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Titanium Catalysis in the Ugi Reaction of α-Amino Acids with Aromatic Aldehydes

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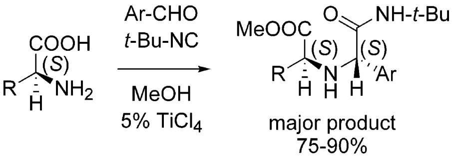
ABSTRACT

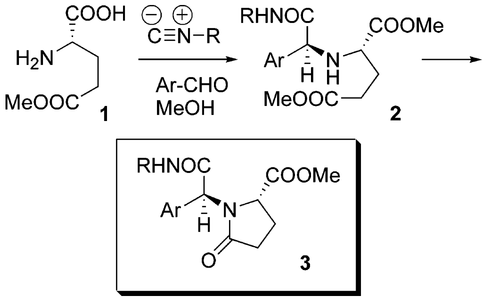


Ugi reaction between an (*S*)-α-amino acid, an aromatic aldehyde, and an isonitrile proceeds best under catalysis by $TiCl_4$ in MeOH. The sense of diastereoinduction is (*S*,*S*).

An ongoing synthetic project required a method for the rapid assembly of hybrid arylglycine-pyroglutamic acid intermediates **3**. These substances may be prepared by amidoalkylation chemistry[1] and related reactions.[2] An attractive alternative involves an Ugi condensation of (*S*)-glutamic acid 5-methyl ester, **1**, an aromatic aldehyde, and an isonitrile (Scheme 1). Ugi reactions[3] of α-amino acids are documented in pioneering reports by Ugi himself,[4] but overall they have received only sporadic attention,[5] and their sense of diastereoinduction has been the subject of conflicting reports.[6] Moreover, the literature records only instances of such reactions with *aliphatic* aldehydes. This prompted us to investigate the desired transformations in some detail. Herein, we describe initial results in this area.

Reaction of **1** with **4** and **5** under Ugi conditions[4] was slow. The reaction was accelerated by heating to 40 °C, whereupon even after 4 days some starting material (5−10%) remained. Compound **6** was formed as the major product of a 6:1 mixture of diastereomers but in a modest 30% yield (Scheme 2). The stereochemical assignment rests on an X-ray

Scheme 1. Possible Avenue to Desired Intermediate **3**



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(1) Cf.: Roth, E.; Altman, J.; Kapon, M.; Ben-Ishai, D. *Tetrahedron* **1995**, *51*, 801.

(2) E.g., Gosselin, F.; Roy, A.; O'Shea, P. D.; Chen, C.; Volante, R. P. *Org. Lett.* **2004**, *6*, 641.

(3) Recent review: Dömling, A.; Ugi, I. *Angew. Chem., Int. Ed.* **2000**, *39*, 3168.

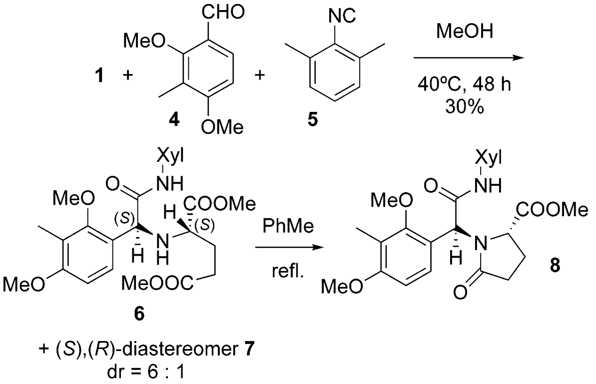
(4) For instance: (a) Demharter, A.; Hörl, W.; Herdtweck, E.; Ugi, I. K. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 173. (b) Ugi, I.; Hörl, W.; Hanusch-Kompa, C.; Schmid, T.; Herdtweck, E. *Heterocycles* **1998**, *47*, 955.

(5) For instance: (a) Janvier, P.: Sun, X.; Bienaymé, H.; Zhu, Z. *J. Am. Chem. Soc.* **2001**, *124*, 2560. (b) Dyker, G.; Breitenstein, K.; Henkel, G. *Tetrahedron: Asymmetry* **2002**, *13*, 1929. Brief review: (e) Dyker, G. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1700.

(6) Cf. Park, S. J.; Keum, G.; Kang, S. B.; Koh, H. Y.; Kim, Y. *Tetrahedron Lett.* **1998**, *39*, 7109.

10.1021/ol048850x CCC: $27.50

Scheme 2. Uncatalyzed Ugi Rection of Glutamate **1**



diffractometric study of crystalline **8**, a congener of **3** obtained by refluxing a toluene solution of **6**. In accord with Ugi's work, the sense of diastereoinduction is (*S*,*S*), but the kinetics, yield, and diastereoselectivity of the reaction were significantly poorer than expected on the basis of those reports. However, Ugi's published results with aliphatic aldehydes were readily duplicated, signaling that the inefficiency of the transformation leading to **6** is attributable to the aromatic nature of aldehyde **4**.

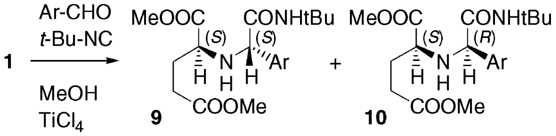
Reasoning that the observed difficulties were likely to ensue from the reduced electrophilicity of aromatic aldehydes relative to aliphatic ones and, consequently, from a slower rate of formation of an iminium ion intermediate from **1** and **4**, we explored the effect of solvents and of Lewis acid promoters on the process.

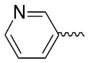
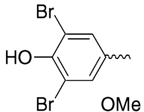
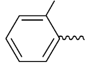
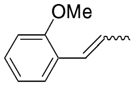
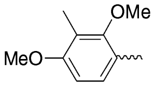
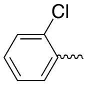
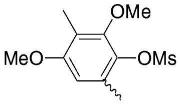
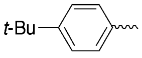
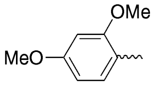
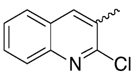
Alternative reaction solvents were no cure for the problem. In particular, isonitrile-based multicomponent condensations may proceed more efficiently in trifluoroethanol (TFE)[6] or in water.[7] In the present case, the desired material was obtained as a component of a complex mixture of products when the reaction was conducted in TFE, whereas in water, formation of the desired product was suppressed altogether, perhaps because of the poor solubility of **4** in an aqueous medium. The use of surfactants as a means to circumvent such solubility issues[8] would introduce needless complications and was not explored.

Turning then to the effect of acidic catalysts, we screened 2 protonic acids (MsOH and TFA) and 13 Lewis acids[9] as promoters of the reaction of **1** with **4** and **5**. These experiments were carried out at a constant 5 mol % amount of catalysts, over reaction times ranging from 12 to 144 h. Bronsted acids proved to be ineffective promoters, and indeed they may be harmful. For instance, no desired product was obtained from a reaction run in the presence of 5 mol % MsOH, perhaps due to polymerization of the isonitrile, whereas the weaker TFA produced results essentially identical to those of the uncatalyzed process, suggesting that no proton source is really necessary beyond the substrate. By contrast, a number of Lewis acids had a beneficial effect on yields and rates. Best results were observed with $TiCl_4$ as the catalyst.[10] Thus, the transformation proceeded to completion in less than 24 h and the yield of desired product doubled relative to the uncatalyzed reaction. On the other hand, only small changes in diastereomeric ratios were detected as a function of the promoter, and transformations catalyzed by $TiCl_4$ afforded essentially the same diastereomeric ratios (6:1 in favor of the (*S*,*S*)-diastereomer) as the uncatalyzed process. This seems to imply that the catalyst is involved primarily in the formation of an iminium ion from **1** and **4** but that probably it plays a marginal role in the nucleophilic addition of the isonitrile thereto.

Complex mixtures of products were again obtained when

Table 1. $TiCl_4$-Catalyzed Ugi Reactions of 5-Methyl Glutamate



entry[a]	Ar	ratio (*S,S*) / (*S,R*)	yield[b,c]
a		5	80 (62)
b		9	86 (51)
c		3.5	83 (66)
d		1.5	86 (58)
e		6	91
f		5	90
g		10	75
h		5	86
i		6	85
j		5	86

[a] All reactions carried out in a 0.15 M solution at room temperature for 12 h. [b] Chromatographed yield of the mixture of **9** and **10**. [c] In parentheses: chromatographed yield of the mixture of **9**/**10** for the uncatalyzed reaction run under the conditions of refs 4.

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(7) Pirrung, M. C.; Das Sarma, K. *J. Am. Chem. Soc.* **2004**, *126*, 444.

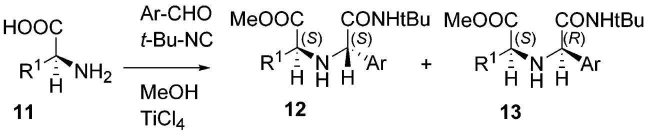
(8) Cf., e.g.: Saito, K.; Tago, T.; Masuyama, T.; Nishide, H. *Angew. Chem., Int. Ed.* **2004**, *43*, 730

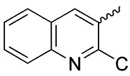
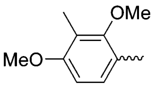
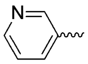
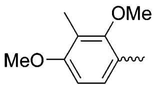
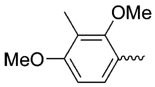
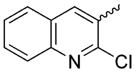
(9) Lewis acids have been used in certain multicomponent condensations involving isonitriles; cf.: Keung, W.; Bakir, F.; Patron, A. P.; Rogers, D.; Priest, C. D.; Darmohusodo V. *Tetrahedron Lett.* **2004**, *45*, 733.

the reaction was carried out in TFE instead of MeOH. On the other hand, the use of *t*-Bu-NC, in lieu of **5**, resulted in an appreciable improvement in yields (>75%) and kinetics (completion in 6−12 h). A summary of several reactions of **1** run under optimized conditions appears in Table 1.[11] Yields are significantly higher and reaction times are considerably shorter relative to the uncatalyzed reactions run under Ugi's original conditions.[4]

The optimal procedure devised for **1** proved to be quite suitable for analogous reactions of other amino acids with aromatic aldehydes. Representative examples with valine, serine, phenylalanine, and tryptophan appear in Table 2. Again, the yields of the much faster catalyzed reaction (12 h or less vs 4 days) were double or triple those of the uncatalyzed process conducted as detailed in refs 4.[12]

Table 2. $TiCl_4$-Catalyzed Ugi Reactions of Other Amino Acids

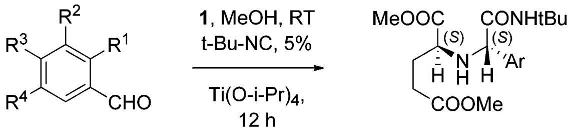


entry[a]	R^1	Ar	ratio (*S*,*S*) / (*S*,*R*)	yield[b,c]
a	$PhCH_2$		6	92 (26)
b	HO-CH_2		5	79 (55)
c	(3-Indolyl)CH_2		5	84 (32)
d	(3-Indolyl)CH_2		3	90 (43)
e	*i*-Pr		10	81 (35)
f	*i*-Pr		11	82

[a] All reactions carried out in a 0.15 M solution at room temperature for 12 h. [b] Chromatographed yield of the mixture of **12** and **13**. [c] In parentheses: chromatographed yield of the mixture of **12**/**13** for the uncatalyzed reaction run under Ugi conditions (refs 4).

The unusual nature of our reaction medium begs the question of whether the catalytic efficacy of $TiCl_4$ is primarily attributable to its Lewis acidity or to its being an agent for the in situ generation of strong protonic acids such as HCl. We tend to ascribe the catalytic effect of the adjuvant primarily to its Lewis acidity. The notion that the efficacy of the promoter may be attributable to in situ release of HCl generated through methanolysis of $TiCl_4$ would be inconsistent with the observation that strong Bronsted acids are poor promoters for the reaction. Indeed, a reaction between **1**, **4**, and *t*-Bu-NC run in the presence of 5% HCl in MeOH[13] showed little improvement in yield (42%) or selectivity (6:1) relative to the uncatalyzed process, just as observed with TFA. Furthermore, $Ti(OiPr)_4$, which cannot generate HCl, displayed catalytic efficacy comparable to that of $TiCl_4$ (Scheme 3). However reactions catalyzed by $Ti(OiPr)_4$ proceeded somewhat slower and afforded slightly lower stereoselectivities, rendering $TiCl_4$ the promoter of choice.

Scheme 3. Catalytic Effect of $Ti(OiPr)_4$

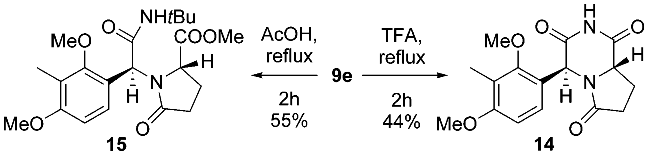


R^1 = OMe; R^2 = Me; R^3 = OMe; R^4 = H → **9e** + (*S*, *R*) diast. **10e** (74%, dr = 5:1)

R^1 = OMs; R^2 = OMe; R^3 = Me; R^4 = OMe → **9g** + (*S*, *R*) diast. **10g** (70%, dr = 8:1)

Amides **9** and **10** undergo a useful dealkylative cyclization under acidic conditions. For instance, brief refluxing of **9d** in trifluoroacetic acid induced conversion to **14** (Scheme 4), a crystalline substance whose structure was confirmed by single-crystal X-ray diffractometry.[14] Notice again the structural analogy between **14** and **3**. The use of the weaker AcOH in this reaction resulted only in formation of **15**, a substance more readily obtained by plain thermal activation of the Ugi product (cf. Scheme 2).

Scheme 4. Dealkylative Cyclization of Amides **9**



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[10] Other Lewis acids examined in the course of this work: $AlMe_3$ (72 h, 39% yield, diastereomeric ratio *S,S*/*S,R* = 10), BF_3OEt_2 (complex mixture); $Cu(OAc)_2$ (144 h, 37%, dr = 10), $Cu(OTf)_2$ (144 h, 37%, dr = 3), $Eu(hfc)_3$ (72 h, 39%, dr = 11), $Sc(OTf)_3$ (24−96 h, 40−45%, dr = 10), Cp_2TiCl_2 (72 h, 33%), $YbCl_3$ (48−72 h, 45%, dr = 5−9), $Yb(OTf)_3$ (48 h, 40%, dr = 5), $Yb(hfc)_3$ (24−96 h, 46−48%, dr = 9), $Yb(fod)_3$ (48 h, 40%, dr = 10), $ZnCl_2OEt_2$ (72 h, 50%, dr = 9).

[11] **Typical Procedure.** A 0.15 M solution of **1** and an aldehyde in MeOH was stirred at rt for 20 min, and then 1.2 equiv of *t*-Bu-NC was added, followed by 5 mol % $TiCl_4$. The mixture was stirred at rt for 12 h, and then it was diluted with EtOAc and washed with water. The organic phase was dried (Na_2SO_4), filtered, and concentrated. The residue was purified by silica gel chromatography.

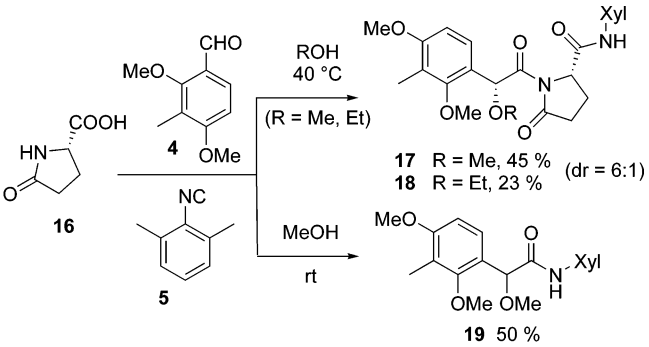
[12] The $TiCl_4$/MeOH procedure is applicable to reactions involving aliphatic aldehydes. While excellent yields of products are obtained, the substantial increase of the rate of such reactions results in significant erosion of diastereoselectivity relative to the original Ugi procedure, consistent with the reactivity−selectivity principle.

[13] Prepared by addition of acetyl chloride to dry MeOH.

[14] The same product was obtained upon refluxing a solution of **9e** in HCOOH but in a diminished 30% yield.

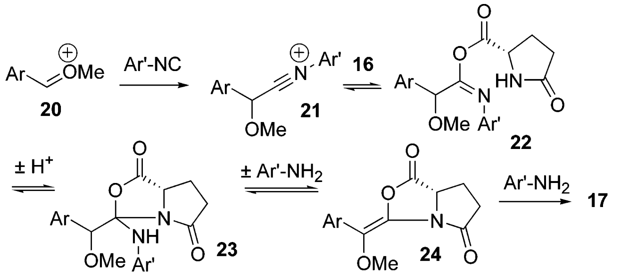
On a final note, we entertained the possibility of creating the desired **3** by an Ugi-like condensation of **4** and **5** with pyroglutamic acid, **16**. Ugi-type reactions in which the nitrogenous component is an amide or a lactam appear to be undocumented, hence the interest of exploring such an opportunity. Whereas direct formation of **3** in this guise proved ultimately not to be possible, an interesting transformation took place when **16**, **4**, and **5** were admixed in MeOH at 40 °C for 48 h: a 6:1 mixture of two diastereomers of imide **17**[15] emerged in moderate yield (Scheme 5). The sense of diastereoinduction is now (*S*,*R*). Conducting the reaction in EtOH under otherwise identical conditions led to **18**, whereas at room temperature the Passerini product **19** was obtained.[16] Contrary to the previous case, Lewis acids had no effect on the yield and the selectivity of this unusual reaction,[17] a mechanism for which is proposed in Scheme 6.

Scheme 5. Attempted Ugi Reaction with Pyroglutamic Acid



We presume that oxonium ion **20** results reversibly upon acid-promoted combination of **4** with, e.g., MeOH. Sequential addition of the isonitrile to **20** and of the carboxylate anion of **16** to **21** produces **22**. At lower temperatures, **22** may be sufficiently long-lived to react with methanol, resulting in formation of methyl pyroglutamate and **19**. On the other hand, thermal activation promotes cyclization of **22** to **23**, which then suffers reversible loss of xylidine to give **24**. Being an activated ester, **24** reacts with the liberated amine to yield **17**. This step is presumed to involve diastereoselective protonation of the putative intermediate **24** as the event that determines the configuration of **17**.

Scheme 6. Mechanistic Hypothesis



In summary, $TiCl_4$ catalysis extends the scope of the Ugi reaction of α-amino acids to the aromatic series of aldehydes. The new process should find widespread application in the stereoselective synthesis of nitrogenous substances. Investigations in that sense are ongoing in our laboratory and will be the subject of future reports.

Acknowledgment. We thank the MRT, the CNRS, and the Région Rhône-Alpes for support of our research. We are grateful to Ms. Laurence Rousset and Dr. Denis Bouchu for the mass spectral data, to Dr. Bernard Fenet for the NMR data, and to Mr. Sylvain Canesi for helpful discussion. M.A.C. is the recipient of a Merck & Co. Academic Development Award.

Supporting Information Available: Experimental procedures and spectral data of key compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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[15] The major isomer, a crystalline substance, was characterized by X-ray diffractometry.

[16] The structure of this racemic product was confirmed by X-ray diffractometry.

[17] Bronsted acids were also ineffective promoters.