JOC The Journal of Organic Chemistry

Note

pubs.acs.org/joc

A Successful Replacement of Phenols with Isocyanides in the Bargellini Reaction: Synthesis of 3-Carboxamido-Isobutyric Acids

Mariateresa Giustiniano,*[,†] Sveva Pelliccia,[‡] Ubaldina Galli,[§] Jussara Amato,[†] Fabio Travagin,[§] Ettore Novellino,[†] and Gian Cesare Tron*[,§]

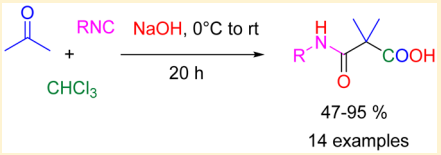
[†]Dipartimento di Farmacia, Università degli Studi di Napoli "Federico II", via D. Montesano 49, 80131 Napoli, Italy

[‡]Istituto Pasteur-Fondazione Cenci Bolognetti, Dipartimento di Chimica e Tecnologie del Farmaco, Sapienza Università di Roma, Piazzale Aldo Moro 5, I-00185 Roma, Italy

[§]Dipartimento di Scienze del Farmaco, Università del Piemonte Orientale "A. Avogadro", Largo Donegani 2, 28100 Novara, Italy

Supporting Information

ABSTRACT: Old multicomponent reactions are still a source of inspiration for discovering novel combinations of three or more reactants. A simple idea is to replace one of the educts of a known multicomponent reaction with another functional group and still be able to mimic the same reactivity. Following this line of thought, we report a three-component reaction in which isocyanides are able to open the epoxide intermediate of the Bargellini reaction affording 3-carboxamido-isobutyric acids in yields of 47−95%.



3-Carboxamido-isobutyric acids (3-CIAs) are important chemical intermediates for the synthesis of a large array of pharmaceutically relevant scaffolds. They have been reported, to cite a few, as intermediates for the synthesis of CCRs antagonists for the treatment of HIV infection (**1**),[1] γ-secretase inhibitors (**2**),[2] inverse agonists of ROR-γ receptors (**3**),[3] thrombin inhibitors (**4**),[4] Glp-1 receptor agonists (**5**),[5] bromodomain inhibitors (**6**),[6] isomalyngamide A analogues (**7**) with antimigratory activity in human breast cancer cells,[7] and plasma stable hydroxamates (**8**)[8] (Figure 1).

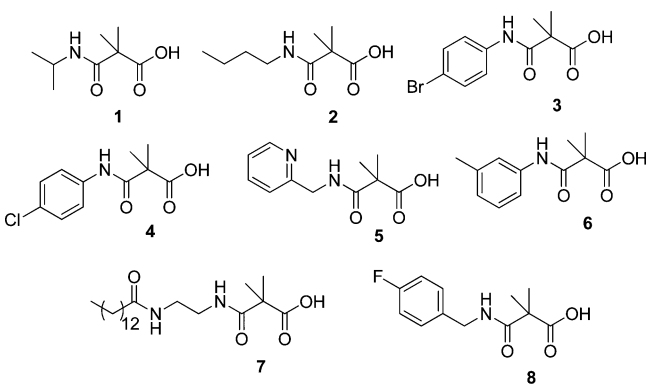
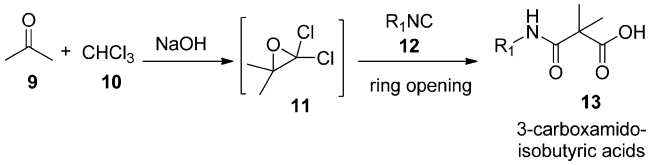


Figure 1. Examples of 3-CIAs as key intermediates in the synthesis of pharmaceutically relevant compounds.

Usually, 3-CIAs are synthesized from diethylmalonate through a base-promoted dimethylation and a sequence of three synthetic steps, namely, (i) mono ester hydrolysis, (ii) coupling with an amine, and (iii) saponification.[8] More recently, the use of Meldrum's acid allowed for an improved and faster two-step synthesis of these compounds.[7]

As a continuation of our research interest in the identification of novel suitable electrophiles as partners of isocyanides,[9] we envisaged the possibility of obtaining 3-carboxamido-isobutyric acid derivatives **13** in a single chemical operation, through the *in situ* formation of Bargellini epoxide **11**, (2,2-dichloro-3,3-dimethyloxirane), and subsequent epoxide ring opening with isocyanides **12** (Scheme 1).

Scheme 1. Synthesis of 3-CIAs via Ring Opening of Bargellini Epoxide

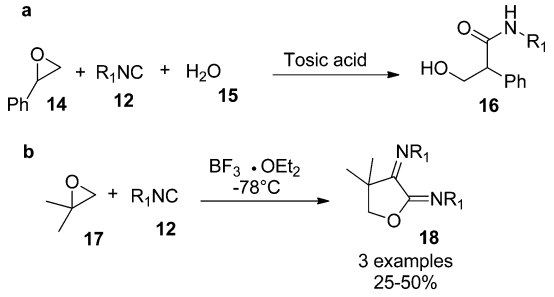


It should be mentioned that it is known from the literature that isocyanides are not sufficiently nucleophilic to open epoxides by themselves, requiring the assistance of a strong Brønsted or Lewis acid.[10,11] Unfortunately, both acids can activate undesired synthetic pathways: Brønsted acids (e.g., tosic acid) trigger a pinacol-type rearrangement with the formation of a carbonyl compound (Scheme 2a),[10] while Lewis acids (e.g., $BF_3{\cdot}Et_2O$ or $AlCl_3$) lead to a rapid cationic polymerization of the isocyanides and to the formation of 2,3-diiminofurans **18** in modest yields (25−50%) (Scheme 2b).[11] Despite these evident problems with the epoxides, we reasoned that, because of its carbocationic nature, intermediate **11** might

Received: August 29, 2016
Published: October 18, 2016

DOI: 10.1021/acs.joc.6b02130
J. Org. Chem. 2016, 81, 11467−11471

Scheme 2. Literature-Reported Epoxide Ring Opening with Isocyanides



be more prone to be intercepted by isocyanides without the necessity of activators.

The original Bargellini reaction, reported in 1907, involves a base-mediated ring formation of an epoxide, starting from acetone, chloroform, and sodium hydroxide, and its opening with phenols to give α-phenoxyisobutyric acids.[12] Despite the evident potentiality of this transformation, it was neglected for more than 40 years when Galimberti and co-workers at Schering (Milan, Italy) resumed the use of this reaction, demonstrating the successful replacement of the phenol group with other nucleophiles such as thiophenols,[13] ureas and thioureas,[14] semicarbazides and thiosemicarbazides,[15] secondary alcohols, benzotriazoles, and guanidine.[12a,16,17] Other authors showed that anilines,[18a,b] imidazole,[18b] or bifunctionalized substrates such as diamines and β-amino alcohols[19] and 2-aminobenzamide[20] were also valuable replacements for the phenol group.

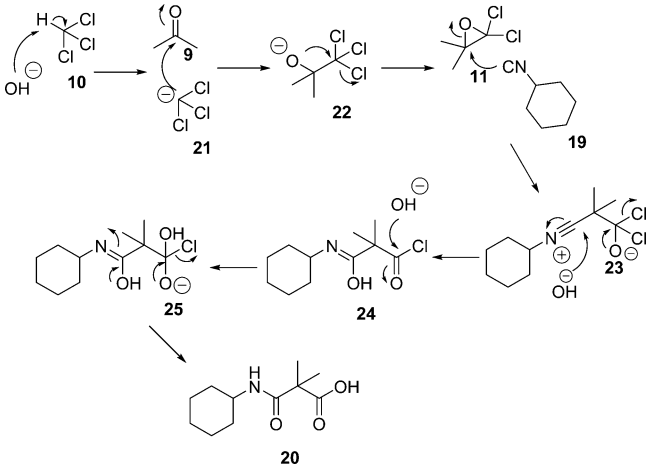
Stimulated by these results[21,22] and because of the fact that the basic conditions of Bargellini reaction are compatible with the survival of the isocyano group, we evaluated the ability of isocyanides to open epoxide intermediate **11**.

In a first attempt, a two-step, one-pot reaction was performed using the classical conditions reported for the Bargellini reaction.[21a] Acetone (**9**), chloroform (**10**), and sodium hydroxide were reacted for 30 min at 0 °C to preform the 2,2-dichloro-3,3-dimethyloxirane (**11**); cyclohexylisocyanide (**19**) was then added, and the reaction mixture was stirred for 20 h at room temperature. To our delight, the desired compound (**20**) was obtained in 70% yield (Scheme 3a).

This encouraging result prompted us to investigate the feasibility of a one-pot procedure. We therefore mixed acetone (**9**), chloroform (**10**), sodium hydroxide, and cyclohexylisocyanide (**19**) at 0 °C, so that the 2,2-dichloro-3,3-dimethyloxirane intermediate (**11**) could be intercepted by the isocyanide as soon as it has been formed *in situ*. The desired product (**20**) was obtained in 90% yield (Scheme 3b).

A working hypothesis for the formation of **20** is reported in Scheme 4. In detail, sodium hydroxide abstracts a proton from

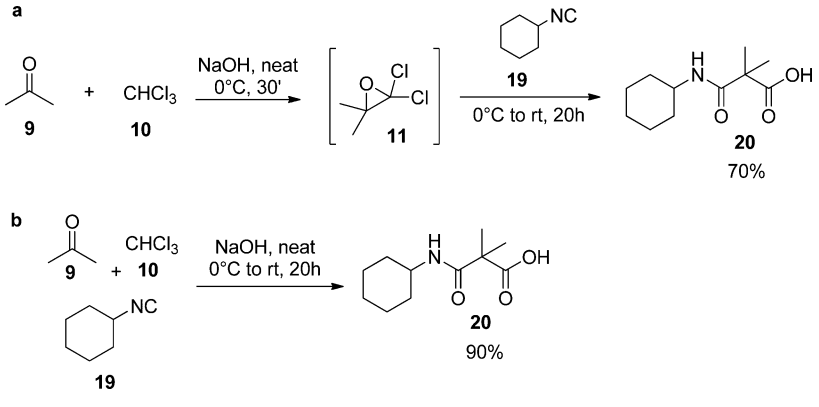
Scheme 4. Proposed Reaction Mechanism for the Formation of 3-Carboxamido-Isobutyric Acids



chloroform (**10**), forming a carbanion (**21**), which is able to attack acetone (**9**) to give the unstable carbinol (**22**). The latter cyclizes to give the 2,2-dichloro-3,3-dimethyloxirane intermediate (**11**), as shown by Weizmann,[23] which is then intercepted by cyclohexylisocyanide (**19**) in an S_N2 reaction with substantial S_N1 character. The resulting nitrilium ion (**23**) is intercepted by the hydroxide ion to form the iminol (**24**), which then tautomerizes to the more stable amide (**20**). Concomitantly, the acyl chloride is hydrolyzed to the carboxylate ion. Besides the energy released by the epoxide ring opening, the whole process is thermodynamically favored by the oxidation of both the isocyanide and chloroform carbon atoms.

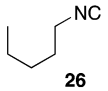
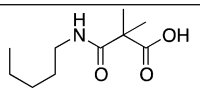
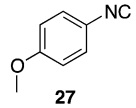
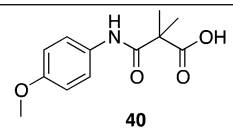
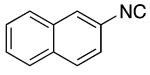
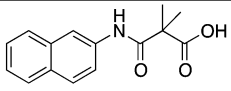
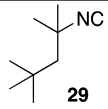
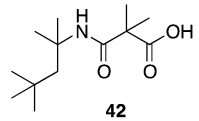
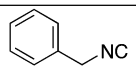
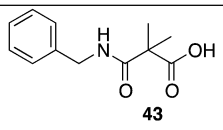
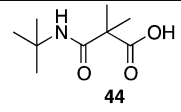
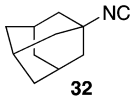
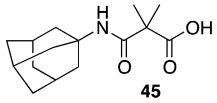
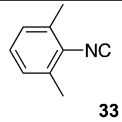
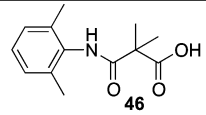
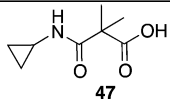
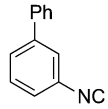
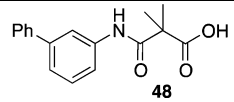
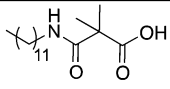
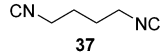
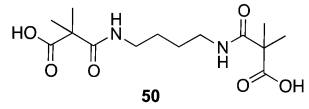
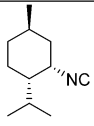
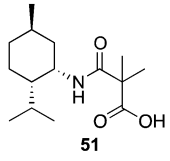
The scope of this novel multicomponent reaction was then examined using different isocyanides. As shown in Table 1, the corresponding 3-carboxamido isobutyric acids were always obtained in excellent yields. In particular, primary (**26**, **36**, and **37**), secondary (**19**, **34**, and **38**), and tertiary isocyanides (**29**, **31**, and **32**) as well as aromatic (**27**, **28**, **33**, and **35**) and benzylic isocyanides (**30**), and even 1,4-diisocyanobutane (**37**), were able to open the Bargellini epoxide to give a wide library

Scheme 3. Test Reactions for the One-Pot Formation of 3-Carboxamido-Isobutyric Acids



DOI: 10.1021/acs.joc.6b02130
J. Org. Chem. 2016, 81, 11467−11471

Table 1. Library of Synthesized 3-Carboxamido-Isobutyric Acids[a]

Isocyanide	Product	Yield	Isocyanide	Product	Yield
 26	 39	80 %	 27	 40	47 %
 28	 41	57 %	 29	 42	95 %
 30	 43	69 %	 31	 44	95 %
 32	 45	85 %	 33	 46	53 %
 34	 47	80 %	 35	 48	56 %
 36	 49	78 %	 37	 50	52 %
 38	 51	75 %			

[a]Reaction conditions: acetone (5 equiv), chloroform (7.5 equiv), sodium hydroxide (7.5 equiv), isocyanide (1 equiv), stirring at 0 °C for 30 min and then at rt overnight.[27]

of 3-carboxamido-isobutyric acids (**20** and **39**−**51**). In the work with the carbonyl component, it has been demonstrated that classical Bargellini reaction works well only with acetone, fails with acetophenones, diethylketone, and diphenylketones, and is rather capricious with methylethylketone and methylpropylketone.[24] To date, to the best of our knowledge, no attempt has been made to rationalize these puzzling results. Despite in some literature reports successful examples of Bargellini reaction with cyclohexanone,[25] *N*-*tert*-butyloxycarbonyl-4-piperidone[18c] and ninhydrin[26] have been described; in our case, we obtained excellent results only with acetone as a carbonyl partner.

In conclusion, in this note we report a new multicomponent process involving the ring opening of the Bargellini epoxide with isocyanides, yielding, in good to excellent yields (47−95%), 3-carboxamido-isobutyric acid derivatives without the need for protection−deprotection maneuvers or the use of condensation agents. Albeit a particular case, this is the first report of a successful nucleophilic addition of isocyanides to epoxides, and also the first case of a Bargellini reaction involving a carbon nucleophile. It is noteworthy that, according to the principle of MCRs, the newly discovered transformation is characterized by ease of performance and a high bond-forming efficiency as two new C−C bonds and three new C−O bonds are formed in the one-pot process. The wide use of 3-carboxamido isobutyric acids as synthetic intermediates to obtain pharmaceutically relevant molecules, as supported by the many patent applications, allows us to hope that a synthetic procedure employing simple and cheap starting materials such as acetone, chloroform, and sodium hydroxide will be welcomed. Finally, we highlight the fact that the successful identification of a neglected nucleophile for the Bargellini reaction casts doubt on the use of other ignored nucleophiles.

EXPERIMENTAL SECTION

General Information. Commercially available reagents and solvents were used without further purification. Melting points were determined in open glass capillaries and are uncorrected. All the compounds were characterized by IR. ^{1}H and ^{13}C APT NMR spectra

DOI: 10.1021/acs.joc.6b02130
J. Org. Chem. 2016, 81, 11467−11471

were recorded on 400 and 300 MHz instruments. High-resolution ESI-MS spectra were recorded on a LTQ Orbitrap mass spectrometer. The spectra were recorded by infusion into the ESI source using MeOH as the solvent. Chemical shifts (δ) are reported in parts per million relative to the residual solvent peak. Column chromatography was performed on silica gel (70−230 mesh ASTM) using the reported eluents. Thin layer chromatography (TLC) was conducted on 5 cm × 20 cm plates with a layer thickness of 0.25 mm (Silica gel 60 F254). They were developed with Bromocresol Green.

Caution: *One known disadvantage of Bargellini reaction concerns safety issues resulting from the exothermic nature of the reaction when it is performed on a large scale.*

General Preparation of 3-Substituted 3-Amino-2,2-dimethyl-3-oxopropanoic Acids (20 and 39−51). In a round-bottom flask, acetone (0.368 mL, 5 mmol), chloroform (0.601 mL, 7.5 mmol), sodium hydroxide (0.300 g, 7.5 mmol), and the isocyanide (1 mmol) were mixed and stirred at 0 °C for 30 min and then at room temperature overnight. The reaction mixture was diluted with water, washed with EtOAc (three times); the aqueous phase was acidified to pH 2 with 2 M HCl and extracted with EtOAc (three times). The organic layers were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. Compounds **40**, **41**, **46**, and **48−51** were further purified by column chromatography.

*3-(Cyclohexylamino)-2,2-dimethyl-3-oxopropanoic Acid (**20**).* Reddish solid (201 mg, 95% yield): ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.39 (br s, -COO*H*), 7.26 (br d, -N*H*), 3.52−3.46 (m, 1H), 1.65−1.52 (m, 6H), 1.24 (s, 6H), 1.20−1.16 (m, 4H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 175.7, 171.6, 49.7, 48.4, 32.5, 25.7, 25.3, 23.6; IR (KBr) ν_{max} 3346, 2983, 2851, 1725, 1550, 1237, 908 cm^{-1}; mp 150−151 °C; HRMS (ESI) m/z (M + H)$^+$ calcd for $C_{11}H_{20}NO_3^+$ 214.1438, found 214.1432 [M + H]$^+$.

*2,2-Dimethyl-3-oxo-3-(pentylamino)propanoic Acid (**39**).* Yellowish solid (161 mg, 80% yield): ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.38 (br s, -COO*H*), 7.54 (br d, -N*H*), 3.02−2.98 (m, 2H), 1.38−1.35 (m, 2H), 1.26−1.18 (m, 10H), 0.84−0.81 (m, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 175.8, 172.5, 50.0, 39.5, 29.3, 29.1, 23.8, 22.5, 14.6; IR (KBr) ν_{max} 3395, 2934, 2857, 1739, 1604, 1467, 1144, 877 cm^{-1}; mp 85−86 °C; HRMS (ESI) m/z (M + H)$^+$ calcd for $C_{10}H_{20}NO_3^+$ 202.1438, found 202.1432 [M + H]$^+$.

*3-[(4-Methoxyphenyl)amino]-2,2-dimethyl-3-oxopropanoic Acid (**40**).* The crude material was purified by column chromatography using a 7:3 *n*-hexane/EtOAc eluant to give a brownish solid (112 mg, 47% yield): ^{1}H NMR (400 MHz, $CDCl_3$/CD_3OD) δ 8.73 (br d, -N*H*), 7.36 (br d, J = 8.1 Hz, 2H), 6.80 (br d, J = 8.1 Hz, 2H), 5.45 (br s, -COO*H*), 3.73 (s, 3H), 1.51 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.7, 170.8, 156.9, 130.1, 122.5, 114.1, 55.4, 49.9, 23.9; IR (KBr) ν_{max} 3351, 2983, 2846, 1720, 1552, 1240, 913 cm^{-1}; mp 123−124 °C; HRMS (ESI) m/z (M + H)$^+$ calcd for $C_{12}H_{16}NO_4^+$ 238.1074, found 238.1069 [M + H]$^+$.

*2,2-Dimethyl-3-(naphthalen-2-ylamino)-3-oxopropanoic Acid (**41**).* The crude material was purified by column chromatography using a 7:3 *n*-hexane/EtOAc eluant to give a brownish solid (147 mg, 57% yield): ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.68 (br s, -COO*H*), 9.67 (br s, -N*H*), 8.27 (s, 1H), 7.83−7.77 (m, 3H), 7.68−7.66 (m, 2H), 7.46−7.36 (m, 2H), 1.44 (s, 6H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 175.5, 172.6, 140.2, 128.6, 127.2, 127.0, 49.9, 42.7, 23.6; IR (KBr) ν_{max} 3340, 2978, 2939, 1709, 1657,1240, 806 cm^{-1}; mp 179−180 °C; HRMS (ESI) m/z (M + H)$^+$ calcd for $C_{15}H_{16}NO_3^+$ 258.1125, found 258.1122 [M + H]$^+$.

*2,2-Dimethyl-3-oxo-3-[(2,4,4-trimethylpentan-2-yl)amino]-propanoic Acid (**42**).* Yellowish solid (230 mg, 95%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.21 (br s, -COO*H*), 6.22 (br s, -N*H*), 1.68 (s, 2H), 1.43 (s, 6H), 1.37 (s, 6H), 0.96 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$/CD_3OD) δ 177.9, 172.2, 55.8, 51.9, 49.5, 31.5, 31.4, 28.6, 23.9; IR (KBr) ν_{max} 3302, 2961, 2890, 1607, 1467, 1163, 913 cm^{-1}; mp 103−104 °C; HRMS (ESI) m/z (M + H)$^+$ calcd for $C_{13}H_{26}NO_3^+$ 244.1908, found 244.1900 [M + H]$^+$.

*3-(Benzylamino)-2,2-dimethyl-3-oxopropanoic Acid (**43**).* Yellowish solid (152 mg, 69% yield): ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.51 (br s, -COO*H*), 8.21 (br t, -N*H*), 7.31−7.17 (m, 5H), 4.26 (br d, 2H), 1.31 (s, 6H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 175.5, 172.5, 140.2, 128.6, 127.2, 127.0, 49.9, 42.7, 23.6; IR (KBr) ν_{max} 3401, 3032, 2939, 1725, 1541, 1146, 735 cm^{-1}; mp 96−97 °C; HRMS (ESI) m/z (M + H)$^+$ calcd for $C_{12}H_{16}NO_3^+$ 222.1125, found 222.1122 [M + H]$^+$.

*3-(tert-Butylamino)-2,2-dimethyl-3-oxopropanoic Acid (**44**).* White solid (177 mg, 95% yield): ^{1}H NMR (400 MHz, $CDCl_3$/CD_3OD) δ 4.69 (br s, -N*H*), 1.37 (s, 6H), 1.28 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.0, 172.6, 51.3, 49.6, 28.3, 23.8; IR (KBr) ν_{max} 3357, 2978, 2598, 1728, 1547, 1390, 1229, 905 cm^{-1}; mp 151−152 °C; HRMS (ESI) m/z (M + H)$^+$ calcd for $C_9H_{18}NO_3^+$ 188.1282, found 188.1278 [M + H]$^+$.

*3-(Adamantan-2-ylamino)-2,2-dimethyl-3-oxopropanoic Acid (**45**).* White solid (226 mg, 85% yield): ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.45 (br s, -COO*H*), 6.55 (br s, -N*H*), 1.98 (s, 3H), 1.90 (s, 6H), 1.59 (s, 6H), 1.25 (s, 6H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 176.0, 171.6, 51.5, 50.4, 41.1, 36.5, 29.3, 23.8; IR (KBr) ν_{max} 3335, 2972, 2851, 1706, 1536, 1308, 1190, 954 cm^{-1}; mp 169−170 °C; HRMS (ESI) m/z (M + H)$^+$ calcd for $C_{15}H_{24}NO_3^+$ 266.1751, found 266.1743 [M + H]$^+$.

*3-[(2,6-Dimethylphenyl)amino]-2,2-dimethyl-3-oxopropanoic Acid (**46**).* The crude material was purified by column chromatography using an 8:2 PE/EtOAc eluant to give a white solid (124 mg, 53% yield): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.93 (br s, -N*H*), 7.09−7.00 (m, 3H), 2.15 (br s, 6H) 1.58 (br s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.3, 172.1, 135.5, 133.4, 128.2, 127.7, 49.6, 24.2, 18.2; IR (KBr) ν_{max} 3320, 2982, 1720, 1670, 1506, 1470, 1286, 1164, 925 cm^{-1}; mp 140−141 °C; HRMS (ESI) m/z (M + Na)$^+$ calcd for $C_{13}H_{17}NNaO_3$ 258.1106, found 258.1110.

*3-(Cyclopropylamino)-2,2-dimethyl-3-oxopropanoic Acid (**47**).* The crude was taken up with cold diethyl ether (0 °C), and the resulting precipitate was filtered. The solid was dried *in vacuo* to give a white solid (137 mg, 80% yield): ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.3 (br s, -COO*H*), 7.57 (br s, -N*H*), 2.63−2.58 (m, 1H), 1.25 (s, 6H), 0.61−0.55 (m, 2H), 0.45−0.40 (m, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 175.0, 173.3, 49.2, 23.0, 22.9, 5.6; IR (KBr) ν_{max} 3310, 2990, 1740, 1713, 1513, 1475, 1295, 1147, 873 cm^{-1}; mp 144−146 °C; HRMS (ESI) m/z (M + Na)$^+$ calcd for $C_8H_{13}NNaO_3$ 194.0793, found 194.0792.

*3-[(1,1′-Biphenyl)-3-ylamino]-2,2-dimethyl-3-oxopropanoic Acid (**48**).* The crude material was purified by column chromatography using an 8:2 PE/EtOAc eluant to give an off-white solid (158 mg, 56% yield): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.36 (br s, -N*H*), 7.78 (s, 1H), 7.60−7.57 (m, 2H), 7.49−7.32 (m, 6H), 1.64 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.2, 170.8, 142.2, 140.5, 137.7, 129.4, 128.8, 127.6, 127.2, 123.8, 119.5 (2-C), 50.3, 23.9; IR (KBr) ν_{max} 3340, 3031, 2978, 2937, 1718, 1667, 1560, 1481, 1171, 758 cm^{-1}; mp 138−140 °C; HRMS (ESI) m/z (M + Na)$^+$ calcd for $C_{17}H_{17}NNaO_3$ 306.1106, found 306.1112.

*3-(Dodecylamino)-2,2-dimethyl-3-oxopropanoic Acid (**49**).* The crude material was purified by column chromatography using an 8:2 PE/EtOAc eluant to give a white solid (233 mg, 78% yield): ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.19 (br s, -N*H*), 3.26−3.22 (m, 2H), 1.61−1.52 (m, 8H), 1.30−1.25 (m, 18H), 0.87 (br t, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.2, 174.4, 48.8, 40.3, 32.0, 29.8 (2-C), 29.7, 29.6, 29.4, 29.3 (2-C), 26.9, 24.3, 22.8, 14.2; IR (KBr) ν_{max} 3378, 2920, 2850, 1746, 1605, 1549, 1473, 1138, 884 cm^{-1}; mp 74−76 °C; HRMS (ESI) m/z (M + Na)$^+$ calcd for $C_{17}H_{33}NNaO_3$ 322.2358, found 322.2368.

*3,3′-[Butane-1,4-diylbis(azanediyl)]bis(2,2-dimethyl-3-oxopropanoic acid) (**50**).* The reaction was conducted with acetone (10 mmol), chloroform (15 mmol), sodium hydroxide (15 mmol), and the isocyanide (1 mmol). The crude material was purified by column chromatography using an EtOAc eluant to give a white solid (164 mg, 52% yield): ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.60 (br s, -2N*H*), 3.02 (br s, 4H), 1.43−1.26 (16H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 175.1, 172.0, 49.3, 38.7, 26.3, 23.2; IR (KBr) ν_{max} 3364, 2979, 2939, 1725, 1616, 1556, 1458, 1265, 1187, 878 cm^{-1}; mp 156−158 °C; HRMS (ESI) m/z (M + Na)$^+$ calcd for $C_{14}H_{24}N_2NaO_6$ 339.1532, found 339.1531.

*3-{[(1S,2S,5R)-2-Isopropyl-5-methylcyclohexyl]amino}-2,2-dimethyl-3-oxopropanoic Acid (**51**).* The crude material was purified by

DOI: 10.1021/acs.joc.6b02130
J. Org. Chem. 2016, 81, 11467−11471

column chromatography using an 8:2 PE/EtOAc eluant to give a white solid (202 mg, 75% yield): ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.0 (br s, -COO*H*), 6.73 (br d, -N*H*), 4.33−4.26 (m, 1H), 1.89−1.70 (m, 3H), 1.49 (s, 1H), 1.44−1.42 (m, 1H), 1.29−1.19 (m, 1H), 1.09−1.02 (m, 1H), 0.88−0.83; ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.0, 172.8, 49.2, 46.9, 46.3, 39.8, 34.7, 29.9, 27.1, 25.7, 24.2, 22.3, 21.1, 20.6; IR (KBr) ν_{max} 3402, 2943, 2919, 1739, 1618, 1549, 1459, 1163, 1138 cm^{-1}; mp 113−115 °C; HRMS (ESI) *m*/*z* (M + H)$^+$ calcd for $C_{15}H_{28}NO_3$ 270.2069, found 270.2073; $[\alpha]_D^{20}$ + 35 (*c* 1.0, $CHCl_3$).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b02130.

Spectra for all new compounds (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: giancesare.tron@pharm.unipmn.it.
*E-mail: mariateresa.giustiniano@unina.it.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Financial support from Università del Piemonte Orientale, Novara, and Università degli Studi di Napoli "Federico II" is acknowledged. This research was funded by Regione Campania under POR Campania FESR 2007-2013-O.O.2.1 (FarmaBioNet, CUP B25C13000230007).

■ REFERENCES

(1) Kazmierski, W. M.; Aquino, C. J.; Bifulco, N.; Boros, E. E.; Chauder, B. A.; Chong, P. Y.; Duan, M.; Deanda, F., Jr.; Koble, C. S.; Mclean, E. W.; Peckham, J. P.; Perkins, A. C.; Thompson, J. B.; Vanderwall, D. PCT 2004054974, 2004.

(2) Flohr, A.; Roland, J.-R.; Wolfgang, W. U.S. Patent Appl. 2006012168, 2006.

(3) Chao, J.; Enyedy, I. J.; Guertin, K.; Hutchings, R. H.; Jones, J. H.; Powell, N.; Vanvloten, K. D. PCT 2014008214, 2014.

(4) Brundish, D.; Bull, A.; Donovan, V.; Fullerton, J. D.; Garman, S. M.; Hayler, J. F.; Janus, D.; Kane, P. D.; McDonnell, M.; Smith, G. P.; Wakeford, R.; Walker, C. V.; Howarth, G.; Hoyle, W.; Allen, M. C.; Ambler, J.; Butler, K.; Talbot, M. D. *J. Med. Chem.* **1999**, *42*, 4584−4603.

(5) Kodra, J. T.; Madsen, J. PCT 2011073328, 2011.

(6) Samajdar, S.; Abbineni, C.; Sasmal, S.; Hosahalli, S. PCT 2015104653, 2015.

(7) (a) Chang, T. T.; More, S. V.; Lu, I.-H.; Hsu, J.-C.; Chen, T.-J.; Jen, Y. C.; Lu, C.-K.; Li, W.-S. *Eur. J. Med. Chem.* **2011**, *46*, 3810−3819. (b) More, S. V.; Chang, T. T.; Chiao, Y.- P.; Jao, S.-C.; Lu, C.-K.; Li, W.-S. *Eur. J. Med. Chem.* **2013**, *64*, 169−178.

(8) Flipo, M.; Charton, J.; Hocine, A.; Dassonneville, S.; Deprez, B.; Deprez-Poulain, R. *J. Med. Chem.* **2009**, *52*, 6790−6802.

(9) (a) Pirali, T.; Mossetti, R.; Galli, S.; Tron, G. C. *Org. Lett.* **2011**, *13*, 3734−3737. (b) Giustiniano, M.; Novellino, E.; Tron, G. C. *Synthesis* **2016**, *48*, 2721−2731.

(10) (a) Kern, O. T.; Motherwell, W. B. *Chem. Commun.* **2003**, 2988−2989. (b) Revised structure: Kern, O. T.; Motherwell, W. B. *Chem. Commun.* **2005**, 1787.

(11) Saegusa, T.; Takaishi, N.; Takami, M.; Ito, Y. *Synth. Commun.* **1971**, *1*, 99−102.

(12) The roots for the discovery of this three-component reaction have to be found in a German patent published in 1864 (Deutsches Patentamt 80986, 1864) and in the work of Bischoff (*Ber* **1900**, *33*, 933). The merit of Guido Bargellini was to identify the right product of the reaction and to demonstrate the generality of this transformation. See: *Gazz. Chim. Ital.* **1906**, *36*, 329−338.

(13) Carminati, G.; Galimberti, P.; Melandri, M. *Boll. Chim. Farm.* **1963**, *102*, 522−540.

(14) (a) Buttini, A.; Galimberti, P.; Gerosa, V. *Boll. Chim. Farm.* **1963**, *102*, 91−98. (b) Buttini, A.; Galimberti, P.; Gerosa, V. *Boll. Chim. Farm.* **1963**, *102*, 156−160.

(15) Buttini, A.; Melandri, M.; Galimberti, P. *Ann. Chim.* **1964**, *54*, 1112−1121.

(16) Galimberti, P.; Gerosa, V.; Melandri, M. *Farmaco* **1959**, *14*, 584−593.

(17) Melandri, M.; Buttini, A.; Gallo, G.; Pasqualucci, C. R. *Ann. Chim.* **1966**, *56*, 1259−1266.

(18) (a) Banti, G. *Gazz. Chim. Ital.* **1929**, *59*, 819−824. (b) Lai, J. T. *J. Org. Chem.* **1980**, *45*, 3671−3673. (c) Butcher, K. J.; Hurst, J. *Tetrahedron Lett.* **2009**, *50*, 2497−2500.

(19) Lai, J. T. *J. Org. Chem.* **1980**, *45*, 754−755.

(20) Mahdavi, M.; Asadi, M.; Saeedi, M.; Rezaei, Z.; Moghbel, H.; Foroumadi, A.; Shafiee, A. *Synlett* **2012**, *23*, 2521−2525.

(21) (a) For the first review of the Bargellini reaction see: Melandri, M. M.; Galimberti, P. *Chim. Ther.* **1967**, *2*, 9−15. (b) For another excellent review covering the Bargellini reaction, see: Snowden, T. S. *ARKIVOC* **2012**, *ii*, 24−40.

(22) We feel that many modifications of the Bargellini reactions are not known in detail, as Galimberti and co-workers reported them in Italian and in minor journals. We are preparing a review article on the Bargellini reaction and its modifications as well as on the figure and life of Guido Bargellini.

(23) Weizmann, C.; Sulzbacher, M.; Bergmann, E. *J. Am. Chem. Soc.* **1948**, *70*, 1153−1158.

(24) Julia, M.; Baillarge, M.; Tchernoff, G. *Bull. Chim. Farm.* **1963**, *102*, 777−783.

(25) Phelps Grella, M. O.; Safo, M. K.; Danso-Danquah, R.; Joshi, G. S.; Kister, J.; Marden, M. C.; Hoffman, S. J.; Abraham, D. J. *J. Med. Chem.* **2000**, *43*, 4726−4737.

(26) Rashid, Z.; Ghahremanzadeh, R.; Naeimi, H. *New J. Chem.* **2013**, *37*, 1−3.

(27) Attempts to reduce or to increase the number of equivalents of acetone, chloroform, and sodium hydroxide have always produced a reduced yield.

DOI: 10.1021/acs.joc.6b02130
J. Org. Chem. 2016, 81, 11467−11471