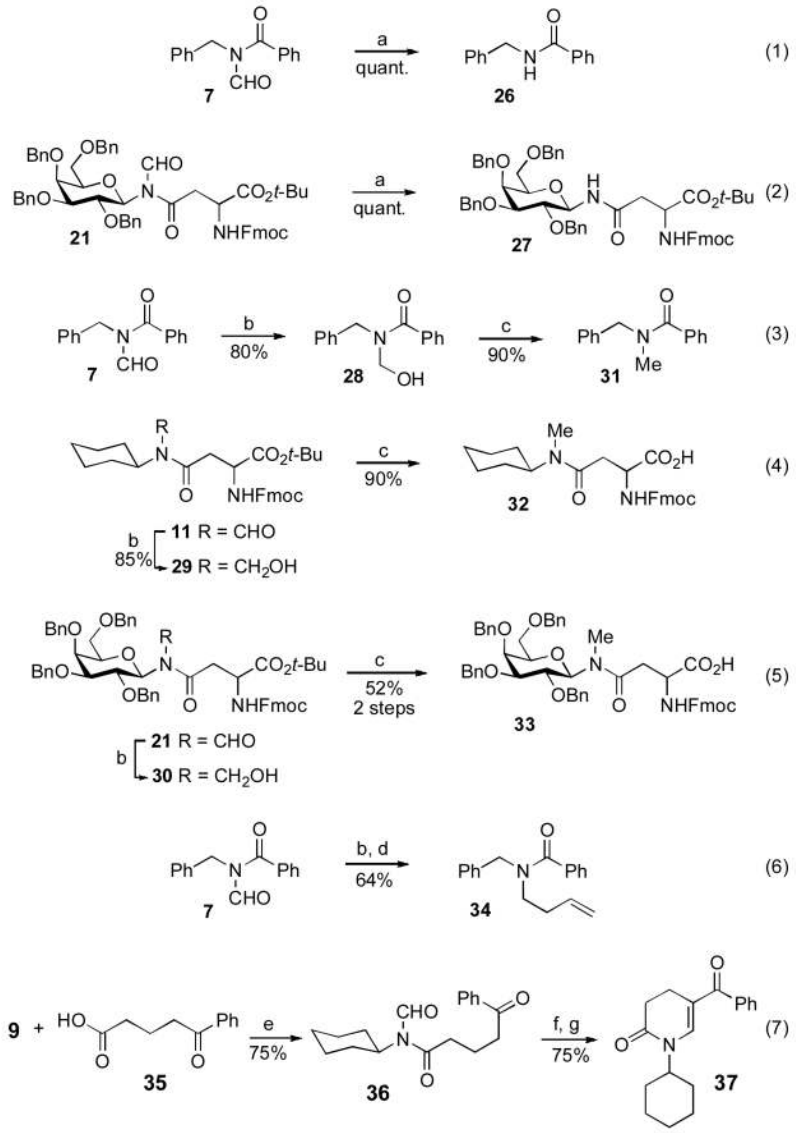


Scheme 2.



Scheme 3.

[a]Key: (a) $CHCl_3$, 150 °C (Microwave), 30–45 min; (b) (1) Pd/C, H_2, Et_3N, EtOAc; (2) HC(O)OC(O)CH_3; (c) (1) $(NH_4)_2MoS_4$, MeCN/EtOH; (2) HC(O)OC(O)CH_3, EtOAc, 53%; (d) Triphosgene, Et_3N, CH_2Cl_2, 0 °C to rt, 75–90%



Scheme 4a.

[a]Key: (a) NaOMe, MeOH, 0 °C; (b) $NaBH_4$, MeOH, 0 °C; (c) TFA, Et_3SiH, CH_2Cl_2; (d) TFA, allyltrimethylsilane, CH_2Cl_2; (e) $CHCl_3$, 150 °C (Microwave), 30 min; (f) $LiN(TMS)_2$, THF; (g) TFA, CH_2Cl_2