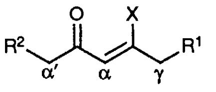
Selectivity in *C*-Alkylation of Dianions of Acyclic β-Enamino Ketones

Giuseppe Bartoli,*[,a] Marcella Bosco,[b] Cristina Cimarelli,[a] Renato Dalpozzo,[b] Maurizio Guerra*[,c] and Gianni Palmieri[a]
[a] *Dipartimento di Scienze Chimiche, via S. Agostino 1, I-62032 Camerino (Mc), Italy*
[b] *Dipartimento di Chimica Organica 'A. Mangini', viale Risorgimento 4, I-40136 Bologna, Italy*
[c] *ICoCEA-CNR, via della Chimica 8, I-40064 Ozzano Emila (Bo), Italy*

The regioselectivity of dianion formation from 4-(*N*-alkylamino)pent-3-en-2-one has been probed by deuteriation and alkylation techniques. The results obtained indicate that the regioselectivity can be controlled almost absolutely without resorting to classical conditions used to favour either the kinetic or the thermodynamic products. In fact, the kinetic (α′-dianion) and the thermodynamic dianion (γ-dianion) are preferentially formed in THF at 20 °C with a slight excess of Li-TMP (α′-conditions) or of MeLi/TMEDA (γ-conditions) respectively. While under γ-conditions, alkylation in the γ-position is almost exclusively observed, kinetic preference for the α′-dianion is dependent on the size of the alkyl group linked to the nitrogen atom. The preference for alkylation at the α′-position increases from methyl to the bulky *tert*-butyl group. Once formed, the α′-dianion very slowly interconverts into the more stable γ-dianion, even in the presence of TMEDA, whereas, when the dianion is formed under γ-conditions, the rate of equilibration is comparable with that of its formation, with the result that γ-dianion is exclusively formed. Theoretical calculations (HF/6-31G//3-21G) on the more stable conformation of the monoanion, both 'naked' and as a lithium ion pair, provide convincing explanations of these findings.

Regiospecific alkylation of 1,3-diketones and their derivatives represents a considerable problem in organic synthesis. Several general solutions to direct the attack of carbon electrophiles at either the α-, α′- or γ-positions have been proposed.[1] Among these are techniques for selective anion generation from β-alkoxy,[2] β-dialkylamino[3] and β-hydrazino[4] α,β-unsaturated ketones.

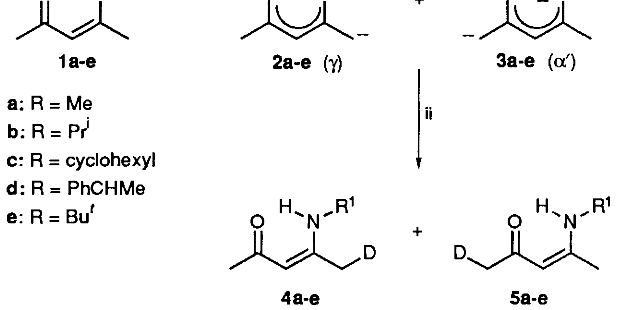


X = OH, OR, NHR, NR_2, $NHNR_2$

Pioneering works[5] reported that metallation of anilino derivatives of acetylacetone by metallo amides in liquid ammonia, followed by addition of an electrophile, resulted in almost exclusive attack at the α′-position. However the yield never exceeded 40%. More recently, efficient experimental procedures for regiocontrolled alkylation in cyclic systems have been proposed, employing alkyllithium or lithium dialkylamides as metallating agents.[2–4] For example, in cyclic enamino and enol ether ketones, if the anion is generated under kinetic control conditions, alkylation occurs almost exclusively at the α′-position. On the other hand, under conditions which encourage thermodynamic anion formation, alkylation occurs almost exclusively at the γ-position. In contrast, acyclic systems display a more complex reactivity spectrum. In fact Mariano *et al.*[6] reported that in both enol ether and enamino ketone systems it is impossible to prepare the kinetic anion without contamination by the more stable thermodynamic one. Moreover, using lithium diisopropylamide (LDA) as the metallating agent, in ketone enol ether systems, very complex mixtures of alkylated products were obtained, including α-mono- and di-alkylated products, while enamino ketones underwent mainly γ-dialkylation. On the other hand, Japanese workers[7] were able to obtain exclusive γ-monoalkylation, using butyllithium as the metallating agent. Recently, we have reported[8] that dianions of 1-aryl-3-(*N*-isopropylamino)but-2-en-1-ones, easily generated by treatment with lithium tetramethylpiperidide, react efficiently at the γ-position with carbon electrophiles. These preliminary results prompted us to investigate whether β-*N*-monoalkylamino α,β-unsaturated ketones were able to resolve definitively the problem of alkylation at the α′- and γ-positions. In this work we report the optimum experimental conditions for regiocontrol of the formation of the most simple dianions of this class [*i.e.* those generated from 4-(*N*-alkylamino)pent-3-en-2-one] and a theoretical justification of the experimental results.

Results

Following suggestions from the literature,[9,10] we surveyed many different base, solvent and temperature combinations for efficient and regiocontrolled dianion generation. Since treatment of **1** with a base did not generally give clear solutions, we excluded the use of a direct NMR analysis to detect dianion formation, and followed the method of quantifying deuterium incorporation at the α′- or γ-positions (products **5** and **4** respectively) by NMR and MS techniques after quenching the reaction mixture with deuteriated acetic acid (Scheme 1). *A priori* two deuterium atoms must be incorporated in the product, however the deuterium bonded to the nitrogen atom exchanged very fast with any proton source in our experimental



Scheme 1 *Reagents:* i, B (2.5 equiv.); ii, 1, CH_3COOD, 2, $NaHCO_3$ aq.

Table 1 Formation of dimetallated species **2** and **3** under various experimental conditions,[a] determined as deuteriated derivatives **4** and **5**

Starting enaminone	Base and solvent	Reaction time/h	Conversion (%)[b]	Relative amounts[c] **5**	Relative amounts[c] **4**
1b	LiTMP/TMEDA/THF	2	>95	60	40
1b	MeLi/HMPA/THF	2	>99	40	60
1b	MeLi/TMEDA/THF	2	>99	<2	>98
1b	MeLi/THF	2	22	80	20
1b	MeLi/Et$_2$O	3	5	78	22
1b	LDA/THF	2	95	82	18
1b	LiTMP/THF	1	87	88	12
1b	LiTMP/THF	2	>99	87	13
1a	LiTMP/THF	2	>99	66	34
1c	LiTMP/THF	2	>99	88	12
1d	LiTMP/THF	2	>99	91	9
1e	LiTMP/THF	2	>99	>98	<2

[a] In all experiments the solution of base (2.5 equiv.) was dropped at 0 °C into the substrate solution; the mixture was allowed to warm to 20 °C and to stand at this temperature for the reported time. [b] The percentage of conversion was calculated by comparing the integration of ^{1}H NMR signals of the sum of the methyl groups in the α′- and γ-positions with respect to the signals of the R groups. [c] The relative amounts of **5** and **4** were calculated by comparing the integration of ^{1}H NMR signals of the methyl groups in the α′- and γ-positions, taking into account the conversion.

Table 2 Studies on isomerization of dianion **2b** and **3b** under the optimum conditions for their regioselective formation. Dianions were quenched with methyl iodide and recognized as methyl derivatives **7ba** and **8ba**

Conditions[a]	Time/h	Conversion[b] (%)	**8ba**:**7ba** ratio[b]
MeLi/TMEDA/THF	0.5	66	1:26
MeLi/TMEDA/THF	1	97	1:38
MeLi/TMEDA/THF	2	100	1:41
LiTMP/THF	1	85	7.3:1
LiTMP/THF	2	98	6.5:1
LiTMP/THF	5	100	5.2:1

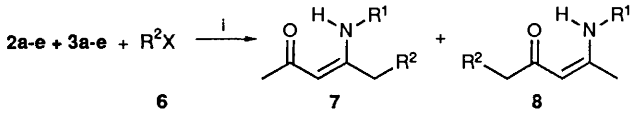
[a] See footnote *a* of Table 1. [b] Conversions and **8**:**7** ratio were calculated by quantitative GC–MS analysis of the reaction mixture.

conditions, so that, in practice, only deuterium incorporation at the α′- or γ-position was observed. We also verified that products **4** and **5** do not exchange deuterium to an appreciable extent in weakly acidic or basic media.

Dimetallation of 4-(*N*-isopropylamino)pent-3-en-2-one **1b** requires strong bases and relatively drastic conditions (Table 1). At temperatures below 0 °C formation of the dianion is too sluggish for practical applications. Methyllithium, both in diethyl ether and THF, does not give extensive dimetallation within a few hours even at 20 °C and using a large excess. As expected, data reported in Table 1 show that in the presence of TMEDA* or HMPA† (polar conditions) the formation of the γ-dianion **2b** is favoured, while the α′-dianion **3b** is formed in less polar conditions. The optimum conditions for the preferential formation of α′-dianions **3a–e** are LDA or lithium 2,2,6,6-tetramethylpiperidide (Li-TMP) (2.5 equiv.) in THF at 20 °C for 2h.‡ The more sterically crowded Li-TMP also ensures a higher selectivity. Conversely, the optimum conditions for the formation of γ-dianions **2a–e** are MeLi (2.5 equiv.)/TMEDA (2.5 equiv.) in THF at 20 °C for 2 h.§

Regioselectivity is strongly dependent on the size of the R group linked to the nitrogen atom. Under the α′-conditions the α′:γ ratio increases from 2:1 when R^1 = Me to 6:1 when R^1 = Pr^i and to the exclusive formation of the α′-dianion when R^1 = Bu^t. Conversely, the size of the alkyl group does not influence the α′:γ ratio under the γ-conditions.

Dianion **3b** equilibrates very slowly with **2b**. In fact, under α′-conditions, the α′:γ ratio decreases from *ca* 7:1 to *ca.* 5:1 over a period of four hours (Table 2). On the other hand, under γ-conditions, after half an hour and at 66% conversion, the α′:γ ratio is already largely shifted towards the γ isomer and a small but significant variation is observed at 100% conversion. Moreover if the dianion is generated under the α′-conditions, a subsequent addition of TMEDA (2.5 equiv.) does not perceptibly affect the rate of isomerisation of **3b** into **2b**. All measurements were performed by quenching dianions with methyl iodide (Scheme 2) and quantifying the alkylated products by GC–MS analysis, since this technique allows a much more sensitive determination of the products than NMR spectroscopy.



6
a: MeI
b: EtI
c: Pr^{i}Br
c′: Pr^{i}I
d: PhCH$_2$Cl
d′: PhCH$_2$Br

7 **8**
aa: R^1 = Me, R^2 = Me
ab: R^1 = Me, R^2 = Et
ac: R^1 = Me, R^2 = Pr^i
ad: R^1 = Me, R^2 = PhCH$_2$
ba: R^1 = Pr^i, R^2 = Me
bd: R^1 = Pr^i, R^2 = PhCH$_2$
ca: R^1 = cyclohexyl, R^2 = Me
da: R^1 = PhCHMe, R^2 = Me
dd: R^1 = PhCHMe, R^2 = PhCH$_2$
ea: R^1 = Bu^t, R^2 = Me

Scheme 2 *Reagents:* i, NH$_4$Cl aq.

In Table 3, examples of alkylation of dianions **2** and **3** are reported. Products **7** and/or **8** are obtained in very good yields. In contrast to the work of Mariano,[6] who reported that in cyclic systems extensive *N*-alkylation was observed and that it always overwhelmed *C*-alkylation, in our system, using a slight excess of alkylating agent, only monoalkylation is observed. Both primary and secondary alkyl groups can be introduced. Both bromide and iodides can be efficiently used. In fact, isopropyl iodide and isopropyl bromide gave comparable yields. Peculiarly reactive alkyl chlorides such as benzyl chloride also work well in this reaction. The distribution of the alkylated products is in good agreement with the regioselectivity rules established from the metallation studies.

Product Identification.—Products arising from quenching with methyl iodide were recognized by comparison with

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* *N*,*N*,*N′*,*N′*-Tetramethylethylenediamine.
† Hexamethylphosphoric triamide.
‡ These conditions will be named α′-conditions throughout.
§ These conditions will be named γ-conditions throughout.

Table 3 Reaction of alkyl halides **6** with dianions **2** and **3** generated in the optimum conditions favouring γ- (**7**, method A) and α′-alkylated products (**8**, method B)

Starting material	R^2X	Method[a]	Yield (%)[b,c] **7**	**8**
1a	**6a**	A	92 (**aa**)	trace (**aa**)
1a	**6a**	B	29 (**aa**)	54 (**aa**)
1a	**6b**	A	94 (**ab**)	trace (**ab**)
1a	**6c**	A	82 (**ac**)	trace (**ac**)
1a	**6c′**	A	86 (**ac**)	trace (**ac**)
1a	**6d**	A	92 (**ad**)	trace (**ad**)
1a	**6d′**	A	87 (**ad**)	trace (**ad**)
1b	**6a**	A	85 (**ba**)	trace (**ba**)
1b	**6a**	B	10 (**ba**)	66 (**ba**)
1b	**6d′**	B	10 (**bd**)	65 (**bd**)
1c	**6a**	B	11 (**ca**)	72 (**ca**)
1d	**6a**	B	9 (**da**)	72 (**da**)
1e	**6a**	B	trace (**ea**)	85 (**ea**)
1e	**6a**	A	83 (**ea**)	trace (**ea**)
1e	**6d′**	B	trace (**ed**)	84 (**ed**)

[a] Method A: MeLi (2.5 equiv.)/TMEDA (2.5 equiv)/THF from 0 °C to 20 °C, 2 h. Method B: LiTMP (2.5 equiv.)/THF from 0 °C to 20 °C, 2 h. [b] Yield calculated on pure isolated product. [c] Trace indicates a weak signal in GC–MS analysis but the corresponding product cannot be isolated.

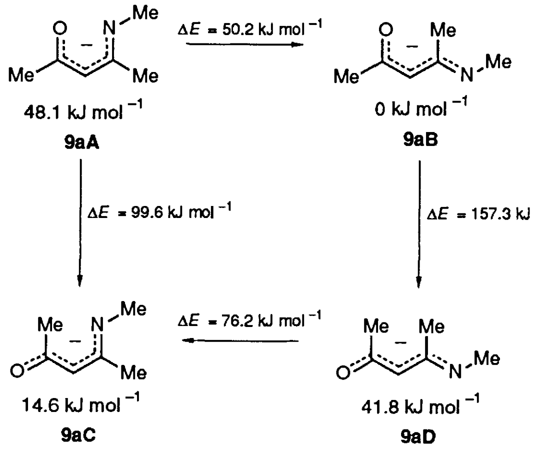


Fig. 1 Relative energies of stable conformations of the monoanion of 4-(*N*-methylamino)pent-3-en-2-one (**9aA**) along with the energy barriers to interconversion

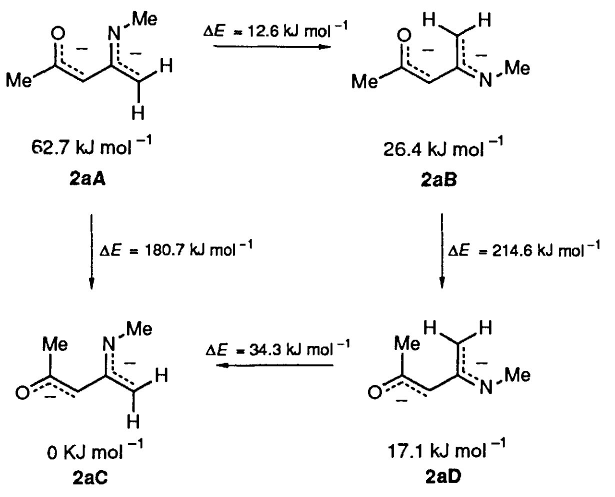


Fig. 2 Relative energies of stable conformations of the γ-dianion of 4-(*N*-methylamino)pent-3-en-2-one (**2aA**) along with the energy barriers to interconversion

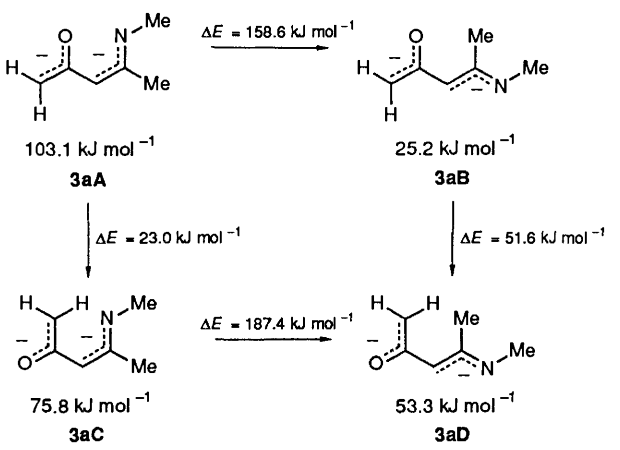
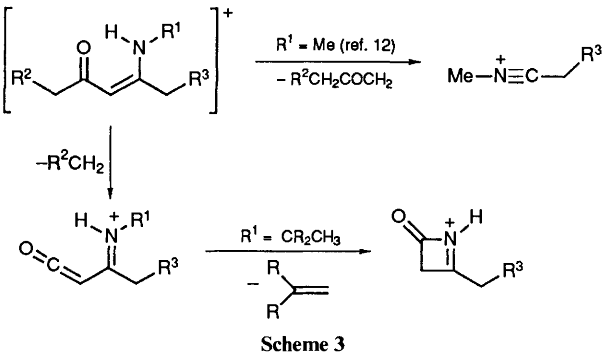


Fig. 3 Relative energies of stable conformations of the α′-dianion of 4-(*N*-methylamino)pent-3-en-2-one (**3aA**) along with the energy barriers to interconversion

independently synthesized authentic samples.[11] We also found that the mass spectrum fragmentation pattern offers analytical advantages on the location of branches in the carbon atom chain. It was known[12] that *N*-methyl derivatives ionise and fragment to some extent in the imino form with loss of $CH_2COCH_2R^2$ (Scheme 3). Moreover, when a hydrogen atom is present in the 2-position of the alkyl chain bound to the nitrogen atom fragmentation proceeds *via* loss of olefin and formation of a four-membered ring. Therefore identification of products was made on the mass of these fragments.



Scheme 3

Theoretical Calculations.—To better understand factors controlling the regiocontrol of dianion formation, *ab initio* calculations at the HF/6-31G//3-21G level of theory were carried out on the mono *N*-anion **9a**, *N*,γ-dianion **2a** and *N*,α′-dianion **3a**. Higher-level calculations do not significantly affect relative energies (see Experimental). Four stable conformers were found for each structural isomer, since the molecular skeleton was found to be essentially planar in all conformers. Energy stabilities relative to the most stable conformer are reported for each isomer in Figs. 1–3.

A unique reference energy was taken in comparing dianion stability (Figs. 2 and 3). Optimized structural parameters and total energies are available as supplementary material.* The theoretical calculations show that the hydrogen-bond inter-

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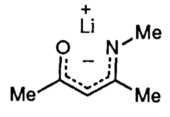
* Optimized structural parameters and total energies of the *N*-monoanion (Table 1s), *N*,γ-dianion and *N*,α′-dianion (Table 2s) and Li–enaminone ion pair (Table 3s) and relative energies of stable conformers of the Li–enaminone ion pair (Fig. 1s), are available as supplementary material. [Supp. pub. no. 56869 (5 pp.)]. For details of the supplementary Data Scheme, see 'Instructions for Authors', *J. Chem. Soc., Perkin Trans. 2*, 1992, in the January issue.

action determines the relative stability of the conformers in the monoanion **9a**. In fact the conformers in which this interaction is operative (**9aB** and **9aC**) are much more stable than the other ones. The *oxygen–hydrogen* bond is found to be more effective in stabilizing the anion (*ca.* 40 kJ mol^{-1}) than the nitrogen–hydrogen bond (*ca.* 25 kJ mol^{-1}). The π-electron system is fully delocalized, since the values of the optimized bond lengths, which are found not to be significantly affected by conformation, lie intermediate between normal single and double bonds. As a result the energy barriers (ΔE) to rotation around the C(2)–C(3) and C(3)–C(4) bonds are found to be relatively small ($<$ 100 kJ mol^{-1}) except for the interconversion of **9aB** and **9aD** because of the strong oxygen–hydrogen bond occurring in **9aB**.

The optimized bond lengths do not change significantly with conformation of the dianions, and their values indicate that both **2a** and **3a** consist of two weakly interacting enolate and imino anion fragments as depicted in Fig. 2 and 3. Inspection of the theoretical results indicates that three main factors dictate the relative stability of the conformers in dianions: (i) the relative stability of the γ- and α'-carbanions; (ii) the stabilizing hydrogen-bond interaction and (iii) the repulsive interactions between the π electrons of the two allyl-type anion fragments. The strength of these interactions can be easily estimated by comparing the energy of conformers in which only one interaction is operative. However in one case [point (iii)] a previously determined value [point (i)] has ben utilized. The γ *vs.* α'-carbanion stability is computed to be *ca.* 40 kJ mol^{-1} from the **2aA**/**3aA** and **2aD**/**3aD** energy differences. An examination of the electronic charge distribution in mono- and di-anions indicates that the larger stability of the *N*,γ-dianion probably depends on the capability of the methylamino group to better delocalize the second negative charge over the pseudo π^* MO localized at the methyl group. In fact, the second negative charge is localized to a greater extent at the imino fragment in **2a** and at the enolate fragment in **3a**. Hydrogen bonding is slightly less effective in stabilizing both dianions than the monoanion because of the lower acidity of the hydrogens. The oxygen–hydrogen bond and the nitrogen–hydrogen bond are estimated to be *ca.* 30 kJ mol^{-1} and 20 kJ mol^{-1} from the **3aB**/**3aD** and **2aC**/**2aD** energy difference, respectively. The π repulsive interaction between the two allyl-type anion fragments is stronger in the *cis* than in the *trans* arrangement of the π electrons by *ca.* 45 kJ mol^{-1}, as can be estimated from the **2aC**/**2aA** and **3aA**/**3aB** energy differences by taking into account the previously determined hydrogen-bond interactions. Because of the different strength of the examined interactions [(iii) > (i) > (ii)] conformers bearing the two allyl-type fragments in a *trans* arrangement are the more stable conformers in both dianions, and each conformer of the γ-dianion is found to be more stable than the corresponding one of the α'-dianion, except for the **B** conformer because both (ii) and (iii) interactions energetically favour the α'-dianion. The energy barriers (ΔE) reported in Figs. 2 and 3 are consistent with the localization properties of the π electrons. Rotation about a formal single bond, *i.e.* C(3)–C(4) in **2a** and C(2)–C(3) in **3a**, is nearly free (ΔE < 40 kJ mol^{-1}) whereas rotation about a formal double bond, *i.e.* C(2)–C(3) in **2a** and C(3)–C(4) in **3a**, is highly hindered (150–200 kJ mol^{-1}) being significantly higher than in the monoanion where the π electrons are fully delocalized. For the mono-*N*-anion the lithium ion pair was also investigated. The ion pair exists as a bridged structure **9a′A**, in which the lithium atom interacts with both the oxygen and nitrogen atoms. This structure is much more stable than the Li–O **9a′** (*ca.* 150 kJ mol^{-1}) and Li–N **9a″** (*ca.* 200 kJ mol^{-1}) open structures owing to the electrostatic nature of the lithium–enaminone interaction (see Supplementary material, Fig. 1s). Indeed, the extent of electron transfer from the monoanion to the lithium ion is small (*ca.* 0.30 e). Thus, the strength of the ion pair (O–Li–N $\gg$ Li–O > Li–N) follows the same trend as the distribution of the negative atomic charges in the 'naked' anion, the net atomic charge in **9a** being about -0.76 (O), -0.65 (N), 0.48 [C(2)], -0.41 [C(3)] and 0.33 [C(4)]. The bridged structure also gains stability from the aromatic configuration of its π system. Indeed, six electrons are delocalized over a six-membered ring as the optimized bond lengths suggest. Comparison with the bond lengths of the 'naked' anion and of the γ- and α'-dianions indicates that the π system of the bridged structure resembles that of the monoanion. The relative energies of the lithium–enaminone conformers are not relevant to the discussion, therefore they are available as supplementary material (Fig. 1s).



9a′A

Discussion

Our results show that almost complete regiocontrol of dianion formation is possible in the β-monoalkylamino α,β-unsaturated ketone system depending on the conditions of metallation and on the size of the *N*-substituent. Data reported in Table 2 suggest that the α'-dianion is the kinetically favoured isomer, while the γ-dianion is the thermodynamically more stable one. The preferential formation of each dianion was not obtained by resorting to classical conditions used to favour either the kinetic or the thermodynamic products,[6,13] but by adopting conditions which favour or disfavour a rapid interconversion of the kinetic into the thermodynamic isomer, although always in the presence of an excess of base. Since the substantial difference between γ- and α'-conditions is the presence of a strong lithium complexing agent in the former conditions, the logical hypothesis that the 'naked' dianion may interconvert much more rapidly than the ion paired one can be suggested. However this hypothesis is ruled out by the observation that the α'-dianion formed under the α'-conditions interconverts very slowly even if TMEDA is added. Therefore it is necessary to assume that the α'-dianion is formed with different geometries under the α'- and γ-conditions. In the latter case the conformation should be able to give a rapid intramolecular 1,5-hydrogen shift, allowed by an aromatic orbital array.[14] The most suitable conformation for this process to occur, is **3aD** (Fig. 3) in which the involved termini of the rearrangement face each other. A 1,5-shift might also occur in the form **3aB**, although in this case a stronger C–H bond is broken to form a weaker O–H bond.

Theoretical studies provide convincing support for this interpretation. Owing to the high difference in acidity of the hydrogen atom linked to the nitrogen atom and of those of the methyl groups, the reaction must proceed with formation of the monoanion followed by further metallation to give the dianion. Probably under the α'-conditions monoanion **9** is generated as a tight ion pair because of the greater complexing power of **9** with respect to both tetramethylpiperidine and THF. Theoretical calculations on **9a** confirm that the more stable conformation of such an ion pair is **9a′A**.

This conformation is directly achieved by the metallation process, because the starting enaminone **1a** is in a similar conformation.[15] The planarity of the system constrains the alkyl group bound to the nitrogen (R^1) to shield hydrogens in the γ-position, hindering an attack from this side of the molecule. Also, the hydrogen atom in the α-position hinders the opposite side. On the other hand attack at the α'-position probably suffers only the latter steric hindrance. Experimental results reported in Tables 1 and 3 demonstrate that the preference for attack at the α′-position increases, when the bulkiness of R^1 is increased. Furthermore the more sterically hindered Li–TMP ensures a greater selectivity of attack at the less crowded position than does LDA (see Table 1). Assuming that the geometry of the system does not change during the second metallation, under α′-conditions, **9a′A** should give the α′-dianion in the ion paired conformation similar to **3aA** (Fig. 3). Our calculations on the 'naked' dianion **3a** showed that, while conversion of **3aA** into **3aC** is an easy process involving rotation around the single C(2)–C(3) bond (1.498 Å) with an energy barrier of 23 kJ mol^{-1}, the conversion of **3aA** into **3aB** and of **3aC** into **3aD** has to overcome too high a barrier (158.6 and 187.4 kJ mol^{-1}, respectively) involving a rotation around a formal double bond [C(3)–C(4) = 1.371 Å]. Since both conformations suitable for the 1,5-hydrogen shift to occur cannot be easily achieved by the system, according to experimental data reported in Table 2, equilibration should occur very slowly. Moreover it was found[16] that lithium imines are more stable in a σ-(*N*) conformation. Since, on the basis of bond lengths, in dianion **3a** as well as in dianion **2a** both enolate and imino ions can be considered as two separate entities, it is reasonable to assume that in **3a** the lithium ion is mainly bound to the nitrogen and oxygen atoms and therefore the double bond character of C(3)–C(4) must increase in the tight ion pair with respect to the 'naked' dianion with a consequent increase in the magnitude of the energy barrier associated with rotation.

When the metallation process is carried out in the presence of powerful complexing agents of the lithium cation such as TMEDA, **9a** should exist as the 'naked' anion or loose ion pair. Theoretical calculations show that, in this situation, conformation **9aB** is the most stable arrangement of the molecule (Fig. 1) easily achieved from **9aA**, by the feasible rotation around the C(3)–C(4) bond (ΔE = 50.2 kJ mol^{-1}). If the geometry of the system does not change during the metallation process, and if the kinetic preference for the α′-position is still present, the α′-dianion should be generated in the conformation **3aB**. Moreover a rotational barrier of only 51.6 kJ mol^{-1} must be overcome to obtain the other conformation **3aD** able to give the 1,5-hydrogen shift. Then the system can undergo a smooth isomerization into the more stable dianion **2a**. These considerations are based on the assumption that theoretical calculations offer a quite reliable picture of the dianion under γ-conditions. Both relative stabilities and energy barriers among the conformations can be modified in the presence of lithium counter ions and of the solvent. However, lithium cations being removed by complexing agents (TMEDA), a solvent such as THF seems very unlikely to affect markedly either relative stabilities or energy barriers among the different rotamers.

The alternative hypothesis, that under γ-conditions the kinetic preference is shifted towards the γ-dianion, seems less convincing. In fact it is conceivable that the steric hindrance exerted by the alkyl group bonded to the nitrogen atom inhibits attack at the γ-position in conformation **9aB** as it does in **9aA**.

Finally, equilibration of α′- into γ-dianions *via* an intermolecular pathway must be ruled out owing to the bulkiness of the system which would require more acidic proton sources than those present in the reaction mixture.

In conclusion, a method is now available for the almost exclusive regiocontrol of alkylation in the two useful positions (α′ and γ) of acyclic 1,3-diketone derivatives, which allows preparation of complex derivatives starting from easily available materials. This methodology cannot be applied to cyclic systems owing to their rigidity which does not allow the conformational flexibility required for the intramolecular isomerisation process. Nevertheless, in these systems the selectivity can be efficaciously controlled with monoanions of both dialkylamino enones or ketone enol ethers[6] under kinetic or thermodynamic conditions for α′- and γ-anion formation respectively. We wish to underline that since, in monoanion alkylation techniques, the equilibration process is based on intermolecular proton exchange, it can be easily achieved using a slight deficiency of base. On the other hand, in dianion alkylation techniques, equilibration must occur through an intramolecular 1,5-hydrogen shift, because the monoanion is not an efficient proton source. Moreover, to favour equilibration by an intermolecular pathway, a weaker metallating agent must be chosen with the risk of only partial dimetallation.[6] In our opinion therefore, dianions offer a good solution to the problem of regioselective alkylation in acyclic systems, while monoanions are more suitable in cyclic systems.

Experimental

^{1}H and ^{13}C NMR spectra were recorded with a Varian VXR 300 instrument. Chemical shifts are given in ppm downfield from Me_4Si in $CDCl_3$ solutions. Coupling constants are given in Hertz. IR spectra were recorded with a Perkin-Elmer 257 spectrometer. GC–MS analyses were performed with an HP 59970 workstation formed by an HP-5890 gas chromatograph equipped with a methyl silicone capillary column and by an HP-5970 mass detector. THF and diethyl ether were dried by refluxing over sodium wires until the blue colour of benzophenone ketyl persisted and then distilling into a dry receiver under nitrogen atmosphere. Starting 4-(*N*-alkylamino)pent-3-en-2-ones were prepared from acetylacetone and the appropriate amine: **1a–d** according to Sing's procedure;[17] **1e** was prepared according to Weingarten's procedure.[18] Lithium tetramethylpiperidide and lithium diisopropylamide were prepared from equimolecular amounts of butyllithium and amine in THF at 0 °C. Commercial methyllithium solutions (Aldrich) and deuteriated acetic acid (Aldrich) were employed under dry atmosphere. Commercial alkyl iodides, TMEDA and HMPA (Aldrich) were distilled and dried before use.

Metallation of Enaminones **1a–e** *followed by Deuteriation*.—A solution of 5 mmol of the appropriate metallating agent (Table 1) was dropped into a stirred solution of **1a–e** (2 mmol), to which was added TMEDA or HMPA (5 mmol) at 0 °C under nitrogen. The temperature was allowed to rise to 20 °C and the mixture stirred at this temperature for the times reported in Table 1.5%. Solution of CH_3COOD in D_2O (5 cm^3) was then added, the organic layer was washed with saturated aqueous $NaHCO_3$ and with water, dried, evaporated under reduced pressure and submitted to NMR and GC–MS analyses. Samples were shaken for some hours with both acetic acid and $NaHCO_3$ solutions. The deuterium incorporation at the α′- and γ-positions was substantially unaffected. Metallation experiments carried out at −20 °C did not show significant deuterium incorporation.

The ratio between the deuteriated isomers and the percentage of deuteration were determined as follows: (*a*) percentage of deuteration by calculation of the ratio between M + 1 and M ions; isomer ratio from the ratio of the following fragments: $DCH_2C{\equiv}N^+{-}R^1$ and $CH_3C{\equiv}N^+{-}R^1$. (*b*) The percentage of conversion was calculated by comparing the integration of ^{1}H NMR signals of the sum of the methyl groups in the α′- and γ-positions with respect to the signals of the R^1 groups. The isomer ratio was calculated from the ratio of the signals of α′- and γ-methyls, both deuteriated and not; δ_H 1.910 (t, J_{HD} 2.2, γ-CH_2D), 1.924 (s, γ-CH_3), 1.948 (t, J_{HD} 2.2, α′-CH_2D), 1.963 (s, α′-CH_3).

Theoretical Calculations.—*Ab initio* calculations were carried out on the mono *N*-anion **9a**, *N*,γ-dianion **2a** and *N*,α′-dianion **3a** utilizing the GAUSSIAN 82 series of programs[19] running on a FPS array processor attached to a VAX 11/780 computer. Geometrical parameters of the rotational conformers about the C(2)–C(3) and C(3)–C(4) bonds were fully optimized at the Hartree–Fock level by using an analytical gradient procedure with split-valence 3-21G basis set (HF/3-21G). Geometrical parameters of the conformers of the lithium–enaminone ion pair were also determined assuming C_s symmetry since the molecular skeleton of each negatively charged species was found to be essentially planar at the stationary points and exploratory calculations indicated that the lithium atom prefers to lie in the molecular plain. Improved energies of the conformers and energy barriers to rotation about the C(2)–C(3) and C(3)–C(4) bonds, estimated by using the rigid rotor model, have been obtained from higher-level calculations with split-valence 6-31G basis set (HF/6-31G//3-21G). More expensive calculations performed on selected conformers (**A**, **C**) and transition states (**A**→**B**, **A**→**C**) of dianions **2a** and **3a** have shown that inclusion of polarisation *d* functions in the basis set (HF/6-31G*), as well as evaluation of electron correlation at second order Möller–Plesset perturbation theory (MP2/6-31G), does not significantly affect the computed relative energies, changes in energy differences being less than 5 kJ mol^{-1}. For example the **2aA**/**3aA** energy difference is 40.4, 40.0 and 42.6 kJ mol^{-1} at the HF/6-31G//3-21G, HF/6-31G*//3-21G and MP2/6-31G//3-21G levels, respectively. On the other hand, values of total energy computed with standard sp-type diffuse functions (6-31 + G) have no physical meaning since the basis set is linearly dependent. For example, inclusion of diffuse functions lowers the total energy of **2aA** from −361.331 882 to −1843.665 936 a.u. and that of **3aA** from −361.316 487 to −2786.475 221 a.u. Inclusion of diffuse functions is expected to give a better description of negatively charged species.[20] However, the use of standard diffuse functions has been found to provide meaningless values of negative electron affinities (unstable anions)[21,22] and of relative energies of planar cross- and linear-conjugated dianions.[23] Thus, calculations were carried out as a function of the exponents, $\alpha(\lambda)$, of the diffuse function, that were varied proportionally to the difference between the exponent of the outermost valence sp-type function (α_{val}) and that of the standard diffuse functions (α_{diff}).[21]

$$\alpha(\lambda) = \alpha_{val} + \lambda(\alpha_{diff} - \alpha_{val}).$$

These calculations show that the basis set is linearly dependent for $\lambda \geqslant 0.85$ and that relative energies are not affected for $\lambda \leqslant 0.8$. For example, the **2aA**/**3aA** energy difference is 40.4, 39.5, 39.4, 39.8 and 40.2 kJ mol^{-1} for λ = 0.0, 0.2, 0.4, 0.6 and 0.8, respectively.

Metallation of Enaminones **1a–e** *followed by Quenching with Methyl Iodide.—Method A.* A solution of 5 mmol of methyl lithium was dropped into a stirred THF solution of **1b** (2 mmol) and of TMEDA (5 mmol) at 0 °C under nitrogen. The temperature was allowed to rise to 20 °C and the mixture was stirred at this temperature for the times reported in Table 2. A solution of methyl iodide (3 mmol) in THF was then added and the mixture was allowed to stir for 0.5 h before submitting it to GC–MS analysis.

Method B. A solution of Li–TMP (5 mmol) was dropped into a stirred solution of **1b** (2 mmol) in THF at 0 °C under nitrogen. The temperature was allowed to rise to 20 °C and the mixture was allowed to stir at this temperature for the times reported in Table 2. A solution of methyl iodide (3 mmol) in THF was then added and the mixture was allowed to stir for 0.5 h before submitting it to GC–MS analysis.

Products **7ba** and **8ba** were recognized by comparison of their mass spectra and retention times with an authentic sample of **7ba** prepared according to our procedure[11] from ethylpropionate and the lithium salt of acetone isopropylimine. The **7ba** to **8ba** ratio was calculated on the 140 to 126 ratio in single ion mode of GC–MS data acquisition. A solution of Li–TMP (5 mmol) was dropped into a stirred solution of the appropriate enaminone **1b** (2 mmol) in THF at 0 °C under nitrogen. The temperature was allowed to rise to 20 °C and the mixture stirred at this temperature for 2 h. A sample (1 mmol) was then quenched with methyl iodide and the quantitative GC–MS analysis showed as expected a 6.5:1 ratio between α′- and γ-products. To the mixture was added TMEDA (2.5 mmol) and the solution was stirred for an additional 2 h. Quenching with methyl iodide followed by quantitation showed a 5.0:1 ratio between α′- and γ-products, instead of 5.2:1 observed in the absence of TMEDA.

Metallation of Enaminones **1a–e** *followed by Quenching with Alkyl Halides* **6**.*—Method A.* A solution of methyllithium (12.5 mmol) was dropped into a stirred solution of the appropriate enaminone **1** (5 mmol) and TMEDA (12.5 mmol) in THF at 0 °C under nitrogen. The temperature was allowed to rise to 20 °C and the mixture was stirred at this temperature for 2 h. A solution of the appropriate alkyl halide **6** (8 mmol) in THF was then added and the mixture was allowed to stir for 0.5–2 h. Then the solution was poured into saturated aqueous ammonium chloride and extracted with diethyl ether; the organic layer was dried, evaporated under reduced pressure and submitted to a chromatographic separation on a silica gel column (hexane:ethyl acetate 4:1 as eluent).

Method B. A solution of Li–TMP (12.5 mmol) was dropped into a stirred solution of the appropriate enaminone **1** (5 mmol) in THF at 0 °C under nitrogen. The temperature was allowed to rise to 20 °C and the mixture was stirred at this temperature for 2 h. A solution of the appropriate alkyl halide **6** (8 mmol) in THF was then added and the mixture was allowed to stir for 0.5–2 h. Then the solution was poured into saturated aqueous ammonium chloride solution and extracted with diethyl ether; the organic layer was dried, evaporated under reduced pressure and submitted to a chromatographic separation on a silica gel column (hexane:ethyl acetate 4:1 as eluent).

Yields of isomers **7** and **8** prepared by both methods are reported in Table 3. Assignment of the structures was made according to their mass spectrum fragmentation patterns compared with those of authentic samples of **7aa–ea** prepared according to our procedure.[11] Physical data follow: **7aa**: oil; δ_H 1.12 (t, *J* 7.56, 3 H), 1.99 (s, 3 H, α′-CH$_3$), 2.20 (q, *J* 7.56, 2 H), 2.91 (d, *J* 5.29, 3 H, NCH$_3$), 4.98 (s, 1 H, α-CH), 10.75 (br, 1 H, NH). δ_C 11.76 (q), 24.71 (t), 28.97 (q), 29.67 (q), 93.09 (d), 169.01 (s), 195.04 (s). ν_{max}(film)/cm^{-1} 3400 (NH), 1605 (C=O). *m/z* (%) 127 (M$^+$, 39), 112 (100), 98 (18), 82 (9), 70 (32). (Found: C, 66.0; H, 10.3; N, 11.1. $C_7H_{13}NO$ requires: C, 66.1; H, 10.3; N, 11.0%).

8aa: oil; δ_H 1.03 (t, *J* 7.59, 3 H), 1.87 (s, 3 H, γ-CH$_3$), 2.18 (q, *J* 7.59, 2 H), 2.87 (d, *J* 5.25, 3 H, NCH$_3$), 4.93 (s, 1 H, α-CH), 10.75 (br, 1 H, NH). δ_C 10.24 (q), 18.68 (q), 29.38 (q), 34.69 (t), 93.92 (d), 164.21 (s), 198.58 (s). ν_{max}(film)/cm^{-1} 3410 (NH), 1605 (C=O). *m/z* (%) 127 (M$^+$, 17), 98 (100), 56 (43). (Found: C, 66.0; H, 10.2; N, 11.0. $C_7H_{13}NO$ requires: C, 66.1; H, 10.3; N, 11.0%).

7ab: oil; δ_H 0.93 (t, *J* 7.34, 3 H), 1.42–1.58 (m, 2 H), 1.93 (s, 3 H, α′-CH$_3$), 2.10 (t, *J* 7.86, 2 H), 2.87 (d, *J* 5.43, 3 H, NCH$_3$), 4.90 (s, 1 H, α-CH), 10.72 (br, 1 H, NH). δ_C 13.86 (q), 20.86 (t), 28.75 (q), 29.06 (q), 34.54 (t), 94.13 (d), 167.68 (s), 194.67 (s). ν_{max}(film)/cm^{-1} 3400 (NH), 1605 (C=O). *m/z* (%) 141 (M$^+$, 39), 126 (100), 113 (15), 98 (26), 84 (37) (Found: C, 68.1; H, 10.6; N, 10.0. $C_8H_{15}NO$ requires: C, 68.0; H, 10.7; N, 9.9%).

7ac: oil; δ_H 0.80 (d, *J* 6.81, 6 H), 1.60–1.78 (m, 1 H), 1.82 (s, 3 H, α′-CH$_3$), 1.89 (d, *J* 6.81, 2 H), 2.76 (d, *J* 5.43, 3 H, NCH$_3$), 4.75 (s, 1 H, α-CH), 10.70 (br, 1 H, NH). δ_C 22.37 (q), 27.17 (d), 28.58 (q), 29.19 (q), 40.42 (t), 95.30 (d), 166.84 (s), 194.11 (s). ν_{max}(film)/cm^{-1} 3350 (NH), 1605 (C=O). m/z (%) 155 (M$^+$, 58), 140 (100), 113 (47), 98 (88), 84 (58). (Found: C, 69.5; H, 11.0; N, 9.0. $C_9H_{17}NO$ requires: C, 69.6; H, 11.0; N, 9.0%).

7ad: oil; δ_H 2.00 (s, 3 H, α′-CH$_3$), 2.40–2.50 (m, 2 H), 2.77–2.86 (m, 5 H), 5.00 (s, 1 H, α-CH), 7.10–7.35 (m, 5 H), 10.78 (br, 1 H, NH). δ_C 28.90 (q), 29.09 (q), 33.48 (t), 34.06 (t), 94.10 (d), 126.46 (d), 128.26 (d), 128.60 (d), 140.38 (s), 166.75 (s), 195.00 (s). ν_{max}(film)/cm^{-1} 3300 (NH), 1605 (C=O). m/z (%) 203 (M$^+$, 55), 188 (100), 160 (17), 146 (25), 91 (72), 84 (24). (Found: C, 76.9; H, 8.3; N, 7.0. $C_{13}H_{17}NO$ requires: C, 76.8; H, 8.4; N, 6.9%).

7ba: oil; δ_H 1.15 (t, J 7.60, 3 H), 1.23 (d, J 6.41, 6 H), 1.99 (s, 3 H, α′-CH$_3$), 2.23 (q, J 7.60, 2 H), 3.65–3.80 (m, 1 H, NCH), 4.91 (s, 1 H, α-CH), 10.90 (br, 1 H, NH). δ_C 12.67 (q), 23.99 (q), 24.67 (t), 28.74 (q), 44.05 (d), 92.65 (d), 167.07 (s), 194.60 (s). ν_{max}(film)/cm^{-1} 3400 (NH), 1605 (C=O). m/z (%) 155 (M$^+$, 95), 140 (87), 112 (50), 98 (100), 84 (70). (Found: C, 69.5; H, 11.1; N, 9.0. $C_9H_{17}NO$ requires: C, 69.6; H, 11.0; N, 9.0%).

8ba: oil; δ_H 1.04 (t, J 7.54, 3 H), 1.17 (d, J 6.41, 6 H), 1.89 (s, 3 H, γ-CH$_3$), 2.20 (q, J 7.54, 2 H), 3.53–3.72 (m, 1 H, NCH), 4.81 (s, 1 H, α-CH), 10.75 (br, 1 H, NH). δ_C 9.88 (q), 18.68 (q), 23.96 (q), 34.53 (t), 44.55 (d), 93.74 (d), 161.83 (s), 198.14 (s). ν_{max}(film)/cm^{-1} 3400 (NH), 1610 (C=O). m/z (%) 155 (M$^+$, 49), 126 (100), 108 (87), 84 (94), 68 (18). (Found: C, 69.7; H, 11.0; N, 9.1. $C_9H_{17}NO$ requires: C, 69.6; H, 11.0; N, 9.0%).

7bd: oil; δ_H 1.13 (d, J 6.40, 6 H), 1.93 (s, 3 H, α′-CH$_3$), 2.40–2.49 (m, 2 H), 2.75–2.84 (m, 2 H), 3.54–3.72 (m, 1 H, NCH), 4.92 (s, 1 H, α-CH), 7.10–7.30 (m, 5 H), 10.90 (br, 1 H, NH). δ_C 24.03 (q), 28.88 (q), 33.48 (t), 34.93 (t), 44.56 (d), 93.66 (d), 126.42 (d), 128.21 (d), 128.55 (d), 140.33 (s), 164.75 (s), 194.66 (s). ν_{max}(film)/cm^{-1} 3300 (NH), 1605 (C=O). m/z (%) 231 (M$^+$, 57), 216 (51), 188 (49), 174 (18), 140 (71), 91 (100). (Found: C, 78.0; H, 9.3; N, 6.0. $C_{15}H_{21}NO$ requires: C, 77.9; H, 9.2; N, 6.0%).

8bd: oil; δ_H 1.23 (d, J 6.40, 6 H), 1.95 (s, 3 H, γ-CH$_3$), 2.50–2.60 (m, 2 H), 2.90–2.98 (m, 2 H), 3.63–3.78 (m, 1 H, NCH), 4.93 (s, 1 H, α-CH), 7.13–7.15 (m, 5 H), 10.90 (br, 1 H, NH). δ_C 18.69 (q), 23.84 (q), 32.02 (t), 43.47 (t), 44.73 (d), 94.40 (d), 125.74 (d), 128.30 (d), 128.33 (d), 142.23 (s), 162.24 (s), 195.99 (s). ν_{max}(film)/cm^{-1} 3350 (NH), 1605 (C=O). m/z (%) 231 (M$^+$, 69), 188 (6), 126 (100), 108 (38), 99 (52), 84 (92). (Found: C, 77.8; H, 9.3; N, 6.0. $C_{15}H_{21}NO$ requires: C, 77.9; H, 9.2; N, 6.0%).

7da: oil; δ_H 1.00 (t, J 7.51, 3 H), 1.53 (d, J 6.75, 3 H), 1.93–2.25 (q, J 7.51, 2 H), 2.07 (s, 3 H, α′-CH$_3$), 4.60–4.73 (m, 1 H, NCH), 5.01 (s, 1 H, α-CH), 7.20–7.38 (m, 5 H), 11.37 (br, 1 H, NH). δ_C 12.06 (q), 24.89 (q), 25.00 (q), 29.14 (t), 52.47 (d), 93.51 (d), 125.51 (d), 127.17 (d), 128.80 (d), 144.51 (s), 167.60 (s), 195.57 (s). ν_{max}(film)/cm^{-1} 3420 (NH), 1605 (C=O). m/z (%) 217 (M$^+$, 36), 202 (12), 174 (27), 105 (100), 98 (31). (Found: C, 77.5; H, 8.8; N, 6.3. $C_{14}H_{19}NO$ requires: C, 77.4; H, 8.8; N, 6.4%).

8da: oil; δ_H 1.10 (t, J 7.52, 3 H), 1.50 (d, J 6.95, 3 H), 1.78 (s, 3 H, γ-CH$_3$), 2.27 (q, J 7.52, 2 H), 4.58–4.68 (m, 1 H, NCH), 4.98 (s, 1 H, α-CH), 7.18–7.28 (m, 5 H), 11.20 (br, 1 H, NH). δ_C 9.84 (q), 19.23 (q), 24.79 (q), 34.77 (t), 53.07 (d), 94.75 (d), 125.52 (d), 127.15 (d), 128.81 (d), 144.36 (s), 162.55 (s), 199.02 (s). ν_{max}(film)/cm^{-1} 3400 (NH), 1605 (C=O). m/z (%) 217 (M$^+$, 48), 188 (35), 160 (15), 105 (100), 84 (42). (Found: C, 77.5; H, 8.7; N, 6.5. $C_{14}H_{19}NO$ requires: C, 77.4; H, 8.8; N, 6.4%).

7ea: oil; δ_H 1.08 (t, J 7.53, 3 H), 1.30 (s, 9 H), 1.89 (s, 3 H, α′-CH$_3$), 2.28 (q, J 7.53, 2 H), 4.84 (s, 1 H, α-CH), 11.35 (br, 1 H, NH). δ_C 13.37 (q), 25.14 (t), 28.72 (q), 30.68 (q), 52.07 (s), 93.82 (d), 169.46 (s), 193.76 (s). ν_{max}(film)/cm^{-1} 3400 (NH), 1600 (C=O). m/z (%) 169 (M$^+$, 31), 154 (13), 136 (13), 98 (100). (Found: C, 71.1; H, 11.2; N, 8.3. $C_{10}H_{19}NO$ requires: C, 71.0; H, 11.3; N, 8.3%).

8ea: oil; δ_H 1.04 (t, J 7.56, 3 H), 1.36 (s, 9 H), 2.01 (s, 3 H, γ-CH$_3$), 2.20 (q, J 7.56, 2 H), 4.84 (s, 1 H, α-CH), 11.30 (br, 1 H, NH). δ_C 9.98 (q), 20.50 (q), 30.77 (q), 34.63 (t), 52.19 (s), 95.16 (d), 163.26 (s), 197.70 (s). ν_{max}(film)/cm^{-1} 3400 (NH), 1610 (C=O). m/z (%) 169 (M$^+$, 34), 140 (31), 84 (100). (Found: C, 70.9; H, 11.2; N, 8.3. $C_{10}H_{19}NO$ requires: C, 71.0; H, 11.3; N, 8.3%).

8ed: oil; δ_H 1.43 (s, 9 H), 2.08 (s, 3 H, γ-CH$_3$), 2.50–2.60 (m, 2 H), 2.90–3.00 (m, 2 H), 4.91 (s, 1 H, α-CH), 7.05–7.32 (m, 5 H), 11.43 (br, 1 H, NH). δ_C 20.54 (q), 30.81 (q), 32.14 (t), 43.59 (t), 52.36 (s), 95.75 (d), 125.73 (d), 128.05 (d), 128.33 (d), 142.25 (s), 163.67 (s), 195.40 (s). ν_{max}(film)/cm^{-1} 3400 (NH), 1605 (C=O). m/z (%) 245 (M$^+$, 29), 113 (17), 91 (21), 84 (100), 57 (25). (Found: 78.2; H, 9.3; N, 5.6. $C_{16}H_{23}NO$ requires: C, 78.3; H, 9.4; N, 5.7%).

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